Consecutive palladium-catalyzed Hiyama–Heck reactions in aqueous media under ligand-free conditions†

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Symmetric and asymmetric (*E*)-1,2-diarylethenes are synthesized from aryl bromides by consecutive one-pot Hiyama–Heck reactions carried out in water and under air; the only additives required are sodium hydroxide, palladium acetate and poly(ethylene glycol), and the products are isolable in many cases by simple filtration of the water solution.
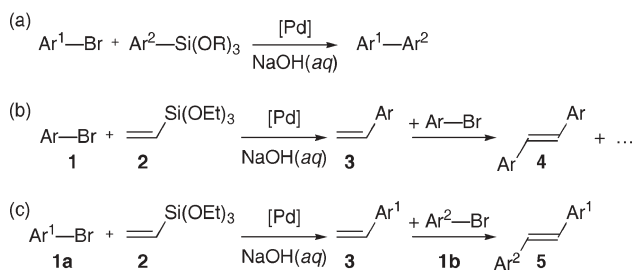
It is widely recognized that water offers practical advantages in several organic reactions involving soluble or non-soluble substrates.[1] Palladium-catalyzed carbon–carbon couplings, which are some of the most common transition-metal-catalyzed processes,[2] are more and more often being performed in aqueous or biphasic media.[3] The Hiyama arylation of haloarenes,[4] for example, has recently been described in water using a variety of Pd precatalysts and, usually, arylsiloxanes activated with sodium or potassium hydroxide (Scheme 1a).[5–7] The most interesting results from these investigations suggested that bromides might react efficiently with arylsiloxanes at high temperatures in the presence of relatively low concentrations of palladium salts and in the absence of phosphanes or other expensive or toxic ligands (ligand-free conditions[8]).[6,7] Herein, we show that this attractive and unique combination of accessible and stable organosiloxanes, aqueous media, low Pd loadings, and aerobic and fluoride- and ligand-free conditions are also valid for sequential reactions that afford more complex products in a one-pot synthesis.

The vinylation of aryl halides with silicon-based vinyl donors[9] is complicated by the fact that palladium catalysts promote the Heck–Mizoroki[10,11] coupling of aryl halides and alkenes under conditions similar to those of the Hiyama reaction. The efficient

Scheme 1

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† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all compounds. See DOI: 10.1039/b707583a

synthesis of vinylarenes (**3**) therefore requires close control of the relative kinetics of the Hiyama and Heck reactions in order to minimize the formation of (*E*)-1,2-diarylethenes (**4**) and other Heck by-products (Scheme 1b). At the same time, the development of procedures that allow good kinetic control makes the sequential combination of the Hiyama and Heck reactions to afford asymmetrically substituted olefins (**5**) in a one-pot reaction more feasible (Scheme 1c). Although palladium-mediated coupling reactions are widely used for the synthesis of functionalized (*E*)-stilbenes and other (*E*)-1,2-diarylethenes,[12] the preparation of asymmetric compounds usually starts from previously isolated vinylarenes.[13] To the best of our knowledge, only two reports have appeared in the literature describing one-pot syntheses of asymmetric (*E*)-1,2-diarylethenes directly from aryl halides, both of which involve aromatic iodides, high catalyst loadings, and phosphine ligands or fluoride additives.[14,15] Herein, we describe remarkable yields and selectivities in the synthesis of vinylarenes and symmetric and asymmetric (*E*)-1,2-diarylethenes in water with modest Pd loadings and under ligand-free conditions.

An exhaustive screening of the Hiyama vinylation of 4-bromoacetophenone in water established that 4-vinylacetophenone was best synthesized at 140 °C in the presence of 0.1 mol% of palladium(II) acetate, five equivalents of NaOH, and four equivalents of triethoxy(vinyl)silane to reduce the undesired formation of Heck by-products **4** and **6** (Table 1, entry 1).[16] Complete conversions were also achieved with lower temperatures and Pd loadings (0.01 mol%), although the longer reaction times required for these conditions produced a decrease in yields due to both extensive polymerization and Heck arylation of the 4-vinyl-acetophenone.[17] The addition of poly(ethylene glycol) (PEG, M_w = 2000) greatly enhanced the selectivity for the vinyl compound (Table 1, entry 2) even in the presence of smaller excesses of silane (Table 1, entry 3).[18,19] Substrates such as 4-bromobenzoic acid or 3-bromopyridine were converted almost quantitatively into the vinyl compound in the absence of PEG (Table 1, entries 4 and 5), although the presence of this additive allowed a substantial reduction in the amount of silane required (Table 1, entry 6). The slower kinetics of the vinylation in the case of electronically inactivated bromoarenes such as 4-bromoanisole (Table 1, entry 8) or 4-bromo-*N*,*N*-dimethylaniline (Table 1, entry 9) favoured the Heck products, therefore these reactions were carried out at higher temperatures in the presence of PEG. It should be stressed that the addition of PEG in these reactions enhances the solubility of the hydrophobic bromoarenes and stabilizes not only the catalyst but also the vinyl compounds against polymerization or decomposition.

