Tetrahedron 66 (2010) 1064–1069

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Copper-Free Sonogashira coupling in water with an amphiphilic resin-supported palladium complex

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ARTICLE INFO

Article history:
Received 26 June 2009
Accepted 16 October 2009
Available online 6 November 2009

ABSTRACT

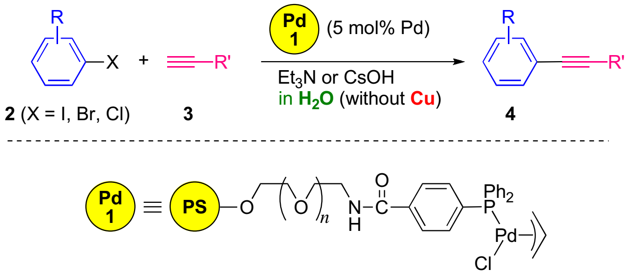
The palladium-catalyzed coupling reaction of aryl halides with terminal alkynes, the Sonogashira coupling, took place in water under copper-free conditions by use of an amphiphilic polystyrene-poly(ethylene glycol) (PS–PEG) resin-supported palladium–phosphine complex to give the corresponding aryl-substituted alkynes in high yields. The PS–PEG resin-supported palladium catalyst was recovered by simple filtration and reused four times without any loss of catalytic activity.

1. Introduction

The palladium-catalyzed coupling of an aryl halide with a terminal alkyne, the Sonogashira coupling,[1] is recognized as the most successful method for forming an sp-sp^2 carbon–carbon bond. Since its discovery by Sonogashira and co-workers in 1975, considerable research has been devoted to the synthetic application of the reaction as well as to improving its efficiency.[2] One of the major problems associated with it lies in the reaction conditions where the use of both a palladium catalyst and a copper reagent (co-catalyst) is frequently required to promote the reaction, resulting in contamination of the coupling products with metal residue. In addition, it has been well-documented that the Sonogashira coupling often suffers from the Glaser-type oxidative dimerization of the alkyne substrate[3] as a side reaction in the presence of a Cu(I) co-catalyst. Recently, quite a few reports addressing these problems have appeared, in which the coupling is carried out with an immobilized palladium catalyst and/or under copper-free conditions.[4,5]

However, given the increasing concern about green and safe chemical processes, it is not surprising that the development of water-based organic transformations has become a burgeoning area of research.[6,7] If the Sonogashira coupling were performed in water with an immobilized catalyst under copper-free conditions,[8] the reaction system would represent a clean, green, and safe application of the coupling in what may be considered an ideal chemical process.

We have recently developed amphiphilic polystyrene-poly(ethylene glycol) (PS–PEG)[9] resin-supported transition metal catalysts, which promote various catalytic transformations,[10] including the palladium-catalyzed π-allylic substitution, cross-coupling reaction, and the Heck reaction, smoothly in water under heterogeneous conditions.[11] Our continuing interest in the catalytic utility of PS–PEG resin-supported palladium complexes led us to examine the Sonogashira coupling in water with the PS–PEG–Pd complex under copper-free conditions.[12] We report herein our results demonstrating that the Sonogashira coupling of various aryl halides with terminal acetylenes proceeds in water in the presence of a palladium complex of an amphiphilic PS–PEG resin-bound triarylphosphine ligand under copper-free conditions (Scheme 1).



Scheme 1. Sonogashira coupling in water.

2. Results and discussion

2.1. Coupling conditions

Upon screening reaction conditions for the copper-free Sonogashira coupling in water with the polymeric palladium **1**, we

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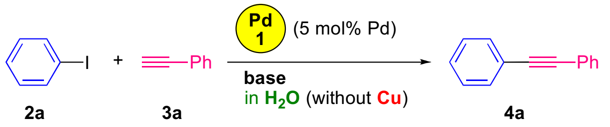
doi:10.1016/j.tet.2009.11.011

found that the reaction efficiency was greatly enhanced by the base employed. Thus, the coupling of iodobenzene (**2a**) and phenylacetylene (**3a**) was carried out in water with the polymeric catalyst **1** (5 mol % to Pd) at 40 °C for 6 h in the presence of 3 equiv of base. The reaction mixture was filtered and the recovered resin beads were rinsed with a small portion of water and extracted with EtOAc to give diphenylacetylene (**4a**). The most effective base proved to be triethylamine as seen in the representative results summarized in Table 1. The coupling with sodium bicarbonate, sodium carbonate, potassium carbonate, and cesium carbonate gave **4a** in <2%, 12%, 12%, and 7% yield, respectively (entries 1–4). The coupling reaction in aqueous potassium hydroxide afforded **4a** in 26% yield (entry 5). Of inorganic bases examined, cesium hydroxide was identified to be an effective base to promote the Sonogashira coupling, which improved the coupling performance to afford diphenylacetylene (**4a**) in 58% yield under otherwise the identical conditions (entry 6). Organic amines were found to promote the Sonogashira coupling smoothly in water. Thus, the reaction with 1.8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave a 63% yield of **4a** under similar conditions (entry 7). When triethylamine was used, the chemical yield of **4a** increased significantly, resulting in the quantitative formation of the coupling product **4a** (entry 8).

