π-Allylic Azidation in Water with an Amphiphilic Resin-Supported Palladium–Phosphine Complex

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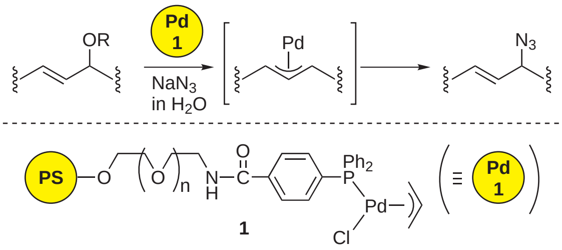
Received 20 June 2006

Abstract: π-Allylic azidation of allyl esters was performed with an amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported phosphine–palladium complex in water under heterogeneous conditions to give allyl azides in good to high yields. The polymeric palladium catalyst can be readily recovered and recycled.

Key words: π-allylpalladium, azide, aqueous media, polymer support, palladium catalyst

Organic azides have found widespread utility as synthetic precursors of various nitrogen functional groups.[1] With the advent of 'click chemistry',[2] the chemistry of alkyl azides has seen an increase in interest over the past few years. The most commonly applied method of preparing alkyl azides is nucleophilic substitution of labile functional groups (e.g. halides, pseudo-halides) by sodium azide. Palladium-catalyzed substitution of allyl esters via π-allylpalladium intermediates, the so-called Tsuji–Trost reaction, is a powerful synthetic means for forming carbon–carbon as well as carbon–nitrogen bonds. While extensive research has been devoted to the π-allylic alkylation and amination, research on π-allylic azidation has been limited to isolated reports.[3] Thus, for example, Murahashi and co-workers have examined the π-allylic azidation of allyl acetates with sodium azide in the presence of $Pd(PPh_3)_4$ to give the corresponding allyl azides where the reactions were carried out in THF–H_2O (5:2) because of the insolubility of sodium azide in organic solvents. If π-allylic azidation took place with sodium azide in water with recyclable palladium catalysts, where neither aqueous–organic solvent wastes nor metal-contaminated wastes were produced, this would go a long way to meeting green chemical requirements.

We have recently developed amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported palladium catalysts which promote various catalytic transformations, including π-allylic substitutions, smoothly in water[4] under heterogeneous conditions[5,6] with high recyclability.[7,8] Our continuing interest in the catalytic utility of PS-PEG resin-supported palladium complexes led us to examine the π-allylic azidation in water with the PS-PEG–Pd complexes.[9] We report herein our results demonstrating that the allylic azidation of various allyl esters with sodium azide proceeds in water in the presence of a palladium complex of an amphiphilic PS-PEG resin-bound triarylphosphine ligand (Scheme 1, Figure 1).



Scheme 1 π-Allylic azidation.

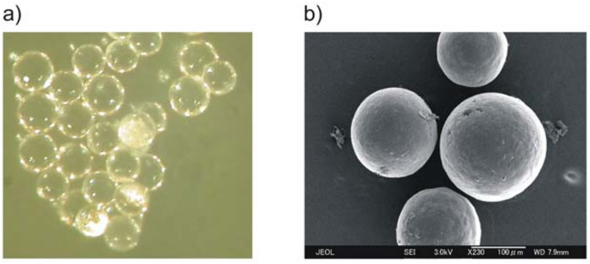


Figure 1 Microscopic images of **1**: (a) optical microscope; (b) scanning-electron microscope (SEM).

Reaction of methyl cinnamyl carbonate (**2a**) with sodium azide was found to take place smoothly in water at 25 °C in the presence of 1 mol% palladium of the PS-PEG (TentaGel) resin-supported π-allylpalladium–triarylphosphine complex (**1**, Figure 1, 1% DVB cross-linked, diameter 130 µm, Pd loading = 0.27 mmol/g). After completion of the reaction in 24 hours (GC monitoring), the reaction mixture was filtered and the recovered resin beads were extracted with ethyl acetate to give 96% yield of cinnamyl azide (**3a**) (Table 1, run 1). To demonstrate the extent of substrate tolerance in this reaction system, various allylic carbonates or acetates were used for the π-allylic azidation in water using the same procedure as employed for run 1. Representative results are summarized in Table 1.

