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New Amphiphilic Palladium-Phosphine Complexes Bound to Solid Supports: Preparation and Use for Catalytic Allylic Substitution in Aqueous Media

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Abstract: New amphiphilic palladium-phosphine complexes were designed and prepared on polyethylene glycol-polystyrene graft copolymer (PEG-PS) resin. The solid-supported palladium complexes showed high catalytic activity in allylic substitution reactions of allyl acetates with various nucleophiles in aqueous media.
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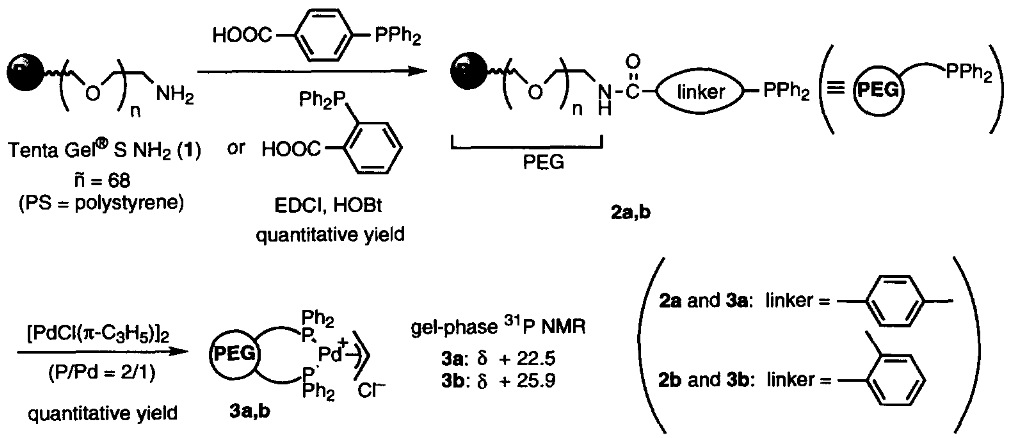
Palladium-phosphine complexes find widespread utilities as catalysts for a variety of organic transformations.[1] In contrast to the vast amount of research on the palladium-catalyzed reactions in organic solvents, only scattered attention has been paid to those in aqueous media.[2,3] Recent development of solid phase synthetic chemistry intrigued us to prepare palladium-phosphine complexes bound to amphiphilic solid supports[4] which are expected to exhibit catalytic activity in water. We report here preparation of palladium-phosphine complexes bound to amphiphilic polymer resin, and their application as catalysts for allylic substitution reactions of allyl acetates in aqueous media.

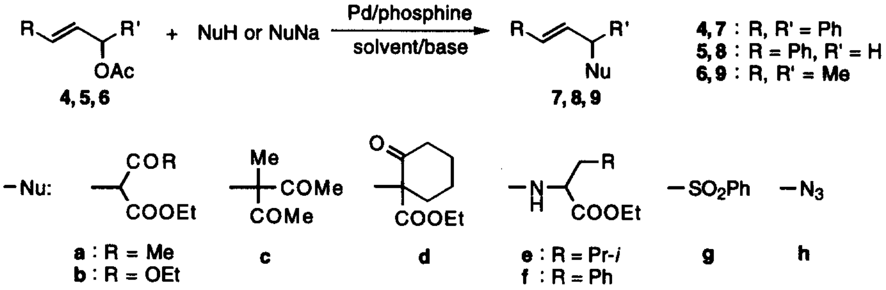
It has been well-documented that polymer resin based on a polyethylene glycol-polystyrene graft copolymer (PEG-PS) exhibits good swelling properties in water as well as in organic solvents.[5] PEG-PS resin having amino group of 0.22 mmol/g of loading value (Tenta Gel S NH_2) (**1**)[5,6] was examined as amphiphilic resin to prepare polymer-supported palladium-phosphine complexes (Scheme 1). A mixture of PEG-PS amino resin (1.0 g), 2 equiv of 4-(diphenylphosphino)benzoic acid, EDCI[7] (3 equiv), and HOBt[7] (4 equiv) in DMF was agitated with shaking on a wrist-action shaker at ambient temperature for 4 h. The resin was washed 5

Scheme 1



times with DMF (20 mL) and 8 times with dichloromethane (30 mL), and then dried under reduced pressure. A negative Kaiser test indicated that the condensation was completed to form polymer-supported triarylphosphine **2a** quantitatively. Formation of a palladium-phosphine complex on the resin was performed by mixing $[PdCl(\pi\text{-}C_3H_5)]_2$ and **2a** (Pd/P = 1/2) in dichloromethane at ambient temperature for 10 min. The reaction progress was conveniently monitored by gel phase ^{31}P NMR spectroscopy of the resin beads dispersed in a mixture of chloroform and benzene.[8] After the reaction being completed, a narrow singlet at δ –5.7 ppm observed for starting phosphine **2a** disappeared and was replaced by a new resonance at δ +22.5 ppm. The remarkable low field shift demonstrates that the phosphino group of **2a** coordinates to palladium forming a π-allylpalladium-bis(phosphine) complex on the amphiphilic solid support. The resulting resin was washed 6 times with dichloromethane to give a solid-supported palladium-phosphine complex **3a**. According to the same procedures, complex **3b**[9] which bound to the solid support by an ortho substituted aromatic linker was prepared from 2-(diphenylphosphino)benzoic acid quantitatively. Complexes **3a** and **3b** showed good swelling properties in water as well as in dichloromethane or THF.