(*E*)-1,2-Diarylethenes **4** were obtained with high selectivities simply by varying the aforementioned conditions. This variation
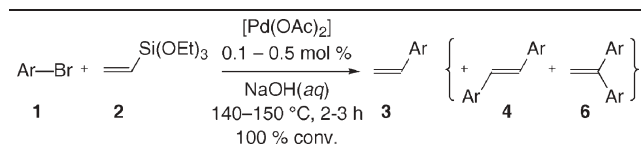
Table 1 Hiyama vinylation of aryl bromides in water[a]

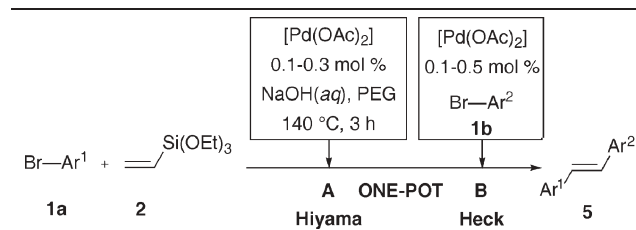| Entry	Ar	Pd^{II} (mol%)/ratio 1 : 2/additive[b]	Selectivity 3 : (4 + 6)[c]	Yield (%)[d]
1	⁒⁒—C₆H₄—COMe	0.1/1 : 4/–	94 : 6	70
2		0.1/1 : 4/PEG	99 : 1	95
3		0.1/1 : 2/PEG	95 : 5	90
4	—C₆H₄—COOH	0.3/1 : 4/–	99 : 1	97
5	pyridine	0.1/1 : 4/–	100 : 0	96
6		0.1/1 : 2/PEG	99 : 1	95
7	quinoline	0.1/1 : 4/PEG	99 : 1	93
8	—C₆H₄—OMe	0.1/1 : 4/PEG	90 : 10[e]	75
9	—C₆H₄—NMe₂	0.5/1 : 4/PEG	91 : 9[e]	86

[a] In a typical experiment, 1 mmol of aryl bromide, triethoxy-(vinyl)silane, and palladium acetate were stirred under air in 0.5 M NaOH at 140 (entries 1–7) or 150 °C (entries 8 and 9) for 2–3 h. All conversions of **1** were quantitative. See ESI for further details. [b] 20 wt% PEG. [c] Selectivities were determined from ¹H NMR spectroscopy of the crude product. [d] Yields of isolated **3**. [e] Ratio **4** : **6** ≈ 75 : 25.

essentially consisted of using a stoichiometric amount or a slight excess of the vinylsilane (Table 2). The addition of PEG was not generally required in these syntheses. Remarkably, a very low

Table 2 Synthesis of symmetric (E)-1,2-diarylethenes by consecutive Hiyama vinylation and Heck arylation in water[a]
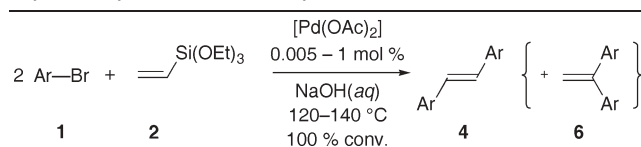
Entry	Ar	Pd^{II} (mol%)	Reaction time/h	Selectivity 4 : 6[b]	Yield (%)[c]
1	—C₆H₄—COMe	0.005	24	100 : 0	97
2		0.3	3	100 : 0	98
3[d]	—C₆H₄—COOH	0.5	5	82 : 18	80
4	pyridine	0.3	3	100 : 0	96
5	quinoline	0.3	3	100 : 0	98
6[e]	—C₆H₄—OMe	1	22	77 : 23	70
7[e]	—C₆H₄—NMe₂	1	5	97 : 3	50

[a] In a typical experiment, 1 mmol of aryl bromide, triethoxy-(vinyl)silane, and palladium acetate were stirred under air in 5 mL of 0.5 M NaOH at 120–140 °C for the specified time. Conversions of **1** were 100%. See ESI for further details. [b] Selectivities were determined from ¹H NMR spectroscopy of the crude product. [c] Yields of isolated product **4**. [d] Addition of 40 wt% PEG was necessary for complete conversion. [e] A larger excess of vinylarene (1 mmol) was employed in these cases.

