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Allylic Substitution in Water Catalyzed by Amphiphilic Resin-Supported Palladium-Phosphine Complexes

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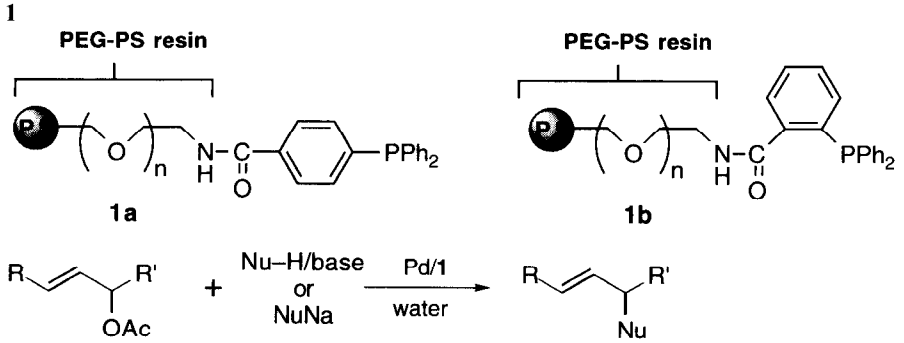
Abstract: New amphiphilic resin-supported triarylphosphines PEP (**1**) were designed and prepared on polyethylene glycol-polystyrene graft copolymer (PEG-PS). Palladium complexes of **1**, $Pd(PEP)_2$ (**4**) and Pd(PEP) (**5**), catalyzed allylic alkylation of 3-acetoxy-1,3-diphenyl-1-propene (**6**) and cinnamyl acetate (**7**) with various nucleophiles including 1,3-dicarbonyl compounds, amino acids, sodium azide, and sodium sulfinate, to give quantitative yields of corresponding allylic substituted products in water.

INTRODUCTION

The development of water-based organic transformations is rapidly becoming an of importance area of chemistry.[1] Water is one of the most suitable solvents for realizing safe, harmless, environmentally friendly processes for the production of fine chemicals.[1,2] On the other hand, immobilization of homogeneous catalysts has been attracting significant interest, because it could combine the advantages of both homogeneous and heterogeneous catalysts in one system.[3] Provided that a solid-supported catalyst exhibits high catalytic activity in water, the catalysis would represent an almost ideal synthetic process.[4,5] Transition metal complexes, palladium-phosphine complexes in particular, find widespread utilities as catalysts for a variety of synthetic organic reactions.[6] Here we report the catalytic allylic substitution of allyl esters with various nucleophiles in water by use of immobilized palladium complexes of a new amphiphilic resin-supported triarylphosphine **1a** (Scheme 1).[7,8,9]

Scheme 1



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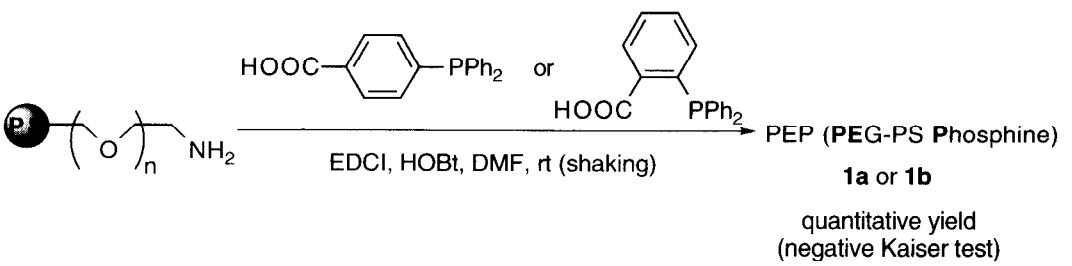
RESULTS AND DISCUSSION

Preparation of Amphiphilic Resin-Supported Phosphine-Palladium Complexes. The most commonly used resin supports for solid-phase organic synthesis include cross-linked polystyrene and poly(ethylene glycol)-polystyrene graft copolymers which are functionalized to allow attachment of linkers and substrate molecules.[3] It is a prominent characteristic of the poly(ethylene glycol)-polystyrene resin (PEG-PS resin) beads that they display relatively uniform swelling in a variety of solvents from medium to high polarity ranging from toluene to water.[10] Accordingly, it was expected that PEG-PS resin bearing a palladium-phosphine complex shows good catalytic activity in palladium-catalyzed transformation in aqueous media. PEG-PS resin having amino group examined as amphiphilic resin to prepare polymer-supported palladium-phosphine complexes (Scheme 2). PEG-PS resin-supported phosphines **1** (PEP)[11] were readily prepared by a standard method of solid-phase amide bond formation.[3] Thus, a mixture of PEG-PS amino resin, 2 equiv (to amino residue) of 4-(diphenylphosphino)benzoic acid,[12] EDCI[13], and HOBt[13] in DMF was agitated with shaking on a wrist-action shaker at ambient temperature for 4 h. A negative Kaiser test[14] indicated that the condensation was completed to form polymer-supported triarylphosphine **1a** quantitatively. According to the same procedures, polymer-supported triarylphosphine **1b** which bound to the solid support by an ortho substituted aromatic linker was prepared from 2-(diphenylphosphino)benzoic acid[15] quantitatively.