2.2. Substrate tolerance

The heterogeneous aquacatalytic copper-free Sonogashira coupling was examined with a variety of haloarenes under the reaction conditions identified above and exhibited wide substrate tolerance. Representative results are summarized in Table 2. The coupling of iodobenzene (**2a**) with phenylacetylene took place smoothly in water at 40 °C in the presence of 3 equiv of Et_3N and 5 mol % palladium of the PS–PEG resin-supported π-allylpalladium-triaryl-phosphine complex **1** to give a quantitative yield of diphenylacetylene (**4a**) (Table 2, entry 1). The Sonogashira coupling of *p*-methoxyiodobenzene (**2b**) and *p*-methyliodobenzene (**2c**) bearing electron donating groups at their *para*-positions gave the corresponding biarylacetylenes **4b** and **4c** in 62% and 92% yield, respectively (Table 2, entries 2 and 3). *p*-(Trifluoromethyl)iodobenzene (**2d**), *p*-acetoxyiodobenzene (**2e**), and *p*-(methoxy-carbonyl)iodobenzene (**2f**) having electron deficient aromatic rings also underwent the Sonogashira coupling with phenylacetylene under similar conditions to afford the corresponding biarylacetylenes **4d**, **4e**, and **4f** in 100%,81%, and 85% yield, respectively (Table 2, entries 4, 5, and 6). The coupling of *meta*- and *ortho*-substituted iodobenzenes **2g–j** having *meta*-methyl, *meta*-chloro, *ortho*-methyl, and *ortho*-chloro groups, took place with phenylacetylene to give the corresponding products **4g–j** in 90%, 91%, 83%, and 87% yield, respectively (entries 7–10). Coupling of 1-iodonaphthalene (**2k**) and **3a** under the aqueous copper-free conditions gave naphthylphenylacetylene **4k** in 73% yield (entry 11). The coupling reactions of the bromoarenes **2n–q** with **3a** were carried out at a higher reaction temperature (refluxing water) to give the corresponding biarylacetylenes in 69–87% isolated yield (entries 13–15), although the electron-rich bromoarene **2m** showed lower reactivity under similar conditions. It should be noted that the coupling reactions of the chloroarenes **2r** and **2s** also took place in water under similar copper-free conditions (entries 16 and 17), though the reactivity was much lower than their iodo and bromo counterparts, **2e**, **2f**, and **2p**.

Table 1
Effect of Base on the Sonogashira coupling of Iodobenzene with Phenylacetylene using Polymeric Catalyst **1** in water[a]



Entry	Bases	Yield of **4a**
1	Na_2CO_3	<2%
2	Na_2CO_3	12%
3	K_2CO_3	12%
4	Cs_2CO_3	7%
5[b]	KOH	26%
6[b]	CsOH	58%
7	DBU	63%
8	Et_3N	99%

[a] All reactions were carried out with iodobenzene (**2a**, 0.4 mmol), phenylacetylene (**3a**, 0.8 mmol), base (1.2 mmol) in the presence of PS–PEG resin-supported palladium–phosphine complex **1** (5 mol % Pd) in 3.0 mL of H_2O at 40 °C for 6 h under nitrogen, unless otherwise noted.

[b] Reaction for 12 h.

Cesium hydroxide was found to promote the Sonogashira coupling of terminal acetylenes bearing aliphatic carboxylic acid groups more efficiently than triethylamine, though the optimal base-substrate combination is not well-rationalized. Thus, the coupling of iodobenzene (**2a**) with 6-heptynoic acid (**3b**) with the polymeric catalyst **1** in water was complete within 6 h at 60 °C by using CsOH to give an 83% isolated yield of 6-phenyl-6-heptynoic acid (**4m**), while the coupling product **4m** was obtained in 35% yield with triethylamine (entry 18 vs entry 19). The reactivity of alkyne carboxylic acids decreased as their hydrophobicity decreased. Thus, pentynoic acid (**3c**) and propiolic acid (**3d**) reacted with **2a** under similar conditions to give **4n** and **4p** in 68% and 58% yield, respectively (entries 20 and 21).

2.3. Recycling experiments

The recyclability of the PS–PEG resin-supported Pd catalyst **1** was examined for the Sonogashira coupling of iodobenzene (**2a**) and phenylacetylene (**3a**). Thus, after the first reaction, which gave a quantitative yield of the coupling product **4a** (Table 2, entry 1), the catalyst beads were recovered and successively subjected to a second through a fifth run of the coupling under the same conditions to afford **4a** in 92%, 81%, 92%, and 87% yield, respectively, (Scheme 2) during which hardly any palladium residue could be detected by ICP-AES analysis from the aqueous or organic filtrates.

