

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

Álvaro Gordillo,^a Ernesto de Jesús^{*b} and Carmen López-Mardomingo^a

Received (in Cambridge, UK) 21st May 2007, Accepted 3rd July 2007

First published as an Advance Article on the web 25th July 2007

DOI: 10.1039/b707583a

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.

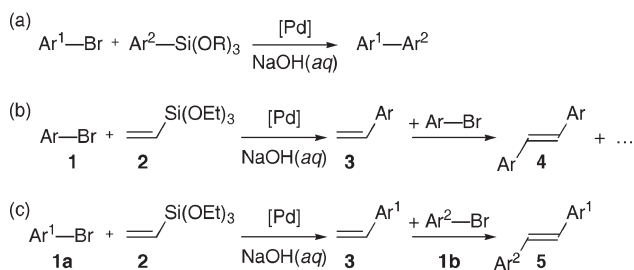
It is widely recognized that water offers practical advantages in several organic reactions involving soluble or non-soluble substrates.¹ Palladium-catalyzed carbon–carbon couplings, which are some of the most common transition-metal-catalyzed processes,² are more and more often being performed in aqueous 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 conditions⁸).^{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 donors⁹ 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

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-vinylacetophenone.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



Scheme 1

^aDepartamento de Química Orgánica, Universidad de Alcalá, 28871 Alcalá de Henares (Madrid), Spain

^bDepartamento de Química Inorgánica, Universidad de Alcalá, 28871 Alcalá de Henares (Madrid), Spain. E-mail: ernesto.dejesus@uah.es; Fax: (+34) 91 885 4683

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

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 ¹H 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.

This work was supported by the Ministerio de Educación y Ciencia of Spain (project CTQ2005-00795/BQU) and the Comunidad de Madrid (project S-0505/PPQ/0328-03). A. G. is grateful to the MEC for a FPU Fellowship.

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%).

- 1 R. Breslow, *Acc. Chem. Res.*, 1991, **24**, 159–164; C. J. Li and T. H. Chan, *Organic Reactions in Aqueous Media*, Wiley, New York, 1997; *Organic Synthesis in Water*, ed. P. A. Greco, Springer, London, 1998; S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2005, **44**, 3275–3279.
- 2 *Aqueous-Phase Organometallic Catalysis: Concepts and Applications*, ed. B. Cornils and W. A. Herrmann, Wiley-VCH, Weinheim, 2nd edn, 2004; F. Joó and Á. Kathó, *J. Mol. Catal. A: Chem.*, 1997, **116**, 3–26.
- 3 J. P. Genet and M. Savignac, *J. Organomet. Chem.*, 1999, **576**, 305–317; C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095–3165; N. E. Leadbeater, *Chem. Commun.*, 2005, 2881–2902; K. H. Shaughnessy, *Eur. J. Org. Chem.*, 2006, 1827–1835.
- 4 Y. Hatanaka and T. Hiyama, *J. Org. Chem.*, 1988, **53**, 918–920; Y. Hatanaka, S. Fukushima and T. Hiyama, *Chem. Lett.*, 1989, **18**, 1711–1714; S. E. Denmark and R. F. Sweis, in *Metal-Catalyzed Cross-Coupling Reactions*, ed. A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2nd edn, 2004, ch. 4; C. J. Handy, A. S. Manoso, W. T. McElroy, W. M. Seganish and P. DeShong, *Tetrahedron*, 2005, **61**, 12201–12225.
- 5 T. Huang and C. J. Li, *Tetrahedron Lett.*, 2002, **43**, 403–405; T. Koike and A. Mori, *Synlett*, 2003, 1850–1852; C. Wolf and R. Lerebours, *Org. Lett.*, 2004, **6**, 1147–1150; R. Lerebours and C. Wolf, *Synthesis*, 2005, 2287–2292.

