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The palladium-catalyzed hydroarylation of propargylic alcohols in room temperature ionic liquids

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Abstract

The palladium-catalyzed hydroarylation of propargylic alcohols with aryl iodides in the presence of $Pd(OAc)_2$, HCOOH, and Et_3N in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) at 40 °C has been investigated. The process is highly stereoselective. Hydroarylation products have been obtained usually in good yields and the use of the ionic liquid has provided better results than molecular solvents in terms of regioselectivity and/or rate of reaction. Hydroarylation products containing a bromo substituent close to the carbon–carbon triple bond can successfully be used for the development of a new route to chromenes through a hydroarylation–cyclization sequence.

Keywords: Palladium; Alkynes; Hydroarylation; Ionic liquids; Chromenes

1. Introduction

Our palladium-catalyzed hydroarylations and hydrovinylations of alkynes have provided a versatile procedure for the synthesis of substituted alkene products and cyclic systems [1]. The reaction most probably proceeds according to the basic steps outlined in Scheme 1. The reaction is usually highly stereoselective and, though the appearance of final products as *trans* derivatives has been reported in some cases, a general predominance of *cis* addition products following the carbopalladation step is observed. With unsymmetrical alkynes, steric and coordinating effects appear to play a major role in controlling the regioselectivity of the process.

Solvents—among other reaction parameters such as the presence or the absence as well as the nature of phosphine ligands, the nature of the C_{sp^2}-donor (for example, organic triflates tend to give better results than organic iodides in terms of regio- and stereoselectivity [2])—have been found to influence the regiochemical outcome [3]. In this context, it seemed of interest to investigate whether room temperature ionic liquids could exhibit some influence on the carbopalladation step of the hydroarylation process, and consequently on the regioselectivity of the hydroarylation with aryl iodides. An "ionic liquid effect" has been observed, for example, in the palladium-catalyzed reaction of aryl iodides with vinyl ethers [4]. In particular, because of our interest in the utilization of propargylic alcohols as building blocks for the preparation of chromene derivatives through a hydroarylation–cyclization process (vide infra), we focused our attention on the hydroarylation of propargylic alcohols.

Hereafter we report the preliminary results of this study.

2. Experimental

Melting points were determined with a Büchi apparatus and are uncorrected. All of the starting materials such as $Pd(OAc)_2$, solvents, and aryl iodides are commercially available and were used as purchased, without further purification. The ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) was prepared as described in [5]. Propargylic alcohols **1** were prepared by the Sonogashira coupling [6] of commercially available 1-propyn-3-ols with aryl iodides. MEM and THP derivatives of propargylic alcohols were prepared by using standard methods. Reaction products were purified on axially compressed columns, packed with SiO_2 25–40 μm (Macherey

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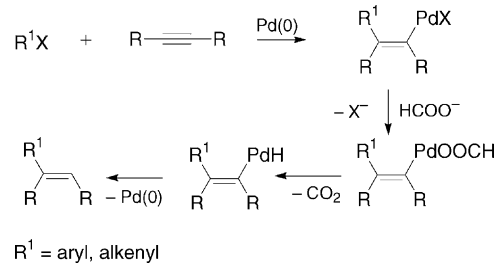


Scheme 1.

Nagel), connected to a Gilson solvent delivery system and to a Gilson refractive index detector, and eluting with *n*-hexane/EtOAc mixtures. ^{1}H NMR (200 and 400 MHz) and ^{13}C NMR (50.3 and 100.6 MHz) spectra were recorded with Bruker Avance 200 and 400 spectrometers. IR spectra were recorded with a Jasco FT/IR 430 spectrometer.

3. Typical procedure for the hydroarylation of propargylic alcohols (Table 1, entry 17)

$Pd(OAc)_2$ (10.5 mg, 0.047 mmol) and [bmim][BF_4] (2 ml) were stirred at 40 °C for 1 h. Then, **1i** (224.1 mg, 0.938 mmol), 4-iodoanisole (329.2 mg, 1.406 mmol), triethylamine (392 μl, 2.814 mmol), and formic acid (71 μl, 1.876 mmol) were added. The reaction mixture was stirred at 40 °C for 30 h. After cooling, the reaction mixture was diluted with ethyl ether, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (*n*-hexane/EtOAc 85/15, v/v) to give 247.7 mg (76%) of **4m** and 60.2 mg (19%) of **3m**.

3.1. *4m*

Oil; IR (neat) 3452, 3027, 2970, 2830, 1383, 1243, 1180 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 7.64–7.60 (m, 1H), 7.44–7.26 (m, 1H), 7.15–7.00 (m, 2H), 7.04 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 4.54 (s, 1H), 3.72 (s, 3H), 1.07 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ (ppm) 158.9, 141.1, 137.7, 136.2, 133.8, 132.9, 132.7, 129.6, 127.8, 127.6, 124.3, 114.2, 70.3, 55.6, 31.0, 30.1. Anal calcd for $C_{18}H_{19}BrO_2$: C, 62.26; H, 5.52. Found: C, 62.35; H, 5.50.