3. Conclusion

In conclusion, we have developed a clean, green, and safe protocol for the Sonogashira coupling of aryl iodides and bromides with terminal acetylenes using a PS–PEG resin-supported palladium catalyst to give various biarylacetylene derivatives. This catalyst was recovered and reused four times without any loss of catalytic activity.

4. Experimental section

4.1. General methods

All manipulations were carried out under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5. Water was deionized with a Millipore system as Milli-Q grade. NMR spectra were recorded on a JEOL JNM-LA 500 spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 25 °C. Chemical shifts were reported in ppm referenced to an internal tetramethylsilane standard for ^1H NMR. Chemical shifts

Table 2
Sonogashira coupling of aryl halides and 1-alkynes with triethylamine and polymeric catalyst **1** in water[a]

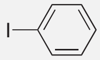
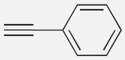
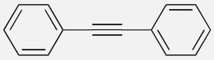
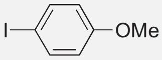
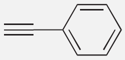
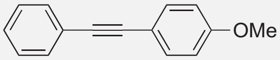
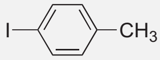
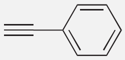
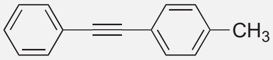
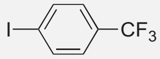
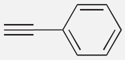
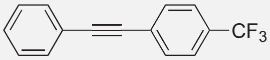
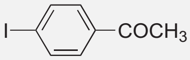
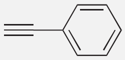
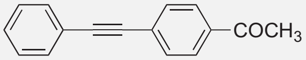
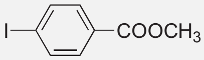
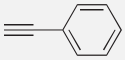
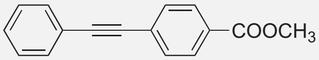
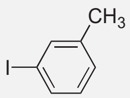
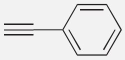
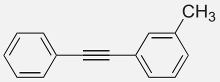
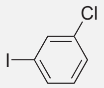
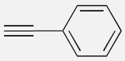
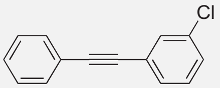
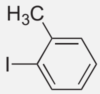
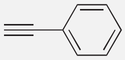
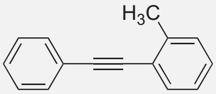
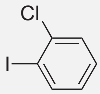
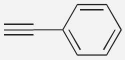
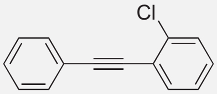
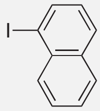
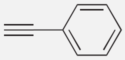
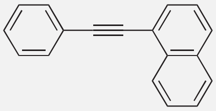
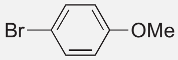
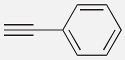
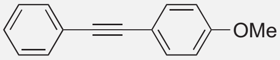
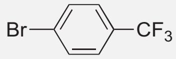
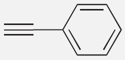
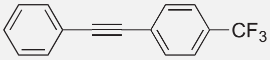
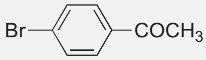
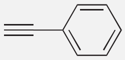
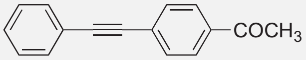
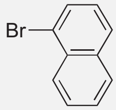
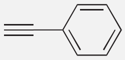
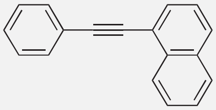
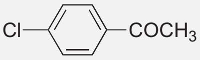
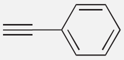
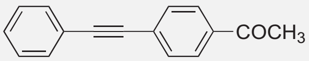
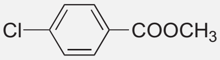
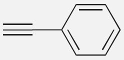
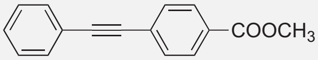
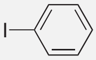
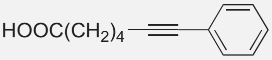
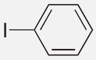
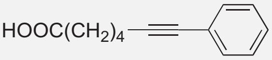
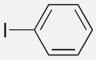
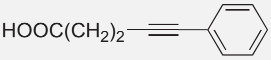
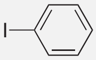
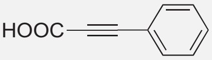
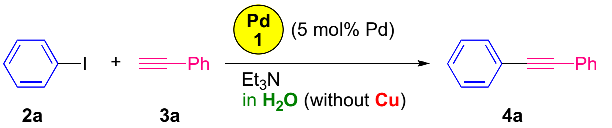
Entry	Aryl halide (**2**)	1-alkyne (**3**)	Temp (°C)	Time (h)	Product (**4**)	Yield (%)
1	 **2a**	 **3a**	40	6	 **4a**	99
2	 **2b**	 **3a**	40	6	 **4b**	62
3	 **2c**	 **3a**	40	6	 **4c**	99
4	 **2d**	 **3a**	40	6	 **4d**	99
5	 **2e**	 **3a**	40	6	 **4e**	81
6	 **2f**	 **3a**	40	6	 **4f**	85
7	 **2g**	 **3a**	40	6	 **4g**	90
8	 **2h**	 **3a**	40	6	 **4h**	91
9	 **2i**	 **3a**	40	6	 **4i**	83
10	 **2j**	 **3a**	40	6	 **4j**	87
11	 **2k**	 **3a**	40	6	 **4k**	73
12	 **2m**	 **3a**	100	24	 **4b**	25
13	 **2n**	 **3a**	100	24	 **4d**	87
14	 **2p**	 **3a**	100	24	 **4e**	81
15	 **2q**	 **3a**	100	24	 **4k**	69