Scheme 2



The palladium-phosphine complexes bound to amphiphilic solid supports prepared above demonstrated their high catalytic activity in water in the allylic substitution of allyl acetates with various nucleophiles (Scheme 2). The representative results are summarized in Table 1. It was found that the solid-supported palladium-phosphine complexes **3** catalyze allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**4**) with some active methylene compounds in aqueous media under very mild alkaline conditions. Thus, a mixture of **4** (0.5 mmol), ethyl acetoacetate (1.5 equiv), and potassium carbonate (4.5 equiv) in 1.5 mL of water was shaken in the presence of 2 mol % of the solid-supported complex **3a** (100 mg, 0.01 mmol Pd) at ambient temperature for 12 h. The reaction mixture was filtered and the resin was rinsed with THF and chloroform. The combined filtrate was concentrated and the residue was chromatographed on silica gel (eluent: hexane/EtOAc = 10/1) to give 98% yield of 4-carboethoxy-1,3-diphenyl-1-hexen-5-one (**7a**) (Table 1, entry 1). The catalytic activity of **3b** was lower than that of **3a** in the present reaction (entry 2). The allylic alkylation with diethyl malonate, 3-methyl-2,4-pentanedione, and ethyl 2-cyclohexanonecarboxylate took place in water under the same reaction conditions to give **7b**, **7c**, and **7d** in 94%, 86%, and 95% yield, respectively (entries 3-5). Cinnamyl acetate (**5**) and 2-acetoxy-3-pentene (**6**) also underwent the alkylation to give **8** and **9** in high yields (entries 6-8). It is noteworthy that potassium carbonate is an effective base in water for the present allylic alkylation catalyzed by the amphiphilic solid-supported palladium complexes **3**. In general, the palladium-catalyzed alkylation with active methylene or methine compounds requires a stronger base; e.g. sodium hydride or tertiary amines.[1] The

Table 1. Allylic Substitution of **4** with Solid-Supported Palladium-Phosphine Catalyst **3**[a]

entry	allyl acetate	catalyst	NuH (or NuNa)	solvent/base	product	yield (%)[b]
1	**4**	**3a**	CH_3COCH_2COOEt	H_2O/K_2CO_3	**7a**	98
2[c]	**4**	**3b**	CH_3COCH_2COOEt	H_2O/K_2CO_3	**7a**	22
3	**4**	**3a**	$CH_2(COOEt)_2$	H_2O/K_2CO_3	**7b**	94
4	**4**	**3a**	$CH_3CH(COCH_3)_2$	H_2O/K_2CO_3	**7c**	86
5	**4**	**3a**	$(O{=})C_6H_9COOEt$	H_2O/K_2CO_3	**7d**	95
6	**5**	**3a**	CH_3COCH_2COOEt	H_2O/K_2CO_3	**8a**[d]	89
7	**5**	**3a**	$CH_3CH(COCH_3)_2$	H_2O/K_2CO_3	**8c**[d]	100
8	**6**	**3a**	CH_3COCH_2COOEt	H_2O/K_2CO_3	**9a**	88
9	**4**	**3a**	CH_3COCH_2COOEt	THF/K_2CO_3	**7a**	6
10	**4**	**3a**	CH_3COCH_2COOEt	THF/DBU	**7a**	17
11	**4**	Pd-TPPTS[e]	CH_3COCH_2COOEt	H_2O/K_2CO_3	**7a**	–[f]
12	**4**	**3a**	Leu-OEt•HCl	H_2O/K_2CO_3[g]	**7e**	98
13	**4**	**3a**	Phe-OEt•HCl	H_2O/K_2CO_3[g]	**7f**	90
14	**4**	**3a**	$NaSO_2Ph$	H_2O/none	**7g**	86
15	**4**	**3a**	NaN_3	H_2O/none	**7h**	79

[a] The reaction was carried out in H_2O with 1.5 equiv of a nucleophile and 4.5 equiv of base in the presence of 2 mol % of a catalyst at room temperature for 12 h. **3** (g)/H_2O (mL) = 1/15.

[b] Isolated yield by silica gel column chromatography.

[c] Carried out at 85 °C. At room temperature, the yield of **7a** was 2%.

[d] The alkylation product, ethyl 2-acetyl-5-phenyl-4-pentenoate (**8a**) (entry 6) or 1-phenyl-4-acetyl-4-methyl-1-hexen-5-one (**8c**) (entry 7) was obtained as a single regioisomer (*cf.* ref 1 and 3e).

[e] A catalyst generated in situ by mixing $[PdCl(\pi\text{-}C_3H_5)]_2$ and TPPTS (Pd/P = 1/2) was used.

[f] No reaction. Starting material **4** was recovered quantitatively.

[g] Six equiv of K_2CO_3 was used.

catalytic activity of complex **3a** was lower in THF in the presence of K_2CO_3 or DBU than in water (entries 9 and 10).[10,11] With a water soluble phosphine ligand, TPPTS,[12] the alkylation did not proceed under the same conditions (entry 11).

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 **4** took place at room temperature under the same reaction conditions to give the corresponding *N*-allylation products **7e** and **7f** in 98% and 90% yields, respectively (entries 12 and 13). Sodium phenylsulfinate and sodium azide reacted with **4** to give allyl sulfone **7g** and allyl azide **7h** in high yields (entries 14 and 15).[13,14]

The solid-supported catalysts can be readily recovered and reused by filtration. Thus, after the reaction of acetoacetate with **4**, the reaction mixture was filtered and the catalyst-resin **3a** was rinsed twice with THF. High yield of **7a** was obtained from the combined filtrate and the recovered **3a** was subjected to the next series of the reaction. The second use of the catalyst gave again **7a** in 99% yield. The recycle of the catalyst was repeated 6 times (1st – 7th use)[15] 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.

The preliminary results presented here open the way for design and preparation of transition metal catalysts which can find utility in aqueous media as well as for preparation of libraries of metal-phosphine complexes.

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