Scheme 2



The gel-phase $^{31}P\{^{1}H\}$ NMR spectra[16] of resin-supported phosphine **1a** in chloroform and water performed by use of standard solution-phase spectroscopic parameters and equipments are shown in Figure 1 (I-C and I-W), which also includes those obtained with poly(ethylene glycol)-bound triarylphosphine **2** (II-C and II-W) and polystyrene-bound triarylphosphine **3** (III-C and III-W) for comparison. It is noteworthy that PEG-PS-phosphine **1a** showed relatively narrow singlets at –5.4 and –5.7 ppm in chloroform and water, respectively (Figure 1; I-C and I-W), though phosphine **1a** is insoluble in either solvent. PEG-phosphine **2** which lacks polystyrene moiety gave homogeneous solution of chloroform and water to exhibit decent traces of singlet at –5.2 and –5.0 ppm, respectively (II-C and II-W). PS-phosphine **3** in which phosphine connects to the sites near the rigid polystyrene backbone showed significant broad spectra (III-C and III-W) due to its insolubility in either solvent. The similarity of the ^{31}P NMR of **1a** to that of **2** indicates that the triarylphosphine group of **1a** is in a relatively mobile "solution-like" environment.

Formation of a palladium(PEP)$_2$ complex [Pd(η^3-C_3H_5)(PEP)$_2$]Cl (**4a**) was performed by mixing di(μ-chloro)bis(η^3-allyl)dipalladium(II) ([PdCl(η^3-C_3H_5)]$_2$) and exact 2 molar equivalents to palladium of phosphine **1a** (Pd/P = 1/2) in dichloromethane at ambient temperature for 10 min (Scheme 3). The reaction

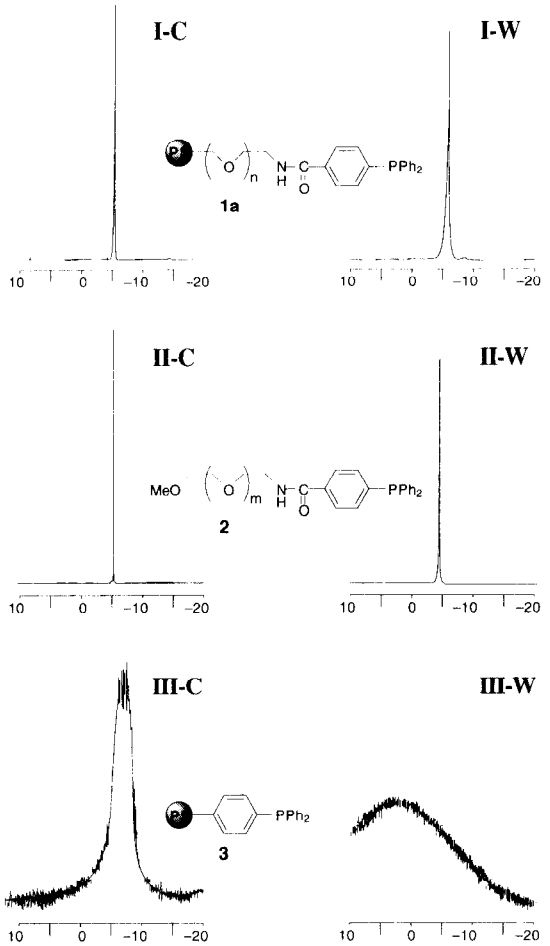
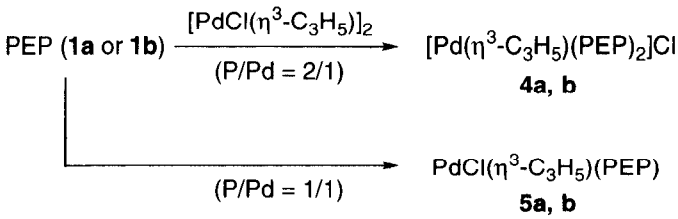


Figure 1. Gel-phase $^{31}P\{^{1}H\}$ NMR of compounds **1a**, **2**, and **3** in chloroform and water. Spectra I–III: phosphines **1**–**3**, respectively. C: In chloroform. W: In water.

progress was conveniently monitored by gel-phase ^{31}P NMR spectroscopy of the resin beads dispersed in a chloroform. After the reaction being completed, a narrow singlet at δ –5.4 ppm observed for starting phosphine **1a** disappeared and was replaced by a new resonance at δ +22.5 ppm. The remarkable low field shift demonstrates that the phosphino group of **1a** coordinates to palladium forming a π-allylpalladium-bis(phosphine) complex on the amphiphilic solid support. According to the same procedures, complex **4b** was prepared from **1b**. It is noteworthy that palladium-monophosphine complexes, Pd-PEP **5**, were readily prepared by treatment of **1** with an excess amount of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ followed by filtration and washing. Thus, a monophosphine complex $PdCl(\eta^3\text{-}C_3H_5)(PEP)$[17] (**5a**) was prepared by treatment of resin-supported phosphines **1a** with an excess amount of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (Pd/P = 1.2/1) followed by removal of unimmobilized $[PdCl(\eta^3\text{-}C_3H_5)]_2$ by washing three times with chloroform to give **5a** as a single product. Upon conversion of PEP **1a** and **1b** to the palladium-phosphine complexes **5a** and **5b**, the phosphorus signals shifted downfield to +23.2 and +23.6 ppm, respectively. The gel-phase $^{13}C\{^{1}H\}$ NMR of **5a** exhibited a singlet signal at 61.4 ppm, and two doublet signals at 80.0 ppm ($^{2}J_{C\text{-}P}$ = 31 Hz) and 118.3 ppm ($^{2}J_{C\text{-}P}$ = 5 Hz), demonstrating that its