Table 2 (*continued*)

Entry	Aryl halide (**2**)	1-alkyne (**3**)	Temp (°C)	Time (h)	Product (**4**)	Yield (%)
16	 **2r**	 **3a**	100	24	 **4e**	22
17	 **2s**	 **3a**	100	24	 **4f**	13
18[b]	 **2a**	$\equiv$—$(CH_2)_4COOH$ **3b**	60	12	 **4m**	83
19	 **2a**	$\equiv$—$(CH_2)_4COOH$ **3b**	60	12	 **4m**	35
20[b]	 **2a**	$\equiv$—$(CH_2)_2COOH$ **3c**	60	12	 **4n**	68
21[b]	 **2a**	$\equiv$—COOH **3d**	60	12	 **4p**	58

[a] All reactions were carried out with Ar-X (**2**; 0.4 mmol), acetylene (**3**; 0.8 mmol), and triethylamine (1.2 mmol) in the presence of the polystyrene-poly(ethylene glycol)-supported palladium-phosphine complex **1** in 3.0 mL of H_2O at 40–100 °C for 6–24 h under nitrogen.

[b] CsOH was used instead of Et_3N.



1st use 99% (Table 2, entry 1)
2nd use 92%; 3rd use 81%;
4th use 92%; 5th use 87%

Scheme 2. Recycling experiments.

of ^{13}C NMR were given relative to $CDCl_3$ as an internal standard (δ 77.0 ppm). Mass spectral data were measured on an Agilent 6890 GC/5973 N MS detector (GC–MS); the abbreviation 'bp' is used to denote the base peak. IR analysis was performed on a JASCO FTIR-460.

4.2. Materials

PS–PEG-supported catalyst **1** was prepared from PS–PEG amino-resin (Tenta Gel S NH_2, average diameter 90 μm, 1% divinylbenzene cross-linked, average graft length=68 units, loading value of amino residue 0.31 mmol/g; purchased from RAPP POLYMERE) according to the reported procedure.[10b]

4.3. Palladium-catalyzed Sonogashira coupling with phenylacetylene; typical procedure

To a mixture of the polymeric catalyst **1** (64 mg, 0.020 mmol) and iodobenzene (**2a**; 81.6 mg, 0.40 mmol) in H_2O (3.0 mL) was added phenylacetylene (**3a**; 81.7 mg, 0.80 mmol) and triethylamine (121 mg, 1.20 mmol). The reaction mixture was shaken at 40 °C for 6 h and filtered. The recovered resin beads were rinsed with H_2O and extracted three times with EtOAc (6 mL). The EtOAc layer was separated and the aqueous layer was extracted with EtOAc (5 mL). The combined EtOAc extracts were washed with brine (2 mL), dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (hexane-EtOAc, 100:1) to give 95.0 mg (quantitative yield) of diphenylacetylene **4a**.

4.4. Spectral and analytical data for the arylacetylenes 4

*4.4.1. Diphenylacetylene (**4a**).* ^1H NMR ($CDCl_3$) δ 7.55–7.51 (m, 4H), 7.36–7.29 (m, 6H): ^{13}C NMR ($CDCl_3$) δ 131.5, 128.3, 128.2, 123.2, 89.4. MS (EI): m/z (rel%) 178 (bp, M^+), 152 (24). IR (ATR): (cm^{-1}) ν 3062, 1598, 1491. CAS registry number: 64666-02-0.

*4.4.2. 1-(p-Methoxylphenyl)-2-phenylacetylene (**4b**).* ^1H NMR ($CDCl_3$) δ 7.55–7.46 (m, 4H), 7.35–7.29 (m, 3H), 6.88 (d, J=8.1 Hz, 2H), 3.83 (s, 3H): ^{13}C NMR ($CDCl_3$) δ 159.6, 133.0, 131.4, 128.3, 127.9, 123.5, 115.3, 113.9, 89.3, 88.0, 55.3. MS (EI): m/z (rel%) 208 (bp, M^+), 165 (76), 139 (27). IR (ATR): (cm^{-1}) ν 3010, 2214, 1604, 1592, 1508, 1458, 1246. CAS registry number: 7380-78-1.