The benzyl carbonate **2b**, the allylic isomer of cinnamyl carbonate **2a**, gave cinnamyl azide (**3a**), exclusively, under similar conditions (run 2), and the benzylic azide **3b** was not detected on GC. The azidation of benzyl esters

SYNLETT 2006, No. 13, pp 2109–2113
Advanced online publication: 09.08.2006
DOI: 10.1055/s-2006-948189; Art ID: D17306ST
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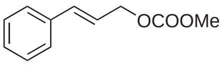
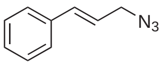
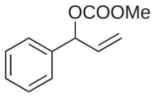
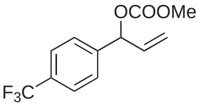
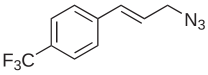
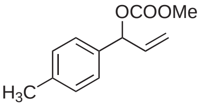
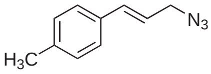
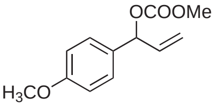
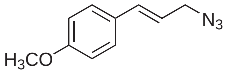
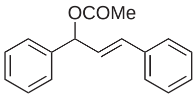
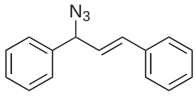
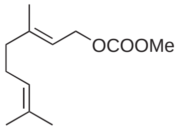
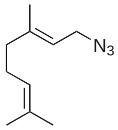
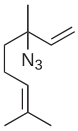
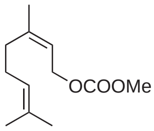
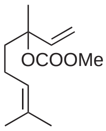
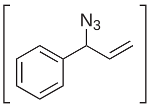
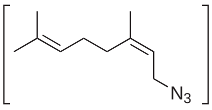
Table 1 π-Allylic Azidation of Allyl Carbonates **2** in H_2O[a]

Run	Allyl ester **2**	Product **3**	Yield (%)
1	 **2a**	 **3a**	96
2	 **2b**	**3a**	88
3	 **2c**	 **3c**	92
4	 **2d**	 **3d**	92
5	 **2e**	 **3e**	95
6	 **2f**	 **3f**	89
7	 **2g**	 **3g**  **3i** (92:8)	81
8	 **2h**	**3g**/**3i** (91:9)	90
9	 **2i**	**3g**/**3i** (90:10)	95

[a] All reactions were carried out in water at 25 °C for 24 h. The ratio of **2** (mol)/NaN_3 (mol)/Pd (mol)/H_2O (L) = 1:1.5:0.01:3.



3b



3h

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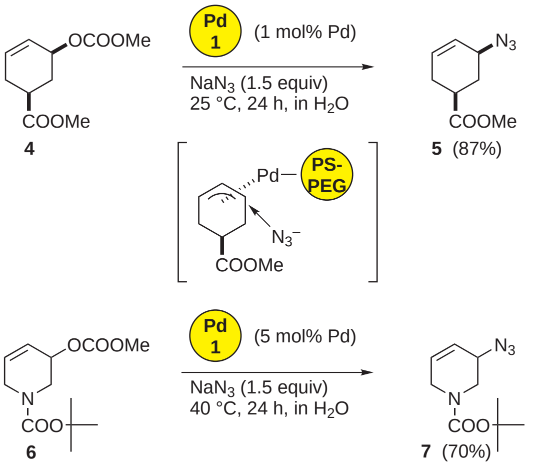
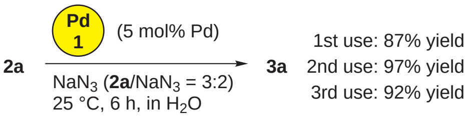
2c–**e** bearing electron-donating and -withdrawing substituents at their *para*-positions gave the cinnamyl azides **3c**, **3d**, and **3e** in 92%, 92%, and 95% yield, respectively (runs 3, 4, and 5). The diphenylpropenyl ester **2f** also underwent the azidation to give **3f** in 89% yield (run 6). Geranyl, neryl, and linalyl carbonates **2g**, **2h**, and **2i** reacted with sodium azide under similar conditions to give 81%, 90%, and 95% yields of a mixture of regioisomeric azidation products **3g** and **3i** (runs 7, 8, and 9). The ratios of geranyl azide **3g** and linalyl azide **3i** obtained from the reactions of **2g**, **2h**, and **2i** were almost the same (**3g**/**3i** = 9:1) and neryl azide **3h** was not observed at all. These results demonstrate that the reactions of **2g**–**i** proceeded by way of the same π-allylpalladium intermediate.