Scheme 3

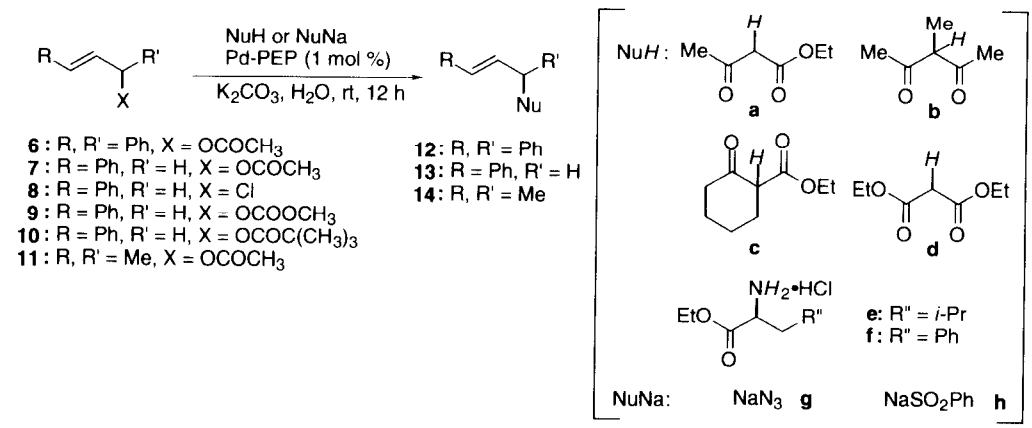


structure is $PdCl(\eta^3\text{-allyl})$(phosphine).[18] In solution-phase preparation, an inexact equimolar of phoshine to palladium forms a mixture of a mono- and bisphosphine complexes, or monophosphine complex and phosphine-free species which sometime causes side catalytic pathway.

Catalytic Allylic Substitution. The palladium-PEP complex **4a** demonstrated its high catalytic activity in the allylic substitution of 1,3-diphenyl-2-acetoxypropene (**6**) in genuine aqueous media under very mild conditions (Scheme 4, Table 1). A mixture of **6** (0.5 mmol), ethyl acetoacetate (1.5 equiv), and potassium carbonate (4.5 equiv) in 1.5 mL of water was shaken on a wrist action shaker in the presence of 1 mol % palladium of resin-supported catalyst **4a** at ambient temperature for 12 h. The reaction mixture was filtered and the resin was rinsed with chloroform. The combined filtrate was concentrated and the residue was chromatographed on silica gel (eluent: hexane/EtOAc = 10/1) to give 4-carboethoxy-1,3-diphenyl-1-hexen-5-one (**12a**) in 98% yield (Table 1, entry 1). It is noteworthy that potassium carbonate is an effective base in water for the present allylic alkylation catalyzed by **4a**. The reaction in THF gave 6% yield of **12a** under the same reaction conditions owing to the insolubility of potassium carbonate (entry 2). Complex **4a** was much less catalytically active in the presence of 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) as a base in H_2O or THF (entries 3 and 4). In general, the palladium-catalyzed alkylation with active methylene or methine compounds requires a stronger base; *e.g.* sodium hydride or tertiary amines. It has been reported[19] that palladium-phosphine complexes catalyze alkylation of allylic acetates with β-ketoesters in the presence of potassium carbonate or DBU as a base in an organic solvent (e.g. THF, dioxane, or toluene) where much higher reaction temperature is required than the temperature in the reaction catalyzed by **4a** in water. The catalytic activity of **4b** was lower than that of **4a** in the present reaction (entries 5 and 6). A monophosphine complex **5a** also showed high catalytic activity as **4a** under the same reaction conditions (entry 7).

Various nucleophiles can be employed for the allylic substitution of allyl acetates catalyzed by **4a** in water. The allylic alkylation of **6** with 3-methyl-2,4-pentanedione, ethyl 2-cyclohexanonecarboxylate, and diethyl malonate took place in water under the same reaction conditions to give **12b**, **12c**, and **12d** in 86%, 100%, and 94% yield, respectively (entries 9-11). Cinnamyl acetate (**7**) and 2-acetoxy-3-pentene (**11**) also underwent the alkylation to give **13** and **14** in high yields (entries 12, 13, and 17). The palladium-catalyzed allylic substitution of cinnamyl chloride (**8**), cinnamyl methyl carbonate (**9**), and cinnamyl trimethylacetate (**10**) with 3-methyl-2,4-pentanedione also proceeded to form **13b** in 72%, 68%, and 71% yield under the same reaction conditions, respectively (entries 14-16).

Scheme 4

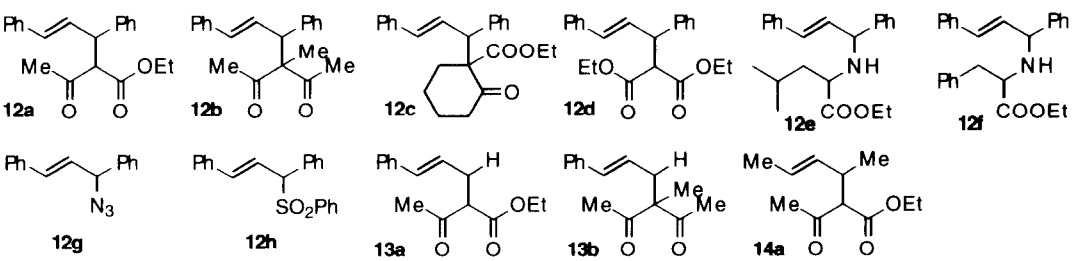


This allylic substitution method was also successfully applied to other nucleophiles which are insoluble or almost insoluble in usual organic solvents. With hydrochloride salts of leucine and phenylalanine ethyl esters, amination of **6** took place at room temperature under the same reaction conditions to give the corresponding *N*-allylation products **12e** and **12f** in 98% and 90% yields, respectively (entries 18 and 19). Sodium phenylsulfinate and sodium azide reacted with **6** to give allyl sulfone **12g** and allyl azide **12h** in high yields (entries 20 and 21).[20]