*4.4.3. 1-Phenyl-2-(p-tolyl)acetylene (**4c**).* ^1H NMR ($CDCl_3$) δ 7.52 (dd, J=8.1, 1.9 Hz, 2H), 7.43 (d, J=8.1 Hz, 2H), 7.38–7.30 (m, 3H), 7.15 (d, J=7.8, 2H), 2.36 (s, 3H): ^{13}C NMR ($CDCl_3$) δ 138.3, 134.8, 131.5, 131.4, 129.1, 128.3, 128.0, 127.7, 120.1, 89.5, 21.5. MS (EI): m/z (rel%) 192 (bp, M^+), 165 (27), 39 (21). IR (ATR): (cm^{-1}) ν 3052, 3029, 2215, 1594, 1509, 1441, 1380. CAS registry number: 185817-85-0.

*4.4.4. 1-Phenyl-2-(p-trifluoromethylphenyl)acetylene (**4d**).* ^1H NMR ($CDCl_3$) δ 7.62 (dd, J=14.1, 8.2 Hz, 4H), 7.56–7.54 (m, 2H), 7.37 (m, 3H): ^{13}C NMR ($CDCl_3$) δ 132.5, 131.8, 131.7, 129.8 (q, J=33.1 Hz, 1C), 128.8, 128.4, 126.4 (q, J=272 Hz, 1C), 125.2 (q, J=272 Hz, 1C), 122.5, 91.7, 87.9. MS (EI): m/z (rel%) 246 (73, M^+), 176 (43), 98 (bp), 75 (49), 51 (46). IR (ATR): (cm^{-1}) ν 3080, 2219, 1508. CAS registry number: 370-99-0.

*4.4.5. 1-(p-Acetoxyphenyl)-2-phenylacetylene (**4e**).* ^1H NMR ($CDCl_3$) δ 7.94 (d, J=8.3 Hz, 2H), 7.61 (d, J=8.3 Hz, 2H), 7.57–7.52 (m, 2H), 7.45–7.36 (m, 3H), 2.62 (s, 3H): ^{13}C NMR ($CDCl_3$) δ 197.0, 136.1, 131.7, 131.6, 128.8, 128.4, 128.2, 128.2, 122.6, 92.7, 88.5, 26.3. MS (EI): *m*/*z* (rel%) 220 (76, M$^+$), 205 (92), 176 (bp), 151, (35). IR (ATR): (cm^{-1}) ν 2915, 1716, 1603, 1507, 1456. CAS registry number: 1942-31-0.

*4.4.6. 1-(p-Methoxycarbonylphenyl)-2-phenylacetylene (**4f**).* ^{1}H NMR (CDCl$_3$) δ 8.02 (d, J=8.5 Hz, 2H), 7.59 (d, J=8.5 Hz, 2H), 7.57–7.53 (m, 2H), 7.38–7.36 (m, 3H), 3.93 (s, 3H): ^{13}C NMR (CDCl$_3$) δ 166.5, 131.7, 131.4, 129.5, 129.4, 128.7, 128.4, 127.9, 122.6, 92.4, 88.6, 52.9. MS (EI): *m*/*z* (rel%) 236 (80, M$^+$), 205 (bp), 176 (91), 151 (34). IR (ATR): (cm^{-1}) ν 2949, 2217, 1718, 1606, 1508, 1455, 1374, 1280. CAS registry number: 42497-80-3.

*4.4.7. 1-Phenyl-2-(m-tolyl)acetylene (**4g**).* ^{1}H NMR (CDCl$_3$) δ 7.51 (d, J=5.8 Hz, 2H), 7.35–7.28 (m, 5H), 7.21 (t, J=7.5 Hz, 1H), 7.12 (d, J=7.5 Hz, 1H), 2.33 (s, 3H): ^{13}C NMR (CDCl$_3$) δ 137.9, 132.1, 131.5, 129.3, 128.6, 128.2, 128.2, 128.1, 123.3, 122.9, 89.5, 89.0, 21.1. MS (EI): *m*/*z* (rel%) 192 (bp M$^+$), 165 (13), 115 (5). IR (ATR): (cm^{-1}) ν 3003, 2919, 1492. CAS registry number: 14635-91-7.