3.2. *3m*

Oil; IR (neat) 3443, 3045, 2972, 2835, 1380, 1245, 1175 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 7.62–7.57 (m, 1H), 7.52–7.47 (m, 1H), 7.34–7.29 (m, 3H), 7.20–7.15 (m, 1H), 6.92–6.88 (m, 2H), 6.08 (s, 1H), 4.41 (s, 1H), 3.77 (s, 3H), 1.17 (s, 6H); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ (ppm) 158.5, 151.2, 140.3, 136.8, 132.2, 132.0, 130.5, 128.8, 128.3, 127.2, 123.5, 113.4, 72.4, 55.6, 31.5. Anal calcd for $C_{18}H_{19}BrO_2$: C, 62.26; H, 5.52. Found: C, 62.18; H, 5.51.

3.3. *3a*

Oil; IR (neat) 3436, 2962, 2874, 1384, 1246, 1106 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.57 (dd, J_1 = 7.8 Hz, J_2 = 2.0 Hz, 2H), 7.45–7.26 (m, 5H), 6.93 (dd, J_1 = 7.8 Hz, J_2 = 2.0 Hz, 2H), 6.75 (s, 1H), 4.84 (t, J = 7.1 Hz, 1H), 3.84 (s, 3H), 2.17 (bs, 1H), 1.70–1.58 (m, 2H), 0.86 (t, J = 7.4 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm) 158.9, 143.8, 137.2, 133.1, 131.5, 129.8, 129.0, 128.3, 127.0, 113.4, 71.7, 55.2, 28.6, 10.2. Anal calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.48; H, 7.53.

3.4. *4a*

Oil; IR (neat) 3430, 2970, 2869, 1381, 1247, 1110 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.4–7.0 (m, 7H), 6.82 (dd, J_1 = 6.8 Hz, J_2 = 2.1 Hz, 2H), 5.98 (d, J = 9.3 Hz, 1H), 4.15–4.0 (m, 1H), 3.80 (s, 3H), 1.77–1.55 (m, 4H), 0.88 (t, J = 7.4 Hz, 2H); Anal calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.49; H 7.52.

3.5. *3b*

Oil; IR (neat) 2933, 2875, 1381 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.57–7.51 (m, 2H), 7.38–7.25 (m, 5H), 6.92–6.87 (m, 3H), 4.87 (t, J = 7.2 Hz, 1H), 4.77 (d, J = 6.7 Hz, 1H), 4.68 (d, J = 6.7 Hz, 1H), 3.83 (s, 3H), 3.71–3.35 (m, 4H), 3.33 (s, 3H), 1.84–1.65 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm) 159.0, 140.7, 137.3, 133.2, 132.8, 129.7, 129.1, 128.2, 128.9, 113.4, 92.8, 75.3, 71.7, 66.9, 59.0, 55.3, 27.06, 10.5. Anal calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.20; H, 7.91.

3.6. *4b*

Oil; IR (neat) 2940, 2871, 1383 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.40–7.15 (m, 8H), 6.83–6.77 (m, 2H), 5.88 (d, J = 9.4 Hz, 1H), 4.76 (d, J = 6.7 Hz, 1H), 4.64 (d, J = 6.7 Hz, 1H), 4.09–3.95 (m, 1H), 3.78 (s, 3H), 3.68–3.33 (m, 4H), 1.73–1.53 (m, 2H), 0.89 (t, J = 7.4 Hz, 2H); Anal calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.05; H, 7.93.

3.7. *3c*

Oil; IR (neat) 3061, 2934, 2877, 1717, 1276 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.03 (dd, J_1 = 6.7 Hz, J_2 = 1.9 Hz, 2H), 7.67 (dd, J_1 = 6.7 Hz, J_2 = 1.9 Hz, 2H), 7.42–7.27 (m, 5H), 6.97 (s, 1H), 4.89 (t, J = 7.3 Hz, 1H), 4.75 (d, J = 6.7 Hz, 1H), 4.69 (d, J = 6.7 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 3.71–3.64 (m, 1H), 3.56–3.49 (m, 2H), 3.42–3.39 (m, 2H), 3.34 (s, 3H), 1.82–1.75 (m, 1H),

1.61–1.54 (m, 1H), 1.43 (t, $J = 7.1$ Hz, 3H), 0.89 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 166.6, 145.6, 140.8, 136.6, 134.7, 129.3, 129.0, 128.5, 128.3, 127.3, 93.0, 75.3, 71.7, 67.0, 60.9, 58.9, 26.7, 14.4, 10.4. Anal calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.41; H, 7.58.