Table 1. Allylic Substitution in Water Catalyzed by Pd-PEP[a]

entry	allylic compound	catalyst	medium/base	nucleophile	product	yield (%)[b]
1	**6**	**4a**	H_2O/K_2CO_3	CH_3COCH_2COOEt	**12a**	98
2	**6**	**4a**	THF/K_2CO_3	CH_3COCH_2COOEt	**12a**	6
3	**6**	**4a**	H2O/DBU	CH_3COCH_2COOEt	**12a**	28
4	**6**	**4a**	THF/DBU	CH_3COCH_2COOEt	**12a**	17
5	**6**	**4b**	H_2O/K_2CO_3	CH_3COCH_2COOEt	**12a**	<2
6	**6**	**4b**	H_2O/K_2CO_3	CH_3COCH_2COOEt	**12a**	22[c]
7	**6**	**5a**	H_2O/K_2CO_3	CH_3COCH_2COOEt	**12a**	97
8	**6**	**5b**	H_2O/K_2CO_3	CH_3COCH_2COOEt	**12a**	<2
9	**6**	**4a**	H_2O/K_2CO_3	$CH_3CH(COCH_3)_2$	**12b**	86
10	**6**	**4a**	H_2O/K_2CO_3	$(O=)C_6H_9COOEt$	**12c**	100
11	**6**	**4a**	H_2O/K_2CO_3	$CH_2(COOEt)_2$	**12d**	94
12	**7**	**4a**	H_2O/K_2CO_3	CH_3COCH_2COOEt	**13a**	89[d]
13	**7**	**4a**	H_2O/K_2CO_3	$CH_3CH(COCH_3)_2$	**13b**	100[e]
14	**8**	**4a**	H_2O/K_2CO_3	CH_3COCH_2COOEt	**13a**	72
15	**9**	**4a**	H_2O/K_2CO_3	CH_3COCH_2COOEt	**13a**	71
16	**10**	**4a**	H_2O/K_2CO_3	CH_3COCH_2COOEt	**13a**	68
17	**11**	**4a**	H_2O/K_2CO_3	$CH_3CH(COCH_3)_2$	**14a**	88
18	**6**	**4a**	H_2O/K_2CO_3	Leu-OEt•HCl	**12e**	98
19	**6**	**4a**	H_2O/K_2CO_3	Phe-OEt•HCl	**12f**	90
20	**6**	**4a**	H_2O/none	NaN_3	**12g**	89
21	**6**	**4a**	H_2O/none	$NaSO_2Ph$	**12h**	86

[a] The reaction was carried out in H_2O with 1.5 equiv of a nucleophile and 4.5 equiv of potassium carbonate in the presence of 1 mol % palladium of Pd-PEP at room temperature for 12 h unless otherwise noted. **4** or **5** (g)/H_2O (mL) = 1/15. [b] Isolated yield by silica gel column chromatography. [c] Carried out at 85 °C. [d] Including 24% of ethyl 5-phenyl-4-pentenoate. [e] Including 11% of 4-methyl-1-phenyl-1-hexen-5-one.



Several palladium-phosphine complexes were also examined for their catalytic activity in the allylic substitution in water (Table 2). This immobilized Pd-PEP complex (**4**) shows higher catalytic activity in water

than other homogeneous as well as heterogeneous palladium-phosphine complexes, while immobilization of catalysts often causes decrease of catalytic activity in general. Thus, a palladium complex of triphenylphosphine-terminated polyethylene glycol **2** which was generated in situ by mixing **2** and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (P/Pd = 2/1) showed lower catalytic activity in the reaction of **6** with ethyl acetoacetate and sodium sulfinate to give **12a** and **12h** in 81% and 19% yields, respectively (entries 2 and 6). With a water-soluble triarylphosphine ligand, 3,3',3"-phosphinidynetris(benzenesulfonic acid), trisodium salt (TPPTS),[21] the alkylation did not proceed under the same conditions (entries 4 and 8). Palladium complexes of triphenylphosphine and polystyrene-supported triphenylphosphine **3** are unsuitable for use in water owing to their insolubility (entries 3 and 7).

Table 2. Allylic Substitution of **6** with Ethyl Acetoacetate Catalyzed by Palladium-Phosphine Catalysts.[a]

entry	catalyst	nucleophile	solvent	base	product	yield (%)[b]
1	**4a**	CH_3COCH_2COOEt	H_2O	K_2CO_3	**12a**	98
2	Pd/**2**[c]	CH_3COCH_2COOEt	H_2O	K_2CO_3	**12a**	81
3	Pd/**3**[d]	CH_3COCH_2COOEt	H_2O	K_2CO_3	**12a**	<2[e]
4	Pd/TPPTS[c]	CH_3COCH_2COOEt	H_2O	K_2CO_3	**12a**	<2[e]
5	**4a**	$NaSO_2Ph$	H_2O	K_2CO_3	**12h**	86
6	Pd/**2**[c]	$NaSO_2Ph$	H_2O	K_2CO_3	**12h**	19
7	Pd/**3**[d]	CH_3COCH_2COOEt	H_2O	K_2CO_3	**12h**	<2[e]
8	Pd/TPPTS[c]	CH_3COCH_2COOEt	H_2O	K_2CO_3	**12h**	<2[e]

[a] The reaction was carried out in tetrahydrofuran or H_2O with 1.5 equiv of ethyl acetoacetate and 4.5 equiv of base in the presence of 1 mol % of a catalyst at room temperature for 12 h. [b] Isolated yield by silica gel column chromatography. [c] A catalyst generated in situ by mixing di(μ-chloro)bis(η^3-allyl)dipalladium(II) and phosphine (Pd/P = 1/2) was used. [d] A catalyst was prepared according to the method of preparation of **4a**. [e] No reaction. Starting material **6** was recovered quantitatively.