*4.4.8. 1-(m-Chlorophenyl)-2-phenylacetylene (**4h**).* ^{1}H NMR (CDCl$_3$) δ 7.46–7.43 (m, 3H), 7.34–7.32 (m, 1H), 7.29–7.27 (m, 3H), 7.23–7.16 (m, 2H): ^{13}C NMR (CDCl$_3$) δ 134.1, 131.6, 131.4, 129.6, 129.5, 128.5, 128.4, 128.3, 124.9, 122.7, 90.5, 87.8. MS (EI): *m*/*z* (rel%) 212 (bp, M$^+$), 176 (46), 151 (13). IR (ATR): (cm^{-1}) ν 3055, 1490. CAS registry number: 51624-34-1.

*4.4.9. 1-Phenyl-2-(o-tolyl)acetylene (**4i**).* ^{1}H NMR (CDCl$_3$) δ 7.44–7.39 (m, 3H), 7.25–7.21 (m, 3H), 7.12–7.10 (m, 2H), 7.08–7.04 (m, 1H), 2.41 (s, 3H): ^{13}C NMR (CDCl$_3$) δ 166.5, 131.7, 131.4, 129.5, 129.4, 128.7, 128.4, 127.9, 122.6, 92.4, 88.6, 52.9. MS (EI): *m*/*z* (rel%) 192 (bp, M$^+$), 165 (27), 115 (11). IR (ATR): (cm^{-1}) ν 3055, 2919, 1600, 1492. CAS registry number: 14309-60-5.

*4.4.10. 1-(o-Chlorophenyl)-2-phenylacetylene (**4j**).* ^{1}H NMR (CDCl$_3$) δ 7.57–7.55 (m, 3H), 7.53–7.50 (m, 1H), 7.34–7.32 (m, 3H), 7.22–7.18 (m, 2H): ^{13}C NMR (CDCl$_3$) δ 135.9, 133.2, 131.7, 129.2, 128.6, 128.3, 126.4, 123.1, 122.8, 94.5, 86.2. MS (EI): *m*/*z* (rel%) 212 (bp, M$^+$), 176 (38), 151 (11). IR (ATR): (cm^{-1}) ν 3057, 1491, 1468. CAS registry number: 10271-57-5.

*4.4.11. 1-(1-Naphthyl)-2-phenylacetylene (**4k**).* ^{1}H NMR (CDCl$_3$) δ 8.44 (d, J=8.3 Hz, 1H), 7.83 (ddd, J=13.2, 13.2, 4.9 Hz, 2H), 7.75 (d, J=7.1 Hz, 1H), 7.64 (d, J=7.3 Hz, 2H), 7.58 (t, J=7.3 Hz, 1H), 7.52 (t, J=7.3 Hz, 1H), 7.44 (t, J=7.6 Hz, 1H), 7.39–7.34 (m, 3H): ^{13}C NMR (CDCl$_3$) δ 133.1, 131.7, 131.6, 130.3, 128.7, 128.4, 128.3, 128.2, 128.2, 126.7, 126.4, 126.1, 125.2, 125.2, 94.3, 87.5. MS (EI): *m*/*z* (rel%) 228 (bp, M$^+$), 202 (6), 113 (13). IR (ATR): (cm^{-1}) ν 3055, 1488, 1396. CAS registry number: 4044-57-9.

*4.4.12. 7-Phenyl-6-heptynoic acid (**4m**).* ^{1}H NMR (CDCl$_3$) δ 11.1 (br s, 1H), 7.39–7.38 (m, 2H), 7.28–7.26 (m, 3H), 2.46–2.41 (m, 4H), 1.85–1.79 (m, 2H), 1.73–1.65 (m, 2H): ^{13}C NMR (CDCl$_3$) δ 179.8, 131.5, 128.2, 127.6, 123.8, 89.4, 81.0, 33.5, 28.0, 23.8, 19.1. MS (EI): *m*/*z* (rel%) 202 (9, M$^+$), 142 (6), 129 (77), 115 (bp). IR (KBr s): (cm^{-1}) ν 3298, 3041, 1709. CAS registry number: 49769-28-0.

*4.4.13. 5-Phenyl-4-pentynoic acid (**4n**).* ^{1}H NMR (CDCl$_3$) δ 11.2 (br s, 1H), 7.40–7.38 (m, 2H), 7.28–7.26 (m, 3H), 2.74–2.70 (m, 4H): ^{13}C NMR (CDCl$_3$) δ 178.0, 131.6, 128.2, 127.9, 123.3, 87.5, 81.3, 33.4, 15.0. MS (EI): *m*/*z* (rel%) 174 (43, M$^+$), 146 (bp), 128 (81), 115 (93). IR (KBr): (cm^{-1}) ν 3278, 3021, 1703. CAS registry number: 3350-92-3.