3.8. *4c*

Oil; IR (neat) 3057, 2933, 2878, 1717, 1276 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.96 (dd, $J_1 = 6.7$ Hz, $J_2 = 1.9$ Hz, 2H), 7.41–7.27 (m, 5H), 7.21 (dd, $J_1 = 6.7$ Hz, $J_2 = 1.9$ Hz, 2H), 6.10 (d, $J = 6.1$ Hz, 1H), 4.78 (d, $J = 6.8$ Hz, 1H), 4.68 (d, $J = 6.8$ Hz, 1H), 4.38 (q, $J = 7.1$ Hz, 2H), 4.17–4.09 (m, 1H), 3.71–3.59 (m, 2H), 3.50–3.45 (m, 2H), 3.35 (s, 3H), 1.71–1.58 (m, 2H), 1.4 (t, $J = 7.1$ Hz, 3H), 0.92 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 166.4, 146.1, 143.5, 138.8, 131.6, 129.7, 129.5, 129.4, 128.4, 127.5, 127.2, 93.3, 75.5, 71.7, 66.8, 60.9, 59.0, 28.7, 14.3, 9.8. Anal calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.39; H, 7.60.

3.9. *3d*

Oil; IR (neat) 3049, 2932, 1445, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58–7.54 (m, 2H), 7.39–7.24 (m, 8H), 6.90 (s, 1H), 4.86 (t, $J = 7.3$ Hz, 1H), 4.76 (d, $J = 6.7$ Hz, 1H), 4.68 (d, $J = 6.7$ Hz, 1H), 3.69–3.63 (m, 1H), 3.54–3.49 (m, 1H), 3.42–3.38 (m, 2H), 3.32 (s, 3H), 1.80–1.56 (m, 2H), 0.89 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 141.8, 141.3, 137.5, 134.1, 129.4, 128.9, 128.6, 128.4, 127.6, 127.4, 93.3, 75.8, 72.1, 67.3, 59.4, 27.4, 10.8. Anal calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 77.10; H, 8.82.

3.10. *4d*

Oil; IR (neat) 3057, 2963, 2932, 2877 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.40–7.20 (m, 1H), 6.00 (d, $J = 9.4$ Hz, 1H), 4.79 (d, $J = 6.7$ Hz, 1H), 4.74 (d, $J = 6.7$ Hz, 1H), 4.13–4.09 (m, 1H), 3.71–3.58 (m, 2H), 3.50–3.45 (m, 2H), 3.35 (s, 3H), 1.77–1.56 (m, 2H), 0.92 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 144.8, 142.2, 139.8, 130.1, 129.8, 128.6, 128.5, 127.9, 127.7, 127.6, 93.4, 75.7, 72.1, 67.1, 59.4, 29.2, 10.2. Anal calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 77.08; H, 8.81.

3.11. *3e*

Oil; IR (neat) 2933, 2976, 1683 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 7.47–7.43 (m, 2H). 7.42–7.28 (m, 5H), 7.18–7.14 (m, 2H), 6.88 (s, 1H), 4.78 (t, $J = 7.3$ Hz, 1H), 4.58 (s, 1H), 3.56–3.50 (m, 1H), 3.44–3.37 (m, 1H), 3.32–3.30 (m, 2H), 3.18 (s, 3H), 2.31 (s, 3H), 1.71–1.63 (s, 1H), 1.51 (s, 1H), 0.79 (t, $J = 7.4$ Hz, 1H); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ (ppm) 140.4, 137.4, 136.7, 136.3, 132.7, 128.8, 128.5, 128.2, 128.1, 126.9, 91.9, 74.4, 71.0, 66.3, 58.0, 26.5, 20.6, 10.2 Anal calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: 77.52; H, 8.28.

3.12. *4e*

Oil; IR (neat) 2930, 2970, 1685 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 7.42–7.34 (m, 2H), 7.00 (m, 7H), 5.93 (d, $J = 9.4$ Hz, 1H), 4.61 (d, $J = 6.8$ Hz, 1H), 4.54 (d, $J = 6.8$ Hz, 1H), 3.96–3.91 (m, 1H), 3.52–3.44 (m, 2H), 3.37–3.35 (m, 2H), 3.17 (s, 3H), 2.27 (s, 3H), 1.63–1.51 (m, 2H), 0.82 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ (ppm) 143.2, 139.1, 138.4, 136.8, 129.2, 128.8, 128.3, 128.2, 127.2, 126.7, 92.1, 74.4, 71.0, 66.1, 58.0, 28.1, 20.6, 9.7. Anal calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.69; H, 8.28.