The solid-supported catalysts can be readily recovered and reused by filtration. Thus, after the reaction of ethyl acetoacetate with **6** the reaction mixture was filtered and the catalyst-resin was rinsed twice with THF. High yield of **12a** was obtained from the combined filtrate and the recovered catalyst resin was subjected to the next series of the reaction. The second use of the catalyst gave again **12a** in 99% yield. The recycle of the catalyst was repeated 6 times (1st-7th use) during which no loss of catalytic activity was observed. The chemical yield observed in the 7 continuous runs ranged from 86 to 99%, the average being 95% yield.

In summary, amphiphilic resin-supported phosphine-palladium complexes were prepared from PEG-PS amino resin and diphenylphosphinobenzoic acid by means of solid phase method. The complexes exhibited high catalytic activity in allylic substitution reaction in genuine aqueous media.

EXPERIMENTAL SECTION

General. All manipulations were carried out under nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5 (Merck, SICAPENT). NMR spectra were recorded on a JEOL JNM-EX270 spectrometer (270 MHz for ^1H and 109 MHz for ^{31}P), JEOL JNM-AL400 spectrometer (400 MHz for ^1H), JEOL JNM-LA400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C), or JEOL JNM-LA500 spectrometer (500 MHz for

^{1}H and 202 MHz for ^{31}P). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^{1}H NMR, and to an external 85% H_3PO_4 standard for ^{31}P NMR. Residual chloroform (δ 77.0 for ^{13}C) was used as internal reference for ^{13}C NMR. ^{1}H, ^{13}C, ^{31}P, NMR spectra were recorded in $CDCl_3$ at 25 °C unless otherwise noted. The agitation of the reaction mixture was performed on a wrist-action shaker (Burrel Scientific, Inc.).

Materials. THF was dried over sodium benzophenone ketyl and distilled prior to use. DMF and dichloromethane was dried over calcium hydride and distilled prior to use. TentaGel® S-NH_2 (Rapp Polymere, Germany) or ArgoGel NH_2® (Argonaut Technology, USA) was used as starting resin supports. The resin beads were washed with acetonitrile (6 × 20 mL, 15 min for 1.0 g of resin) and chloroform (5 × 20 mL, 5 min for 1.0 g of resin) prior to use. Triphenylphosphine, polymer supported (**3**), 3,3',3"-phosphinidynetris(benzenesulfonic acid), trisodium salt (TPPTS), ethyl acetoacetate, diethyl malonate, 3-methyl-2,4-pentanedione, ethyl 2-cyclohexanonecarboxylate, sodium phenylsulfinate, and sodium azide were purchased from Aldrich Co. Inc. *O*-(2-Aminoethyl)-*O'*-methylpolyoxyethylene glycol was purchased from Fluka Chemie AG. Cinnamyl acetate (**7**), cinnamyl chloride (**8**), L-leucine ethyl ester hydrochloride, and L-phenylalanine ethyl ester hydrochloride were purchased from Tokyo Chemical Industry Co. Inc. *Ortho*-diphenylphosphinobenzoic acid (**3b**),[15] 1,3-diphenyl-1-acetoxy-2-propene (**6**),[22] cinnamyl methyl carbonate (**9**)[23] cinnamyl trimethylacetate (**10**),[23] and 2-acetoxy-3-pentene (**11**),[23] were prepared according to the reported procedures. Ethyl 2-carboethoxy-3,5-diphenyl-4-pentenoate (**12d**),[23] *N*-(1,3-diphenyl-2-propenyl)leucine ethyl ester (**12e**),[23,24] ethyl 2-acetyl-5-phenyl-4-pentenoate (**13a**),[23] and 3-carboethoxy-4-methyl-5-hepten-2-one (**14a**)[23] are known compounds.

Preparation of 4-(Diphenylphosphino)benzoic acid. To a solution of methyl 4-hydroxybenzoate (7.61 g, 50.0 mmol) and pyridine (5.20 mL, 65.0 mmol) in dichloromethane (200 mL) was added trifluoromethanesulfonic anhydride (10.1 mL, 60.0 mmol) at 0 °C and the mixture was stirred for 6 h. After the reaction mixture was concentrated under reduced pressure, the residue was diluted with 150 mL of EtOAc and the organic layer was washed with 1% HCl, saturated $NaHCO_3$, and brine (once for each). The organic phase was dried over Na_2SO_4, and concentrated under reduced pressure to give 13.3 g (94%) of methyl 4-(trifluoromethanesulfonyloxy)benzoate as a colorless oil: ^{1}H NMR δ 3.94 (s, 3H), 7.36 (d, J = 9.0 Hz, 2H), 8.14 (d, J = 9.0 Hz, 2H): To a mixture of methyl 4-(trifluoromethanesulfonyloxy)benzoate (13.6 g, 47.9 mmol), diphenylphosphine oxide (15.9 g, 78.6 mmol), palladium diacetate (1.08 g, 4.80 mmol), and 1,4-bis(diphenylphosphino)butane (2.05 g, 4.80 mmol) were added 200 mL of dimethyl sulfoxide and diisopropylethylamine (33.4 mL, 192 mmol), and the mixture was heated with stirring at 100 °C for 12 h. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: EtOAc) to give 15.0 g (93%) of methyl 4-(diphenylphosphinyl)benzoate as a white solid: ^{1}H NMR δ 3.93 (s, 3H), 7.40-7.80 (m, 12H), 8.12 (d, J = 8.5 Hz, 2H); ^{31}P{^{1}H} NMR δ 28.9: To a mixture of methyl 4-(diphenylphosphinyl)benzoate (8.41 g, 25.0 mmol) and triethylamine (64.0 mL, 460 mmol) in toluene (500 mL) was added trichlorosilane (12.0 mL, 120 mmol) at 0 °C. The reaction mixture was refluxed for 12 h. After being cooled to room temperature, the mixture was diluted with 300 mL of ether and quenched with a small amount of saturated $NaHCO_3$. The resulting suspension was filtered through Celite, and the filter cake was washed 3 times with ether. The combined filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: hexane/EtOAc = 10/1) to give 5.18 g (65%) of methyl 4-(diphenylphosphino)benzoate as a white solid: ^{1}H NMR