*4.4.14. 3-Phenyl-2-propiolic acid (**4p**).* ^{1}H NMR (CDCl$_3$) δ 11.1 (br s, 1H), 7.62 (d, J=7.0 Hz, 2H), 7.48 (t, J=7.0 Hz, 1H), 7.40 (t, J=7.0 Hz, 2H): ^{13}C NMR (CDCl$_3$) δ 182.8, 133.2, 131.0, 128.6, 119.1, 88.8, 79.9. MS (EI): *m*/*z* (rel%) 146 (9, bp), 128 (72), 115 (63), 115 (72). IR (KBr): (cm^{-1}) ν 3288, 3003, 1706. CAS registry number: 637-44-5.

Acknowledgements

This work was supported by the Young Scientists Program of University of the Ryukyus and the Joint Study Program of the Institute for Molecular Science. We also thank the MEXT (Scientific Research on Priority Areas #460) for partial financial support of this work.

References and notes

1. Sonogashira, K.; Tohda, Y. *Tetrahedron Lett.* **1975**, 4467; Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46.
2. For reviews, see: (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874; (b) Sonogashira, K. In *Metal-Catalyzed Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, NY, 1998.
3. (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422; (b) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.
4. For reviews on heterogeneous-switching, see: (a) Bailey, D. C.; Langer, S. H. *Chem. Rev.* **1981**, *81*, 109; (b) Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217; (c) Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis* **2000**, 1035; (d) Dörwald, F. Z. *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, 2000; (e) Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217; (f) McNamara, C. A.; Dixon, M. J.; Bradley, M. *Chem. Rev.* **2002**, *102*, 3275; (g) *Chiral Catalyst Immobilization and Recycling*; De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A., Eds.; Wiley-VCH: Weinheim, 2000; (h) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815; (i) Fan, Q.-H.; Li, Y.-M.; Chan, A. S. C. *Chem. Rev.* **2002**, *102*, 3385; (j) Uozumi, Y. *Top. Curr. Chem.* **2004**, *242*, 77; (k) Guino, M.; Hii, K. K. M. *Chem. Soc. Rev.* **2007**, *36*, 608.
5. For recent studies on the copper-free Sonogashira coupling under heterogeneous conditions, see: (a) Lu, N.; Chen, Y.-C.; Chen, T.-L.; Wu, S.-J. *J. Organomet. Chem.* **2009**, *694*, 278 (fluorous biphasic system); (b) Komáromi, A.; Novák, Z. *Chem. Commun.* **2008**, 4968 (palladium on charcoal); (c) Komura, K.; Nakamura, H.; Sugi, Y. *J. Mol. Cat. A* **2008**, *293*, 72 (palladium supported on MCM-41); (d) De Lima, P. G.; Antunes, O. A. C. *Tetrahedron Lett.* **2008**, *49*, 2506; (e) Kim, J.-H.; Lee, D.-H.; Jun, B.-H.; Lee, Y.-S. *Tetrahedron Lett.* **2007**, *48*, 7079 (polymer-support); (f) Cwik, A.; Hell, Z.; Figueras, F. *Tetrahedron Lett.* **2006**, *47*, 3023; (g) Tyrrell, E.; Al-Saardi, A.; Millet, J. *Synlett* **2005**, 487; (h) Djakovitch, L.; Rollet, P. *Adv. Synth. Catal.* **2004**, *346*, 1782 (zeolite); (i) Djakovitch, L.; Rollet, P. *Tetrahedron Lett.* **2004**, *45*, 1367 (zeolite); (j) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691 (ionic liquid); (k) Bakherad, M.; Keivanloo, A.; Bahramian, B.; Mihanparast, S. *Tetrahedron Lett.* **2009**, *50*, 6418.
6. For reviews on aqueous-switching, see: (a) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley-VCH: New York, NY, 1997; (b) Grieco, P. A. *Organic Synthesis in Water*; Kluwer Academic: Dordrecht, 1997; (c) Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524; (d) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751; (e) Li, C.-J.; Chan, T.-H. *Comprehensive Organic Reactions in Aqueous Media*; Wiley-Interscience: New Jersey, 2007; (f) *Aqueous-Phase Organometallic Catalysis*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 2004.
7. For recent studies on the copper-free Sonogashira coupling under aqueous conditions, see: (a) Bakherad, M.; Keivanloo, A.; Bahramian, B.; Hashemi, M. *Tetrahedron Lett.* **2009**, *50*, 1557; (b) Gu, S.; Chen, W. *Organometallics* **2009**, *28*, 909; (c) Chandra, A.; Singh, B.; Upadhyay, S.; Singh, R. M. *Tetrahedron* **2008**, *64*, 11680; (d) Komáromi, A.; Tolnai, G. L.; Novák, Z. *Tetrahadron* **2008**, *49*, 7294; (e) Ines, B.; SanMartin, R.; Churruca, F.; Domingues, E.; Urtiaga, M.; Miren, K.; Arriortua, M. I. *Organometallics* **2008**, *27*, 2833; (f) Shi, S.; Zhang, Y. *Synlett* **2007**, 1843; (g) Kawanami, H.; Matsushima, K.; Sato, M.; Ikushima, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5129; (h) Lipshutz, B. H.; Chung, D. W.; Rich, B. *Org. Lett.* **2008**, *10*, 3793.
8. For copper-free Sonogashira coupling in water with immobilized catalysts, see: (a) Ye, Z.-W.; Yi, W.-B. *J. Fluor. Chem.* **2008**, *129*, 11124; (b) Cai, M.; Xu, Q.; Sha, J. *J. Mol. Cat. A* **2007**, *272*, 293. Also see Ref. 11.
9. (a) Bayer, E.; Rapp, W. In *Chemistry of Peptides and Proteins*; Voelter, W., Bayer, E., Ovchinikov, Y. A., Iwanov, V. T., Eds.; Walter de Gruter: Berlin, 1986; Vol. 3, p 3; (b) Rapp, W. In *Combinatorial Peptide and Nonpeptide Libraries*; Jung, G., Ed.; VCH: Weinheim, 1996; p 425; (c) Du, X.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5678; (d) Gooding, O. W.; Baudert, D.; Deegan, T. L.; Heisler, K.; Labadie, J. W.; Newcomb, W. S.; Porco, J. A., Jr.; Eikeren, P. J. *J. Comb. Chem.* **1999**, *1*, 113.
10. For studies on polymer-supported transition metal complex catalysts from the author's group, see: (a) Uozumi, Y.; Danjo, H.; Hayashi, T. *Tetrahedron Lett.* **1997**, *38*, 3557 (allylic substitution); (b) Danjo, H.; Tanaka, D.; Hayashi, T.; Uozumi, Y. *Tetrahedron* **1999**, *55*, 14341 (allylic substitution); (c) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384 (cross-coupling); (d) Uozumi, Y.; Watanabe, T. *J. Org. Chem.* **1999**, *64*, 6921 (carbonylation reaction); (e) Uozumi, Y.; Nakai, Y. *Org. Lett.* **2002**, *4*, 2997 (Suzuki-Miyaura coupling); (f) Uozumi, Y.; Kimura, T. *Synlett* **2002**, 2045 (Heck reaction); (g) Uozumi, Y.; Shibatomi, K. *J. Am. Chem. Soc.* **2001**, *123*, 2919 (asymmetric alkylation); (h) Uozumi, Y.; Tanaka, H.; Shibatomi, K. *Org. Lett.* **2004**, *6*, 281 (asymmetric amination);