3.13. *3f*

Oil; IR (neat) 2931, 2877, 1683, 1384 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.95 (d, $J = 8.2$ Hz, 2H), 7.70 (d, $J = 8.2$ Hz, 2H), 7.42–7.28 (m, 5H), 4.90 (t, $J = 7.29$, 1H), 4.75 (d, $J = 6.7$ Hz, 1H), 4.69 (d, $J = 6.7$ Hz, 1H), 3.70–3.65 (m, 1H), 3.55–3.51 (m, 1H), 3.43–3.40 (m, 2H), 3.34 (s, 3H), 2.66 (s, 3H), 1.82–1.77 (m, 1H), 1.63–1.56 (m, 1H), 0.89 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 198.2, 146.7, 141.01, 136.9, 136.3, 135.2, 129.4, 129.1, 128.7, 128.5, 127.7, 93.3, 75.6, 72.0, 67.4, 59.4, 27.4, 27.0, 10.8. Anal calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.89; H, 7.65.

3.14. *4f*

Oil; IR (neat) 2942, 2865, 1681, 1380 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.88–7.83 (m, 2H), 7.39–7.31 (m, 5H), 7.20–7.16 (m, 2H), 6.09 (d, $J = 9.3$ Hz, 1H), 4.75 (d, $J = 6.8$ Hz, 1H), 4.66 (d, $J = 6.8$ Hz, 1H), 4.15–4.00 (m, 1H), 3.66–3.58 (m, 2H), 3.45 (t, $J = 4.8$ Hz, 2H), 3.33 (s, 3H), 2.57 (s, 3H), 1.72–1.55 (m, 2H), 0.89 (t, $J = 7.5$ Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 197.7, 146.4, 143.4, 138.8, 136.1, 131.9, 129.7, 128.5, 128.4, 127.7, 127.5, 93.3, 75.4, 71.8, 66.9, 59.1, 28.8, 26.7, 9.9. Anal calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.52; H, 8.30.

3.15. *3g*

Oil; IR (neat) 2940, 2873, 1384, 1247 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.57 (dd, $J_1 = 6.8$ Hz, $J_2 = 2.1$ Hz, 2H), 7.39–7.25 (m, 5H), 6.94 (s, 1H), 6.91 (dd, $J_1 = 6.8$ Hz, $J_2 = 2.1$ Hz, 2H), 5.05 (t, $J = 7.4$ Hz, 1H), 4.65–4.61 (m, 1H), 3.85 (s, 3H), 3.82–3.71 (m, 1H), 3.28–3.20 (m, 1H), 1.92–1.49 (m, 8H), 0.93 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm) 158.9, 140.4, 137.3, 133.5, 133.2, 129.6, 129.0, 128.1, 126.8, 113.4, 95.6, 74.0, 63.0, 55.2, 30.9, 27.0, 25.4, 20.3, 10.5. Anal calcd for $C_{23}H_{28}O_3$: C, 78.38; H, 8.01. Found: C, 78.29; H, 8.02.

3.16. **4g**

Oil; IR (neat) 2935, 2870, 1380, 1250 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.38–7.13 (m, 7H), 6.82 (dd, $J_1 = 6.8$ Hz, $J_2 = 2.0$ Hz, 2H), 5.85 (d, $J = 9.5$ Hz, 1H), 4.69–4.64 (m, 1H), 3.84–3.71 (m, 4H), 3.38–3.30 (m, 8H), 0.91 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm) 159.2, 144.3, 139.6, 134.4, 129.6, 128.4, 128.2, 127.9, 127.2, 113.6, 95.6, 74.0, 62.8, 55.3, 31.2, 29.0, 25.5, 20.2, 10.2. Anal calcd for $C_{23}H_{28}O_3$: C, 78.38; H, 8.01. Found: 78.30; H, 8.00.

3.17. **3h**

Oil; IR (neat) 3438, 2962, 2933, 2874, 2835, 1384, 1246, 1108, cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ (ppm) 7.69–7.64 (m, 4H), 7.61–7.58 (m, 1H), 7.44–7.40 (m, 1H), 6.95 (dd, $J_1 = 6.8$ Hz, $J_2 = 2.0$ Hz, 2H), 6.55 (s, 1H), 5.21 (d, $J = 3.4$ Hz, 1H), 4.42–4.36 (m, 1H), 3.77 (s, 3H), 1.49–1.40 (m, 1H), 1.35–1.26 (m, 1H), 0.60 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ (ppm) 159.5, 145.1, 138.0, 133.5, 133.1, 131.9, 130.2, 130.0, 129.8, 128.2, 124.7, 114.2, 71.2, 55.9, 29.0, 10.7. Anal calcd for $C_{18}H_{19}BrO_2$: C, 62.26; H, 5.52. Found: C, 62.18; H, 5.51.

3.18. **4h**

Oil; selected signals for the (*Z*) isomer: ^1H NMR (400 MHz, d_6-DMSO) δ (ppm) 7.05 (d, $J = 8.8$ Hz, 2H), 6.84 (d, $J = 8.8$ Hz, 2H), 6.03 (d, $J = 9.2$ Hz, 2H), 4.63 (d, $J = 4.1$ Hz, 2H), 3.71 (s, 3H); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ (ppm) 123.5, 113.8, 69.5, 29.7, 9.8; selected signals for (*E*) isomer: ^1H NMR (400 MHz, d_6-DMSO) δ (ppm) 6.89 (d, $J = 8.7$ Hz, 2H), 7.65 (d, $J = 8.7$ Hz, 2H), 6.06 (d, $J = 8.9$ Hz, 1H), 4.51 (d, $J = 5.1$ Hz, 1H); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ (ppm) 123.0, 113.1, 69.6, 30.5, 10.1.