δ 3.89 (s, 3H), 7.24-7.39 (m, 12H), 7.96 (d, J = 8.1 Hz, 2H); $^{31}P\{^{1}H\}$ NMR δ –4.5: To a solution of methyl 4-(diphenylphosphino)benzoate (5.18 g, 16.2 mmol) in 200 mL of methanol was added 40% aqueous potassium hydroxide solution (40.0 mL) at ambient temperature and the reaction mixture was refluxed for 12 h. The solution was acidified (pH = 2) by addition of conc. HCl and then extracted 3 times with EtOAc. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give 4.69 g (95%) of 4-(diphenylphosphino)benzoic acid as a white solid: ^{1}H NMR δ 7.33-7.37 (m, 12H), 8.03 (d, J = 8.0 Hz, 2H); $^{13}C\{^{1}H\}$ NMR δ 128.7, 128.8, 129.1, 129.2, 129.8, 129.9, 133.1, 133.3, 133.9, 134.1, 171.8; $^{31}P\{^{1}H\}$ NMR δ –4.4.

Preparation of Amphiphilic Solid-Supported Phosphine 1a. A Merrifield vessel was charged with TentaGel S-NH_2 (1.00 g, 0.123 mmol/g), 4-(diphenylphosphino)benzoic acid (135 mg, 0.44 mmol), EDCI•HCl (127 mg, 0.66 mmol), HOBt (119 mg, 0.88 mmol), and DMF (20.0 mL), and the reaction mixture was shaken on a wrist-action shaker at 25 °C for 4 h. The reaction mixture was filtered and the resin was washed with DMF (5 × 20 mL) and dichloromethane (8 × 20 mL). The resin was dried under reduced pressure to give 1.04 mg of **1a:** $^{31}P\{^{1}H\}$ (gel-phase) NMR δ –5.4 (s).

Solid-Supported Phosphines 1b. A Merrifield vessel was charged with TentaGel S-NH_2 (1.00 g, 0.123 mmol/g), 2-(diphenylphosphino)benzoic acid (135 mg, 0.44 mmol), EDCI•HCl (127 mg, 0.66 mmol), HOBt (119 mg, 0.88 mmol), and DMF (20.0 mL), and the reaction mixture was shaken on a wrist-action shaker at 25 °C for 4 h. The reaction mixture was filtered and the resin was washed with DMF (5 × 20 mL) and dichloromethane (8 × 20 mL). The resin was dried under reduced pressure to give 1.04 mg of **1b:** $^{31}P\{^{1}H\}$ NMR (gel-phase) δ –8.8 (s).

Preparation of 2. A mixture of *O*-(2-Aminoethyl)-*O'*-methylpolyoxyethylene glycol (≅0.17 mmol NH_2/g, 300 mg), 4-(diphenylphosphino)benzoic acid (24 mg, 0.078 mmol), EDCI•HCl (20 mg, 0.10 mmol), HOBt (17 mg, 0.13 mmol), and DMF (2 mL) was stirred at room temperature for 6h. To a reaction mixture was added ca. 6 mL of dist. Et_2O to give white precipitates. The precipitates were collected by filtration and dried under reduced presure to give 70 mg of 2: $^{31}P\{^{1}H\}$ NMR δ –5.2 (s).

Preparation of Palladium-(PEP)$_2$ Complex 4a. A Merrifield vessel was charged with 1.04 g of resin-supported phosphine **1a** (loading value: 0.118 mmol/g) and 20.0 mL of dichloromethane. To a suspension was added 11.2 mg of di(μ-chloro)bis(η^3-allyl)dipalladium(II) (30.8 μmol) at room temperature and the mixture was shaken on a wrist-action shaker at 25 °C for 10 min. After filtration, the resin was washed with dichloromethane (3 × 20 mL) and dried under reduced pressure to give 1.05 g of **4a:** $^{31}P\{^{1}H\}$ NMR (gel-phase) δ 22.5 (s).

Preparation of Palladium-PEP Complex 4b. A Merrifield vessel was charged with 1.04 g of resin-supported phosphine **1b** (loading value: 0.118 mmol/g) and 20.0 mL of dichloromethane. To a suspension was added 11.2 mg of di(μ-chloro)bis(η^3-allyl)dipalladium(II) (30.8 μmol) at room temperature and the mixture was shaken on a wrist-action shaker at 25 °C for 10 min. After filtration, the resin was washed with dichloromethane (3 × 20 mL) and dried under reduced pressure to give 1.05 g of **1b**: $^{31}P\{^{1}H\}$ NMR (gel-phase) δ 26.1 (s).