The azidation of *cis*-5-carbomethoxy-2-cyclohexenyl methyl carbonate (**4**) was also catalyzed by the PS-PEG–palladium **1** in water at 25 °C to afford the *cis*-5-carbomethoxy-2-cyclohexenyl azide (**5**) in 87% yield (Scheme 2). The exclusive formation of the cycloalkenyl azide **5** having the *cis*-configuration from the *cis*-allylic ester **4** revealed that this π-allylic azidation proceeds via a double-inversion pathway (π-allylpalladium formation and nucleophilic attack with an azide anion) in water under these conditions. The tetrahydropyridyl carbonate **6** reacted with sodium azide under similar reaction conditions to afford the tetrahydropyridyl azide **7** in 70% yield.

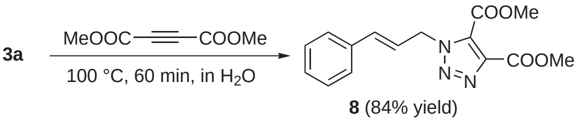


Scheme 2 Preparation of cycloalkenyl azides.

Recycling experiments were examined for azidation of the cinnamyl carbonate (**2a**). After the first use of the polymeric palladium catalyst **1** (Table 1, run 1) to give 87% yield of cinnamyl azide (**3a**), the recovered catalyst beads were taken on to two reuses and exhibited stable catalytic activity (Scheme 3).



Scheme 3 Recycling experiments.



Scheme 4 [3+2] Triazole cycloaddition in H_2O.

The synthetic utility of the allyl azides is demonstrated by the [3+2] triazole synthesis, which has recently attracted significant interest owing to its utility in ‘Click Chemistry’. Preliminary results are shown in Scheme 4. Thus, the [3+2] triazole cycloaddition of cinnamyl azide (**3a**) with dimethyl acetylenedicarboxylate took place smoothly in emulsive aqueous conditions at 100 °C for 60 minutes to give 84% isolated yield of the *N*-cinnamyl triazole (**8**).

In summary, we have developed a practical protocol for azidation of allylic esters with sodium azide using a PS-PEG resin-supported palladium catalyst to give allylic azides including cycloalkenyl derivatives. The π-allylic azidation and the [3+2] triazole cycloaddition were carried out in water without any organic solvents to meet green chemical requirements.

Experimental: Palladium-Catalyzed Allylic Azidation (Table 1)

A typical procedure is given for the reaction of cinnamyl carbonate **2a** (run 1). To a mixture of catalyst **1** (18.5 mg, 0.005 mmol) and cinnamyl carbonate (**2a**, 96.0 mg, 0.5 mmol) in H_2O (3.0 mL) was added NaN_3 (48.7 mg, 0.75 mmol) at 25 °C. The mixture was shaken 25 °C for 24 h and filtered. The recovered resin beads were extracted with EtOAc and methyl *tert*-butyl ether (MTBE). The combined extracts were washed with aq NaCl and dried over anhyd $MgSO_4$. The solvent was evaporated and the residue was chromatographed on silica gel (hexane–EtOAc, 10:1) to give 76.3 mg (96% yield) of cinnamyl azide (**3a**).