3.19. **3i**

mp: 87–88 °C; IR (KBr) 3435, 2929, 1243, 1040 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.58 (dd, $J_1 = 6.8$ Hz, $J_2 = 2.1$ Hz, 2H), 7.47–7.32 (m, 5H), 7.11–6.94 (m, 3H), 4.73 (s, 2H), 3.88 (s, 3H), 1.82 (bs, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm) 159.3, 139.5, 137.2, 132.9, 129.8, 128.9, 128.4, 127.8, 127.2, 114.1, 60.3, 55.3; Anal calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.89; H, 6.70.

3.20. **3j**

Oil; IR (neat) 2970, 2929, 1241, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.57 (dd, $J_1 = 6.7$ Hz, $J_2 = 1.8$ Hz, 2H), 7.78–7.43 (m, 2H), 7.41–7.35 (m, 3H), 7.02 (s, 1H), 6.93 (dd, $J_1 = 6.7$ Hz, $J_2 = 1.8$ Hz, 2H), 4.77–4.70 (m, 2H), 4.44 (d, $J = 11.0$ Hz, 2H), 3.84 (s, 3H), 1.95–1.43 (m, 8H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 158.6, 136.9, 136.8, 133.5, 130.5, 128.5, 127.7, 127.1, 126.6, 113.3, 98.1, 64.6, 61.9, 54.8, 30.3, 25.0, 19.0. Anal Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.68; H, 7.45.

3.21. **3k**

mp: 60–61 °C; IR (KBr) 3502, 3058, 2930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.38–7.34 (m, 4H), 7.31–7.25 (m, 3H), 6.92–6.87 (m, 2H), 6.49 (s, 1H), 3.86 (s, 3H), 1.73 (bs, 1H), 1.39 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 158.6, 150.5, 138.9, 136.0, 130.1, 129.4, 128.8, 128.3, 126.9, 113.3, 74.4, 55.4, 31.3. Anal calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.65; H, 7.49.

3.22. **4k**

mp: 68–69 °C; IR (KBr) 3462, 3050, 2934 cm^{-1}; ^1H NMR (400 MHz, d_6–DMSO) δ (ppm) 7.40–7.29 (m, 3H), 7.17–7.12 (m, 2H), 7.06–7.02 (m, 2H), 6.85–6.84 (m, 2H), 6.17 (s, 1H), 4.54 (s, 1H), 3.72 (s, 3H), 1.05 (s, 6H); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ (ppm) 158.8, 140.6, 137.9, 137.5, 135.9, 130.2, 128.3, 128.1, 127.3, 114.1, 70.2, 55.6, 31.4 Anal calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.49; H, 7.50.

3.23. **3l**

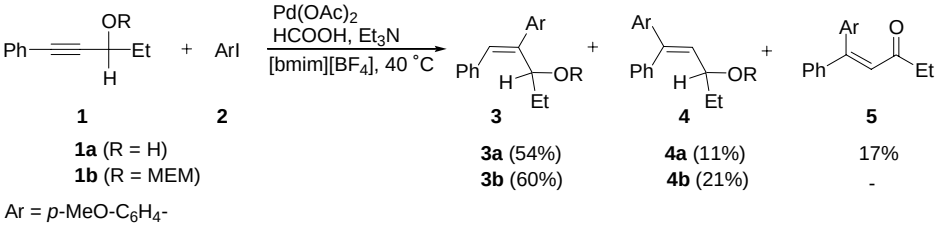
mp: 85–86 °C; IR (KBr) 3416, 3071, 2931, 1680 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ (ppm) 7.90 (d, $J = 8.4$ Hz, 2H), 7.59 (d, $J = 8.4$ Hz, 2H), 7.25 (dd, $J_1 = 6.6$ Hz, $J_2 = 2.1$ Hz, 2H), 6.90 (dd, $J_1 = 6.6$ Hz, $J_2 = 2.1$ Hz, 2H), 6.28 (s, 1H), 4.62 (s, 1H), 3.77 (s, 1H), 2.57 (s, 3H), 1.23 (s, 6H); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ (ppm) 197.4, 157.8, 151.9, 144.1, 136.7, 134.4, 129.8, 129.6, 128.3, 127.2, 112.8, 71.9, 55.0, 31.2, 26.6. Anal calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.30; H, 7.12.