Preparation of Palladium-PEP Complex 5a. A Merrifield vessel was charged with 1.04 g of resin-supported phosphine **1a** (loading value: 0.118 mmol/g) and 20.0 mL of dichloromethane. To a suspension was added 22.5 mg of di(μ-chloro)bis(η^3-allyl)dipalladium(II) (61.5 μmol) at room temperature and the mixture was shaken on a wrist-action shaker at 25 °C for 10 min. After filtration, the resin was washed with dichloromethane

(3 × 20 mL) and dried under reduced pressure to give 1.06 g of **5a:** $^{13}C\{^1H\}$ NMR (gel-phase) δ 39.9, 61.4, 69.7, 70.6, 80.0 (d, J = 30.5 Hz), 118.3 (d J = 5.0 Hz), 127.2, 127.3, 128.8 (d, J = 9.9 Hz), 130.8, 131.6, 132.0, 134.0 (d, J = 11.5 Hz), 136.5, 166.7; $^{31}P\{^1H\}$ NMR (gel-phase) δ 23.2 (s).

Preparation of Palladium-PEP Complex 5b. A Merrifield vessel was charged with 1.04 g of resin-supported phosphine **1b** (loading value: 0.118 mmol/g) and 20.0 mL of dichloromethane. To a suspension was added 22.5 mg of di(μ-chloro)bis(η^3-allyl)dipalladium(II) (61.5 μmol) at room temperature and the mixture was shaken on a wrist-action shaker at 25 °C for 10 min. After filtration, the resin was washed with dichloromethane (3 × 20 mL) and dried under reduced pressure to give 1.06 g of **5b**: $^{31}P\{^1H\}$ NMR (gel-phase) δ 23.6 (s).

Allylic Alkylation with Solid-Supported Palladium-Phosphine Catalyst. A typical procedure is given for the reaction of 3-acetoxy-1,3-diphenyl-1-propene (**6**) and ethyl acetoacetate (Table 1, entry 1). A Merrifield vessel was charged with potassium carbonate (311 mg, 2.30 mmol), **4a** (100 mg, 5.0 μmol Pd) and 1.50 mL of water. To the mixture was added ethyl acetoacetate (98 mg, 0.75 mmol) and **6** (126 mg, 0.50 mmol) at ambient temperature and the reaction mixture was shaken on a wrist-action shaker at 25 °C for 12 h. The reaction mixture was filtered and the resin was extracted with chloroform (4 × 6 mL). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: hexane/EtOAc = 10/1) to give 158 mg (98%) of 4-carboethoxy-1,3-diphenyl-1-hexen-5-one (**12a**) as a 1:1 mixture of diastereoisomers: ^1H NMR δ 0.98 (t, J = 7.3 Hz, 1/2H × 3), 1.21 (t, J = 7.3 Hz, 1/2H × 3), 2.04 (s, 1/2H × 3), 2.30 (s, 1/2H × 3), 3.94 (q, J = 7.3 Hz, 1/2H × 2), 4.08 (d, J = 11.2 Hz 1/2H), 4.11 (d, J = 11.2 Hz 1/2H), 4.17 (q, J = 7.3 Hz, 1/2H × 2), 4.29 (dd, J = 7.9, 11.2 Hz, 1H), 6.24 (dd, J = 7.9, 15.8 Hz, 1/2H), 6.29 (dd, J = 7.9, 15.8 Hz, 1/2H), 6.43 (d, J = 15.8 Hz, 1/2H), 6.46 (d, J = 15.8 Hz, 1/2H), 7.17-7.43 (m, 10H); $^{13}C\{^1H\}$ NMR δ 13.8, 14.2, 29.8, 30.0, 48.7, 49.0, 61.4, 61.6, 65.3, 65.6, 126.3, 126.4, 127.1, 127.2, 127.5, 127.6, 127.97, 128.02, 128.5, 128.7, 128.9, 129.3, 129.5, 131.5, 131.8, 136.7, 136.9, 140.2, 140.4, 167.6, 167.9, 201.4, 201.7; Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.22; H, 6.88. Found: C, 78.04; H, 6.78.

4-Acetyl-4-methyl-1,3-diphenyl-1-hexen-5-one (12b): ^1H NMR δ 1.49 (s, 3H), 1.93 (s, 3H), 2.16 (s, 3H), 4.69 (d, J = 8.1 Hz, 1H), 6.39 (dd, J = 8.1, 15.6 Hz 1H), 6.46 (d, J = 15.6 Hz, 1H), 7.17-7.32 (m, 10H); $^{13}C\{^1H\}$ NMR δ 15.9, 27.5, 27.9, 51.6, 71.6, 126.4, 127.1, 127.6, 127.9, 128.4, 128.5, 129.6, 133.2, 136.9, 139.8, 205.7, 206.5; Anal. Calcd for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.29; H, 7.32.

2-Carboethoxy-2-(1,3-diphenyl-2-propenyl)-cyclohexan-1-one (12c): As a 1:1 mixture of diastereoisomers. ^1H NMR δ 1.06 (t, J = 7.3 Hz, 1/2H × 3), 1.07 (t, J = 7.3 Hz, 1/2H × 3), 1.48-1.76 (m, 4H), 1.89-1.99 (m, 1H), 2.40-2.47 (m, 1/2H × 5), 2.58-2.62 (m, 1/2H × 1), 3.88-4.05 (m, 2H), 4.09 (d, J = 9.5 Hz, 1/2H × 1), 4.24 (d, J = 8.8 Hz, 1/2H × 1), 6.39 (d, J = 15.8 Hz, 1/2H × 1), 6.39 (d, J = 15.8 Hz, 1/2H × 1), 6.69 (dd, J = 8.8, 15.8 Hz, 1/2H × 1), 6.71 (dd, J = 9.5, 15.8 Hz, 1/2H × 1), 7.16-7.43 (m, 10H); $^{13}C\{^1H\}$ NMR δ 22.7, 26.7, 27.1, 33.7, 35.2, 41.9, 42.0, 53.1, 53.8, 61.3, 65.8, 66.0, 126.3, 126.4, 126.8, 126.9, 127.2, 127.3, 128.0, 128.1, 128.41, 128.43, 129.1, 129.4, 129.9, 130.2, 132.3, 137.3, 137.4, 139.8, 140.0, 170.78, 170.80, 206.4, 206.7; Anal. Calcd for $C_{24}H_{26}O_3$: C, 79.52; H, 7.23. Found: C, 79.28; H, 7.20.