(i) Hocke, H.; Uozumi, Y. *Synlett* **2002**, 2049 (asymmetric catalysis); (j) Uozumi, Y.; Nakazono, M. *Adv. Synth. Catal.* **2002**, *344*, 274 (Rh catalysis); (k) Hocke, H.; Uozumi, Y. *Tetrahedron* **2003**, *59*, 619 (asymmetric catalysis); (l) Hocke, H.; Uozumi, Y. *Tetrahedron* **2004**, *60*, 9297 (asymmetric catalysis); (m) Nakai, Y.; Uozumi, Y. *Org. Lett.* **2005**, *7*, 291 (asymmetric cycloisomerization); (n) Uozumi, Y.; Kikuchi, M. *Synlett* **2005**, 1775 (cross-coupling); (o) Uozumi, Y.; Kimura, M. *Tetrahedron: Asymmetry* **2006**, *17*, 161 (asymmetric etherification); (p) Kobayashi, Y.; Tanaka, D.; Danjo, H.; Uozumi, Y. *Adv. Synth. Catal.* **2006**, *348*, 1561 (asymmetric alkylation); (q) Uozumi, Y.; Suzuka, T.; Kawade, R.; Takenaka, H. *Synlett* **2006**, 2109 (allylic azidation); (r) Uozumi, Y.; Suzuka, T. *J. Org. Chem.* **2006**, *71*, 8644 (nitromethylation); (s) Uozumi, Y.; Suzuka, T. *Synthesis* **2008**, 1960 (allylic sulfonylation); (t) Uozumi, Y.; Takenaka, H.; Suzuka, T. *Synlett* **2008**, 1557 (asymmetric desymmetrization); (u) Oe, Y.; Uozumi, Y. *Adv. Synth. Catal.* **2008**, *350*, 1771 (Kharasch reaction); (v) Uozumi, Y.; Matsuura, Y.; Arakawa, T.; Yamada, Y. M. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2708 (asymmetric Suzuki coupling).

11. PS–PEG beads are known to display relatively uniform swelling in a variety of solvents from medium to high polarity ranging from toluene to water to provide a solvent-swollen gel network, which allows relatively rapid diffusional access of reagents to reactive sites (see, Ref. 9 and references cited therein).
12. Preliminary results on aqueous, heterogeneous, copper-free Sonogashira coupling have been reported, see: Uozumi, Y.; Kobayashi, Y. *Heterocycles* **2003**, *59*, 71.