3.24. **4l**

mp: 62–63 °C; IR (KBr) 3432, 3048, 2929, 1666 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ (ppm) 7.95 (d, $J = 8.1$ Hz, 2H), 7.30 (d, $J = 8.1$ Hz, 2H), 7.03 (d, $J = 8.8$ Hz, 2H), 6.84 (d, $J = 8.8$ Hz, 2H), 6.18 (s, 1H), 4.53 (s, 1H), 3.72 (s, 3H), 2.6 (s, 3H), 1.09 (s, 6H); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ (ppm) 198.1, 159.0, 146.2, 137.9, 137.3, 135.8, 135.5, 130.7, 128.3, 128.2, 114.2, 70.2, 55.7, 31.6, 27.2. Anal calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.30; H, 7.13.

3.25. **3n**

Oil; IR (neat) 3407, 2972, 1361, 1144 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ (ppm) 7.59 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz, 1H), 7.53–7.48 (m, 1H), 7.38–7.25 (m, 3H),



Scheme 2.

7.20–7.12 (m, 3H), 6.07 (s, 1H), 4.44 (s, 1H), 2.31 (s, 3H), 1.17 (s, 6H); ^{13}C NMR (100.6 MHz, d$_6$-DMSO) δ (ppm) 150.9, 141.0, 139.6, 135.4, 131.6, 131.4, 128.6, 128.2, 128.0, 127.8, 126.6, 122.9, 71.7, 30.9, 20.7. Anal calcd for $C_{19}H_{23}BrO$: C, 65.71; H, 6.68. Found: C, 65.80; H, 6.67.

3.26. *4n*

Oil; IR (neat) 3399, 2924, 1370, 1130 cm^{-1}; ^{1}H NMR (400 MHz, d$_6$-DMSO) δ (ppm) 7.64–7.60 (m, 1H), 7.43 (dt, $J_1 = 7.4$ Hz, $J_2 = 0.8$ Hz, 2H), 7.34–7.26 (m, 2H), 7.08 (d, $J = 8.3$ Hz, 2H), 7.02 (d, $J = 8.3$ Hz, 2H), 6.28 (s, 1H), 4.59 (s, 1H), 2.25 (s, 3H), 1.08 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100.6 MHz, d$_6$-DMSO) δ (ppm) 141.3, 139.0, 138.9, 137.0, 136.9, 133.3, 133.1, 130.0. 129.7, 128.0, 126.9, 124.6, 70.6, 31.3, 30.4, 21.4. $C_{19}H_{23}BrO$: C, 65.71; H, 6.68. Found: C: 65.65; H, 6.70.

3.27. *8*

mp: 73–74 °C; IR (KBr) 3048, 2977, 1378, 1250 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44 (dd, $J_1 = 6.8$ Hz, $J_2 = 2.2$ Hz, 2H), 7.15–7.06 (m, 2H), 6.96–6.88 (m, 4H), 6.69 (s, 1H), 5.23 (dd, $J_1 = 9.7$ Hz, $J_2 = 3.2$ Hz, 1H), 3.86 (s, 3H), 1.88–1.82 (m, 1H), 1.64–1.59 (m, 1H), 1.05 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 159.5, 151.6, 136.1, 129.9, 128.8, 126.6, 126.5, 123.4, 121.3, 117.8, 116.3, 114.3, 78.1, 55.4, 26.5, 10.3. Anal calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.10; H, 6.79.

3.28. *9*

mp: 93–94 °C (lit. mp: 93–94 °C) [7].

4. Results and discussion

To determine if the hydroarylation of propargylic alcohols in ionic liquids could provide a higher regioselectivity than in classical molecular solvents, we first examined the reaction of **1a** with *p*-iodoanisole in [bmim][BF$_4$] (Scheme 2). The reaction was carried out in the presence of 5 mol% of $Pd(OAc)_2$, 2 eq. of HCOOH, and 3 eq. of Et_3N. Under these conditions, **3a** and **4a** were isolated in 54 and 11% yields, respectively, after 30 h along with a 17% yield of **5**, the latter most probably derived from the carbopalladation adduct leading to **4a** via β-elimination of HPd species and isomerization of the resultant allenyl alcohol [8]. Employing the MEM derivative **1b** as the starting alkyne provided a cleaner reaction mixture and a higher regioselectivity.

Table 1
Solvent effect on the palladium-catalyzed hydroarylation of **1b** with *p*-iodoanisole[a]

Solvent	Total yield (%)[b,c]	**3b**/**4b**
Toluene	38 (51)	70/30
THF	51 (37)	76/24
DMF	55 (37)	66/34
[bmim][BF$_4$]	81	76/24

[a] Reactions were carried out on a 0.469 mmol scale by using 1 eq. of **1a**, 1.5 eq. of *p*-iodoanisole, 5 mol% of $Pd(OAc)_2$, 2 eq. of HCOOH, and 3 eq. of Et_3N, in 1 ml of the selected solvent at 40 °C for 30 h.
[b] Yields are given for isolated products.
[c] Figures in parentheses refer to the recovered propargylic alcohol.