***N*-(1,3-Diphenyl-2-propenyl)phenylalanine Ethyl Ester (12f):** As a 1.2:1 mixture of diastereoisomers. ^1H NMR δ 1.12 (t, J = 7.3 Hz, 1.2/2.2H × 3), 1.16 (t, J = 7.3 Hz, 1/2.2H × 3), 2.91-2.97 (m, 2H), 3.40 (t, J = 7.3 Hz, 1.2/2.2H × 1), 3.68 (t, J = 7.3 Hz, 1/2.2H × 1), 4.01-4.12 (m, 2H), 4.31 (t, J = 7.6 Hz, 1H), 6.09 (dd, J = 7.6, 15.9 Hz, 1/2.2H × 1), 6.21 (dd, J = 7.6, 15.9 Hz, 1.2/2.2H × 1), 6.46 (t, J =

14.9 Hz, 1H), 7.14-7.38 (m, 15H); $^{13}C\{^1H\}$ NMR δ 14.2, 40.1, 40.2, 60.2, 60.5, 60.6, 60.6, 63.7, 64.0, 126.4, 126.5, 126.6, 126.6, 127.3, 127.4, 127.4, 127.4, 127.5, 128.2, 128.3, 128.4, 128.5, 128.6, 129.4, 129.5, 130.3, 130.8, 131.5, 132.5, 136.82, 136.9, 137.5, 137.6, 142.0, 142.9, 174.8, 175.0; Anal. Calcd for $C_{26}H_{29}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 81.05; H, 7.09; N, 3.66.

1-Phenyl-4-acetyl-4-methyl-1-hexen-5-one (13b): ^1H NMR δ 1.38 (s, 3H), 2.14 (s, 6H), 2.75 (dd, *J* = 1.2, 7.6 Hz, 2H), 5.97 (dt, *J* = 7.6, 15.6 Hz, 1H), 6.44 (dt, *J* = 1.2, 15.6 Hz, 1H), 7.19-7.36 (m, 5H); $^{13}C\{^1H\}$ NMR δ 18.3, 26.7, 38.1, 66.8, 124.0, 126.2, 127.5, 128.5, 134.0, 136.9, 206.7; Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.22; H, 7.88.

1,3-Diphenyl-3-phenylsulfonyl-1-propene (12h): A Merrifield vessel was charged with sodium phenylsulfinate (123 mg, 0.75 mmol), **4a** (100 mg, 5.0 μmol Pd), and 1.50 mL of water. To the mixture was added **6** (126 mg, 0.50 mmol) at ambient temperature and the reaction mixture was shaken on a wrist-action shaker at 25 °C for 12 h. The reaction mixture was filtered and the resin was extracted with chloroform (4 × 6 mL). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: hexane/EtOAc = 10/1) to give 144 mg (86%) of 1,3-diphenyl-3-phenylsulfonyl-1-propene (**12h**): ^1H NMR δ 4.84 (d, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.58 (dd, *J* = 8.3, 15.9 Hz 1H), 7.23-7.68 (m, 15H); $^{13}C\{^1H\}$ NMR δ 75.4, 120.0, 126.8, 128.5, 128.6, 128.7, 128.7, 128.9, 129.3, 129.7, 132.3, 133.6, 135.9, 137.4, 138.2; Anal. Calcd for $C_{21}H_{18}O_2S$: C, 75.42; H, 5.43. Found: C, 75.47; H, 5.47.

1-Azido-1,3-diphenyl-2-propene (12g): ^1H NMR δ 5.20 (d, *J* = 7.3 Hz, 1H), 6.28 (dd, *J* = 7.3, 15.6 Hz, 1H), 6.71 (d, *J* = 15.6 Hz, 1H), 7.23-7.41 (m, 10H); $^{13}C\{^1H\}$ NMR δ 67.2, 126.8, 126.9, 127.1, 128.2, 128.3, 128.7, 128.8, 133.0, 135.9, 138.6; Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.78; H, 5.71; N, 17.56.

Allylic Alkylation of 10 with Ethyl Acetoacetate Catalyzed by Palladium-TPPTS Complex. To a mixture of **6** (126 mg, 0.50 mmol), di(μ-chloro)bis(η^3-allyl)dipalladium(II) (910 μg, 2.50 μmol), TPPTS (5.68 mg, 10.00 μmol), and 1,8-diazabicyclo[5.4.0]-7-undecene (190 mg, 1.25 mmol) in 1.50 mL of THF was added ethyl acetoacetate (98 mg, 0.75 mmol), and the mixture was stirred at 25 °C for 12 h. The alkylation product was not detected on TLC analysis.

Recycle Experiment of 4a: A Merrifield vessel was charged with **4a** (331 mg, 38.5 μmol Pd). To the vessel were added 1.50 M of aqueous potassium carbonate solution (5.0 mL), **6** (624 mg, 2.47 mmol), and ethyl acetoacetate (215 mg, 1.65 mmol) and the mixture was shaken on a wrist-action shaker at 25 °C for 12 h. The reaction mixture was filtered and the resin was extracted with THF (2 × 5 mL). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: hexane/EtOAc = 10/1) to give **12a**. The residual beads were dried under reduced pressure for 30 min and reused for the next reaction.

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