Spectral and Analytical Data

Cinnamyl Azide (3a)

CAS registry number: 76024-91-4. ^1H NMR ($CDCl_3$): δ = 7.39 (d, J = 7.3 Hz, 2 H), 7.32 (t, J = 7.3 Hz, 2 H), 7.26 (t, J = 7.3 Hz, 1H), 6.63 (d, J = 15.8 Hz 1 H), 6.23 (td, J = 6.7, 15.8 Hz, 1 H), 3.92 (d, J = 6.7 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 135.9, 134.4, 128.6, 128.1, 126.5, 122.3, 52.9.

3-(*o*-Trifluoromethylphenyl)allyl Azide (3c)

CAS registry number: 164363-74-0. ^1H NMR ($CDCl_3$): δ = 7.58 (d, J = 7.9 Hz, 2 H), 7.48 (d, J = 7.9 Hz, 2 H), 6.67 (d, J = 15.8 Hz, 1 H), 6.32 (td, J = 6.1, 15.8 Hz, 1 H), 3.98 (d, J = 6.1 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 139.4, 132.3, 129.9 (q, J = 33.0 Hz), 126.7, 125.6 (q, J = 4.1 Hz), 125.2, 124.0 (q, J = 270 Hz), 52.6. MS (EI): *m/z* (%) = 227 (2) [M^+], 198 (64), 172 (bp), 151 (44). IR (ATR): ν = 2099, 1321 cm^{-1}. Anal. Calcd for $C_{10}H_9N_3F_3$: C, 52.87; H, 3.55; N, 18.50. Found: C, 52.72; H, 3.56; N, 18.38.

3-(*o*-Tolyl)allyl Azide (3d)

^1H NMR ($CDCl_3$): δ = 7.29 (d, J = 8.0 Hz, 2 H), 7.14 (d, J = 8.0 Hz, 2 H), 6.61 (d, J = 15.8 Hz, 1 H), 6.18 (td, J = 6.7, 15.2 Hz, 1 H), 3.92 (d, J = 6.1 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 138.1, 134.5, 133.2, 129.3, 126.5, 121.2, 53.1, 21.2.

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3-(*o*-Methoxyphenyl)allyl Azide (3e)
CAS registry number: 164363-75-1. ^{1}H NMR ($CDCl_3$): δ = 7.29 (d, *J* = 8.0 Hz, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 6.61 (d, *J* = 15.8 Hz, 1 H), 6.18 (td, *J* = 6.7, 15.2 Hz, 1 H), 3.92 (d, *J* = 6.1 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 138.1, 134.5, 133.2, 129.3, 126.5, 121.2, 53.1, 21.2.

1,3-Diphenyl-2-propenyl Azide (3f)
CAS registry number: 120990-01-4. ^{1}H NMR ($CDCl_3$): δ = 7.41–7.23 (m, 10 H), 6.71 (d, *J* = 15.6 Hz, 1 H), 6.28 (dd, *J* = 15.6, 7.3 Hz, 1 H), 5.20 (d, *J* = 7.3 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ = 138.6, 135.9, 133.0, 128.8, 128.7, 128.3, 128.2, 127.1, 126.9, 126.8, 67.2.

Geranyl Azide (3g)
CAS registry number: 84457-88-5. ^{1}H NMR ($CDCl_3$): δ = 5.34–5.31 (m, 1 H), 5.09–5.08 (m, 1 H), 3.76 (t, *J* = 7.9 Hz, 2 H), 2.13–2.10 (m, 4 H), 1.70 (br s, 3 H), 1.68 (s, 3 H), 1.61 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ = 123.5, 123.4, 117.9, 117.0, 48.0, 39.5, 32.7, 26.6, 26.3, 25.6.