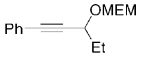
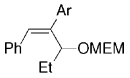
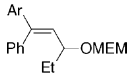
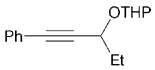
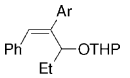
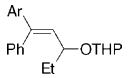
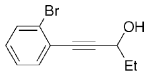
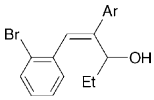
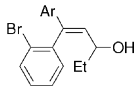
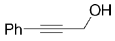
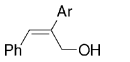
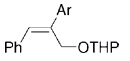
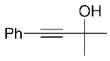
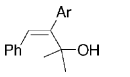
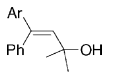
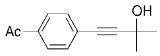
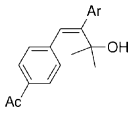
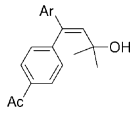
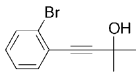
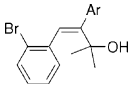
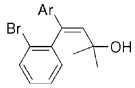
Compound **1b** was then used when, for comparison, we carried out the same reaction in solvents displaying widely different polarities[1] and coordinating ability such as toluene, THF, and DMF. The results are summarized in Table 1 and do not provide a simple explanation for the effect of the solvents investigated on the reaction outcome, but highlight the importance of [bmim][BF$_4$] for attaining the best results. Toluene and THF, with the lowest dielectric constants, give good isomeric ratios; however, the rates of reaction were very low. In DMF, with the highest dielectric constant, the reaction rate was still very low and the isomeric ratio was the lowest among molecular solvents. The best result both in term of rate of reaction and regioselectivity was observed when the reaction was carried out in [bmim][BF$_4$].

It is also remarkable that $Pd(OAc)_2$ in the absence of phosphine ligands can successfully be used in the hydroarylation of alkynes in [bmim][BF$_4$], though it has been reported that palladium without phosphine ligands displays negligent activity in the Heck reaction in the same solvent [4].

On the basis of the above studies, the hydroarylation reaction was extended to other propargylic alcohols and their MEM or THP derivatives and aryl iodides. Our experimental results are summarized in Table 2. The ionic liquid can be recovered and recycled using standard extraction

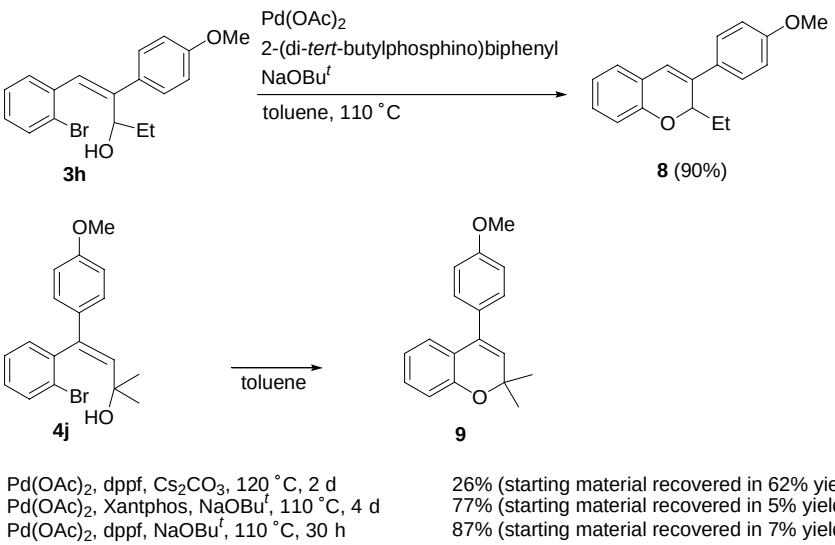
[1] Dielectric constants, which for the three molecular solvents investigated range from 2.4 to 36.7, can be used as a quantitative measure of the solvent polarity.

Table 2
The palladium-catalyzed hydroarylation of propargylic alcohols in [bmim][BF_4][a]