- 6 E. Alacid and C. Nájera, *Adv. Synth. Catal.*, 2006, **348**, 945–962.
- 7 A. Gordillo, E. de Jesús and C. López-Mardomingo, *Org. Lett.*, 2006, **8**, 3517–3520.
- 8 M. T. Reetz and J. G. de Vries, *Chem. Commun.*, 2004, 1559–1563; J. G. de Vries, *Dalton Trans.*, 2006, 421–429.
- 9 Selected recent reports on the Hiyama vinylation of aryl halides: M. E. Mowery and P. DeShong, *J. Org. Chem.*, 1999, **64**, 1684–1688; T. Jeffery, *Tetrahedron Lett.*, 1999, **40**, 1673–1676; H. M. Lee and S. P. Nolan, *Org. Lett.*, 2000, **2**, 2053–2055; S. E. Denmark and J. M. Kallemeyn, *J. Am. Chem. Soc.*, 2006, **128**, 15958–15959; S. E. Denmark and C. R. Butler, *Org. Lett.*, 2006, **8**, 63–66.
- 10 T. Mizoroki, K. Mori and A. Ozaki, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 581; R. F. Heck and J. P. Nolley, Jr., *J. Org. Chem.*, 1972, **37**, 2320–2322; I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009–3066; S. Bräse and A. de Meijere, in *Metal-Catalyzed Cross-Coupling Reactions*, ed. A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2nd edn, 2004, ch. 5.
- 11 Recent reports on Heck reactions between aryl halides and vinylarenes in water: C. Nájera, J. Gil-Moltó, S. Karlström and L. R. Falvello, *Org. Lett.*, 2003, **5**, 1451–1454; L. Botella and C. Nájera, *Tetrahedron Lett.*, 2004, **45**, 1833–1836; R. B. DeVasher, L. R. Moore and K. H. Shaughnessy, *J. Org. Chem.*, 2004, **69**, 7919–7927; H. Hagiwara, Y. Sugawara, T. Hoshi and T. Suzuki, *Chem. Commun.*, 2005, 2942–2944; S. Ogo, Y. Takebe, K. Uehara, T. Yamazaki, H. Nakai, Y. Watanabe and S. Fukuzumi, *Organometallics*, 2006, **25**, 331–338; N. S. C. R. Kumar, I. V. P. Raj and A. Sudalai, *J. Mol. Catal. A: Chem.*, 2007, **269**, 218–224.
- 12 Classical non-catalytic methods such as the Wittig or Horner–Wadsworth–Emmons reaction usually afford poor control over the (*E*) or (*Z*) configuration of the C=C double bonds. Catalytic methods for the synthesis of stilbenes have been recently reviewed: K. Ferré-Filmon, L. Delaude, A. Demonceau and A. F. Noels, *Coord. Chem. Rev.*, 2004, **248**, 2323–2336.
- 13 Asymmetric 1,2-diarylethenes are also prepared by titanium-catalyzed McMurry coupling of aldehydes and ketones or by ruthenium-catalyzed cross-metathesis of vinylarenes, but the first procedure suffers from poor tolerance to functional groups and the second from low selectivities. See, for example: K. Ferré-Filmon, L. Delaude, A. Demonceau and A. F. Noels, *Eur. J. Org. Chem.*, 2005, 3319–3325.
- 14 Itami et al. used a Heck–Hiyama sequence of reactions in THF to couple aryl iodides and 2-pyridyldimethyl(vinyl)silane using 10 mol% of Pd(OAc)₂ and tri-2-furylphosphine: K. Itami, T. Nokami, Y. Ishimura, K. Mitsudo, T. Kamei and J.-I. Yoshida, *J. Am. Chem. Soc.*, 2001, **123**, 11577–11585.
- 15 Jeffery described the synthesis of (*E*)-3,4',5-trimethoxystilbene in 72% yield by two sequential Heck reactions using aryl iodides, trimethyl(vinyl)silane and 4 mol% of Pd(dba)₂: T. Jeffery and B. Ferber, *Tetrahedron Lett.*, 2003, **44**, 193–197.
- 16 We started from the conditions established in our previous study on the Hiyama arylation (ref. 7). Palladium acetate, palladium dichloride and complexes of the latter with the soluble phosphines 1,3,5-triaza-7-phosphaadamantane (PTA) and PPh₂Ar* (Ar* = 3,4-[18-crown-6]-phenyl) produced comparable results.
- 17 In contrast with our observations that short reaction times are key in the efficient synthesis of vinyl derivatives, high yields of 4-vinylacetophenone after 20 h of reaction at 120 °C have been reported during the course of our work by Alacid and Nájera using tetrabutylammonium bromide (TBAB) as a nanoparticle stabilizer: E. Alacid and C. Nájera, *Adv. Synth. Catal.*, 2006, **348**, 2085–2091.
- 18 Poly(ethylene glycol) (PEG), pure or as a co-solvent, is an efficient medium for palladium-catalyzed coupling reactions. S. Chandrasekhar, Ch. Narsihmulu, S. S. Sultana and N. R. Reddy, *Org. Lett.*, 2002, **4**, 4399–4401; C. Luo, Y. Zhang and Y. Wang, *J. Mol. Catal. A: Chem.*, 2005, **229**, 7–12.
- 19 PEG was a more efficient additive than TBAB in Suzuki reactions catalyzed by palladium(II) acetate in water and ligand-free conditions. L. Liu, Y. Zhang and Y. Wang, *J. Org. Chem.*, 2005, **70**, 6122–6125.
- 20 D. G. Blackmond, A. Armstrong, V. Coombe and A. Wells, *Angew. Chem., Int. Ed.*, 2007, **46**, 3798–3800.
- 21 See, for example, the experimental procedures described in the ESI† for (*E*)-1,2-bis-[4-carboxyphenyl]ethene and (*E*)-1,2-bis-(3-quinolylyl)ethene. Carboxy derivatives, which are water-soluble in their basic form, precipitate upon neutralization of the basic solution.