Linaryl Azide (3i)
CAS registry number: 128318-87-6. ^{1}H NMR ($CDCl_3$): δ = 5.78 (dd, *J* = 17.9, 10.9 Hz, 1 H), 5.23 (d, *J* = 17.9 Hz, 1 H), 5.20 (d, *J* = 10.9 Hz, 1 H), 5.09–5.08 (m, 1 H), 2.07 (m, 4 H), 1.79–1.35 (m, 9 H).

***cis*-3-Methoxycarbonyl-2-cyclohexenyl Azide (5)**
CAS registry number: 120990-27-4. ^{1}H NMR ($CDCl_3$): δ = 5.93–5.91 (m, 1 H), 5.67 (d, *J* = 10.3 Hz, 1 H), 3.99 (br s, 1 H), 3.72 (s, 3 H), 2.67 (dddd, *J* = 12.2, 9.7, 6.4, 2.4 Hz, 1 H), 2.42–2.24 (m, 3 H), 1.72 (ddd, *J* = 12.2, 12.2, 10.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ = 174.4, 129.5, 125.8, 56.9, 51.9, 38.1, 30.7, 27.1.

***tert*-Butyl 3-Azido-3,6-dihydropyridine-1(2*H*)-carboxylate (7)**
CAS N/A. ^{1}H NMR ($CDCl_3$, 60 °C): δ = 6.02 (br d, *J* = 9.7 Hz, 1 H), 5.86–5.84 (m, 1 H), 4.08 (br d, *J* = 18.5 Hz, 1 H), 3.80–3.73 (m, 3 H), 3.54–3.51 (m, 1 H), 1.48 (s, 9 H). ^{13}C NMR ($CDCl_3$, –60 °C, mixture of rotamers): δ = 154.6, 154,2, 130.7, 130.0, 121.7, 121.4, 80.4, 80.3, 53.1, 53.0, 45.8, 44.2, 43.2, 42.2, 28.1, 28.1. MS (EI): *m/z* (%) = 196 (0.8) [M$^+$ – Me_2], 140 (7), 94 (80), 41 (bp). IR (ATR): ν = 2976, 2931, 2359, 2341, 2094, 1695 cm$^{–1}$. Anal. Calcd for $C_{10}H_{16}N_4O_2$: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.35; H, 7.16; N, 24.65.

Compound 8 ([3+2] Addition of Cinnamyl azide (3a) with Dimethyl Acetylenecarboxylate; Scheme 4)
To a mixture of cinnamyl azide (**3a**, 63.6 mg, 0.4 mmol) in H_2O (3 mL) was added dimethyl acetylenecarboxylate (71.1 mg, 0.5 mmol) and the mixture was stirred at 100 °C for 1 h. The reaction mixture was extracted with MTBA and the extract was dried over $MgSO_4$, filtered and concentrated to afford a yellow residue. Purification by silica gel chromatography (hexane–EtOAc, 1:1) gave 105 mg (84% yield) of 1-cinnamyl-4,5-dimethoxycarbonyltriazole (**8**). ^{1}H NMR ($CDCl_3$): δ = 7.36–7.27 (m, 5 H), 6.65 (d, *J* = 15.8 Hz, 1 H), 6.29 (td, *J* = 6.1, 15.8 Hz, 2 H), 5.38 (d, *J* = 6.1 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ = 160.3, 158.8, 139.8, 135.8, 135.2, 129.7, 128.5, 128.4, 126.5, 120.9, 53.2, 52.5, 52.3. MS (EI): *m/z* (%) = 301 (1.7) [M$^+$], 183 (32), 115 (bp), 91 (44). IR (ATR): ν = 2360, 2341, 1729, 1219 cm$^{–1}$. FAB-HRMS: *m/e* calcd for $C_{15}H_{15}N_3O_4$: 302.1062; found: 302.1144 [M$^+$ +1].

Acknowledgment

This work was supported by the CREST program, sponsored by the JST. We also thank the JSPS (GRANT-in-AID for Scientific Research, No.15205015) and the MEXT (Scientific Research on Priority Areas, No. 420) for partial financial support of this work.

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(9) One preliminary example (Table 1, run 6) has been reported in ref. 7c.

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