Entry	Propargylic alcohol **1**		Aryl iodide **2** Ar	*t* (h)	Overall yield (%)[b]			Isomeric ratio[c]
					3	**4**		
1		**1b**	*p*-MeO–C_6H_4	30			81	**3b/4b** 76/24
2		**1b**	*p*-MeO–C_6H_4	30			49	**3b/4b** 66/34[d]
3		**1b**	*p*-EtOOC–C_6H_4	26			85[e]	**3c/4c** 75/25
4		**1b**	*p*-EtOOC–C_6H_4	26			79[e]	**3c/4c** 66/34[d]
5		**1b**	Ph	24			79	**3d/4d** 71/29
6		**1b**	Ph	24			71	**3d/4d** 66/34[d]
7		**1b**	*p*-Me–C_6H_4	24			80	**3e/4e** 75/25
8		**1b**	*p*-MeCO–C_6H_4	48			90[e]	**3f/4f** 72/28[d]
9		**1c**	*p*-MeO–C_6H_4	24			91	**3g/4g** 77/23
10		**1c**	*p*-MeO–C_6H_4	24			76	**3g/4g** 68/32[d]
11		**1d**	*p*-MeO–C_6H_4	24			76	**3h/4h** 75/25[f]
12		**1e**	*p*-MeO–C_6H_4	1			51	**3i**
13		**1f**	*p*-MeO–C_6H_4	12			53	**3j**[g]
14		**1g**	*p*-MeO–C_6H_4	26			78	**4k/3k** 83/17
15		**1h**	*p*-MeO–C_6H_4	31			81	**4l/3l** 72/28
16		**1h**	*p*-MeO–C_6H_4	31			91	**4l/3l** 64/36[d]
17		**1i**	*p*-MeO–C_6H_4	24			95	**4m/3m** 80/20
18		**1i**	*p*-MeO–C_6H_4	48			84	**4m/3m** 81/19[d]
19		**1i**	*p*-Me–C_6H_4	48			75	**4n/3n** 77/23

[a] Unless otherwise stated, reactions were carried out on a 0.469 mmol scale by using 1 eq. of **1**, 1.5 eq. of aryl iodide **2**, 5 mol% of $Pd(OAc)_2$, 2 eq. of HCOOH, and 3 eq. of Et_3N, in 1 ml of [bmim][BF_4] at 40 °C.
[b] Yields are given for isolated products.
[c] Isomeric ratios were calculated on isolated products.
[d] In DMF.
[e] With 3 eq. of aryl iodide.
[f] **4h** was isolated as an approximately *E*/*Z* 30/70 stereoisomeric mixture.
[g] A compound whose NMR data are consistent with a 1,3-diene derivative formed through multicarbopalladation reaction was isolated in 12% yield. Its regiochemistry was not established.

protocols followed by vacuum drying, with only small mechanical losses. No evidence of ionic liquid degradation was attained by NMR spectra of the recovered solvent. Its use provided no appreciable decrease in yield or regioselectivity. Notably, when comparison with DMF—one of the most commonly used solvents in this chemistry—was made (Table 1, compare entry 1 with entry 2; entry 3 with entry 4; entry 5 with entry 6; entry 9 with entry 10; entry 15 with entry 16), [bmim][BF_4] provided the highest regioselectivity. And when comparable regioselectivity was achieved (Table 1, compare entry 17 with entry 18), the reaction in [bmim][BF_4] gave a higher yield. According to our previous findings [8,9] and related reactions [10] proceeding through a carbopalladation step, with tertiary propargylic alcohols (Table 2, entries 14–19) the main hydroarylation products contain the new carbon–carbon bond close to the aryl substituent of the starting alkyne. Most probably, steric effects as well as coordination of the oxygen to the incoming palladium during the carbopalladation step can account for the directing effect of the tertiary hydroxy group. With secondary propargylic alcohols the regioselectivity is still good, but the main reaction products contain the added aryl group close



Scheme 3.

to the hydroxy or ether group (Table 1, entries 1–11). In this case, the aryl group of the starting alkyne apparently exerts more influence in directing the carbopalladation than the secondary hydroxy group does. The less branched primary propargylic alcohol **1e** and its THP derivative **1f** gave complex hydroarylation mixtures from which exclusively one regioisomer was isolated, though the yields were not very high (Table 1, entries 12 and 13). However, it seems likely that these results indicate rather a tendency of isomeric carbopalladation adducts (i.e., carbopalladation adducts with the palladium atom close to the oxygen) and products derived from them to enter other reaction pathways than a very high regioselectivity. For example, when **1f** was subjected to our standard hydroarylation conditions, a product whose NMR data are consistent with a 1,3-diene derivative, most probably formed through a multicarbopalladation reaction, was isolated in 12% yield (its regiochemistry was not established).

The results obtained with **1d** and **1i** are particularly rewarding because these compounds have been designed as building blocks for the synthesis of substituted chromenes through a process involving a palladium-catalyzed hydroarylation–cyclization sequence. As examples, the arylchromenes **8** and **9** were prepared in high yields through the palladium-catalyzed cyclization of the corresponding hydroarylation products under the conditions developed by Buchwald and co-workers [11] for the intramolecular C–O bond formation (Scheme 3).

In conclusion, we have shown that the palladium-catalyzed hydroarylation of propargylic alcohols can be successfully carried out in [bmim][BF_4] without using phosphine ligands. The results presented in this paper suggest that there exists an "ionic liquid effect" influencing the regioselectivity and/or the rate of this reaction. Although mixtures of regioisomers are still obtained, the observed effect is significant and holds promise as a useful additional tool for controlling the regiochemical outcome of the process. Work along this line is in progress.

Acknowledgements

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