Table 3 Synthesis of asymmetric (E)-1,2-diarylethenes by consecutive Hiyama vinylation and Heck arylation reactions in water[a]

Entry	Product	Pd^{II} (A/B, mol%)	Yield (%)[b]
1	pyridin-3-yl-CH=CH-C₆H₄-COMe	0.1/0.5	91
2		0.1/0.1	87
3	pyridin-3-yl-CH=CH-quinolinyl	0.1/0.1	81
4	pyridin-3-yl-CH=CH-C₆H₄-OMe	0.1/0.5	71
5	MeOC-C₆H₄-CH=CH-quinolinyl	0.1/0.5	90
6	HOOC-C₆H₄-CH=CH-C₆H₄-COMe	0.3/0.5	89

[a] Typical conditions: reaction **A**: 1.78 mmol of aryl bromide **1a**, 3.54 mmol of triethoxy(vinyl)silane **2**, and palladium acetate were stirred under air in 10 mL of 0.5 M NaOH and 20 wt% PEG for 3 h at 140 °C; reaction **B**: 1.78 mmol of aryl bromide **1b** and palladium acetate were added and the mixture stirred for 3–6 h at 140 °C (20 h, 100 °C for entry 1). All conversions were 100%. See ESI for further details. [b] Yields of isolated product.

catalyst loading was enough to afford (E)-4,4′-bis(acetyl)stilbene (0.005 mol% Pd, 24 h, 120 °C, TON = 19 400; Table 2, entry 1) quantitatively. However, higher catalyst loadings and temperatures are required to complete the conversion of activated substrates in shorter times (Table 2, entries 2–5) or in the case of inactivated bromoarenes (Table 2, entries 6 and 7).

We subsequently attempted the one-pot synthesis of asymmetric (E)-1,2-diarylethenes **5** by combining the Hiyama vinylation of bromoarene **1a** with the *in situ* Heck reaction of the resulting vinylarene with a second bromoarene **1b** (Table 3). Three substrates that yielded almost quantitative conversions and selectivities in the Hiyama vinylation were tested as bromides **1a**, namely 3-bromopyridine (Table 3, entries 1–4), 4-bromoacetophenone (Table 3, entry 5), and 4-bromobenzoic acid (Table 3, entry 6).‡ Full conversions were always attained, irrespective of the electron-withdrawing or -donating nature of the bromoarene, provided that a second load of Pd catalyst was added together with the second bromoarene **1b**. The selectivities for asymmetric (E)-stilbenes or stilbazoles (**5**) were notable, as can be inferred from the high yields of isolated products (81–91%); only small amounts of symmetric 1,2-diarylated derivatives were observed as by-products (<5%). 4-Bromoanisole was the only substrate that afforded significant amounts of other by-products (mainly around 7% of the 1,1-isomer) and therefore lower yields of the asymmetric (E)-1,2-diarylethene (71%, Table 3, entry 4).

Blackmond *et al.* recently pointed out that simply replacing an organic solvent by water does not suppose an automatic

enhancement in the environmental or economical efficiency of a process because the impact of the overall process, including workup, must be considered.[20] The conversions and selectivities of the reactions described here in water compete favourably with those reported in organic solvents, and the use of water has specific advantages over conventional organic solvents: (a) the activation of aryl bromides under ligand-free conditions relies on the use of high temperatures for which a nonflammable solvent such as water is superior on safety grounds; (b) many of the alkenes reported, especially 1,2-diarylethenes, are solids that precipitate from the aqueous reaction medium and can therefore be separated by simple filtration to afford crude products that, in many cases, are pure by ^{1}H NMR spectroscopy.[21]

In conclusion, we have provided an effective method for the sequential performance of Hiyama and Heck reactions in aqueous media that allows the preparation of a variety of symmetrically and asymmetrically functionalized (E)-1,2-diarylethenes in one pot from aryl bromides and triethoxy(vinyl)silane. The only additives required are sodium hydroxide, palladium acetate (0.1 to 0.5 mol%) and, in some cases, poly(ethylene glycol). The reactions are carried out in air and the products can be isolated, in many cases, by simple filtration of the aqueous solution.

Notes and references

‡ The synthesis of (E)-4-[2-(3-pyridyl)vinyl]acetophenone is given as representative: in a 35 mL pressure tube, triethoxy(vinyl)silane (0.77 mL, 3.54 mmol) and a 0.5 M NaOH solution in water (10.70 mL, 5.35 mmol) containing 20% (w/w) of PEG 2000 (2.14 g) were vigorously stirred for 5 min at room temp. 3-Bromopyridine (0.178 mL, 1.78 mmol) and palladium acetate (0.4 mg, 1.8 μmol) were subsequently added and the vigorous stirring was continued for 3 h at 140 °C. 4-Bromoacetophenone (0.3615 g, 1.78 mmol) and palladium(II) acetate (0.4 mg, 1.8 μmol) dissolved in 1 mL of a 20% (w/w) aqueous solution of PEG 2000 were added at room temperature and the reaction warmed for 6 h at 140 °C. The product was extracted with ethyl acetate (3 × 20 mL) and purified by flash chromatography on silica gel with hexane–ethyl acetate 1 : 5 (R_f = 0.24). Yield: 0.3467 g (87%).

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