Palladium-Catalyzed C-C Bond Formation from β-Chloroacroleins in Aqueous Media

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Received 30 January 2001; revised 2 February 2001

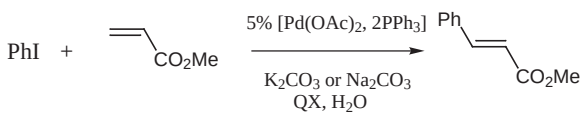
Dedicated to Prof. Emeritus D. Cagniant on the occasion of her 80th birthday

Abstract: The Suzuki coupling of several β-chloroacroleins with arylboronic acids was successfully performed with good yields under mild conditions (3 h at 45 °C) in aqueous media without any organic co-solvent.

Key words: aqueous media, boronic acids, β-chloroacroleins, palladium catalysis, Suzuki coupling

In 1981, Suzuki[1] described the palladium-catalyzed cross-coupling reaction between phenylboronic acids and aryl halides. This reaction constitutes a powerful and general methodology for the formation of C-C bonds. The availability of the reagents and the mild experimental conditions all contribute to the versatility of this reaction.[2] This method of C-C bond formation offers several advantages: boronic acids are largely unaffected by the presence of water and tolerate a broad range of functional groups. Moreover, the inorganic byproduct is non-toxic and can be easily removed from the reaction mixture, thereby making the Suzuki reaction suitable not only for laboratory scale but also for industrial processes.

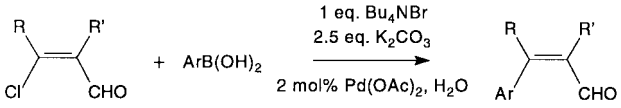
Using water as solvent is safe and inexpensive. Therefore, methods for carrying out organic reactions in aqueous media are of heightened interest. During the past ten years, palladium-catalyzed cross-coupling reactions have been imported into aqueous media, but most of the time water was only used as co-solvent.[3–6] Jeffery[7] has shown that palladium-catalyzed cross-coupling reactions can be performed in water alone, without any organic solvent, under mild conditions, and in the presence of a tetraalkylammonium salt (Scheme 1). In 1997, Badone[8] found that tetrabutylammonium bromide in water, without organic co-solvent, considerably enhances the rate of the Suzuki coupling of aryl bromides with aryl and vinyl boronic acids.



QX = *n*-Bu_4NCl, *n*-Bu_4NBr or *n*-Bu_4NHSO_4

Scheme 1

However, to our knowledge, few publications report cross-coupling under those conditions. Recently, 5-aryl furfurals and aryl thiophene-2-carboxaldehydes were synthesized via palladium-catalyzed C-C bond formation in aqueous media at room temperature.[9] We were greatly interested in this mild procedure and, as a part of our synthetic project, focussed on the synthesis of new tetracyclic systems, we examined the behaviour of a series of β-chloroacroleins. Those compounds were coupled with a wide variety of boronic acids in the presence of 2 mol% of palladium(II) acetate, tetrabutylammonium bromide and potassium carbonate in water (Scheme 2). No organic solvents in addition to water were used. All reactions were almost complete after 3 h at 45 °C.



Scheme 2

Although aryl chlorides are less reactive due to the higher energy required for the oxidative insertion of the palladium catalyst into the C-Cl bond,[10] Suzuki coupling of vinyl chlorides is almost easier. Moreover, the presence of an electron-withdrawing group leads to an increase of the reaction rate allowing the use of derivatives such as 3-chloroenones.[11] Thus, β-chloroacroleins are highly activated substrates and constitute good partners for coupling. They were prepared with good to excellent yields by a Vilsmeier-Haack-Arnold[12] reaction on the corresponding ketones. This kind of compounds, widely used for the synthesis of heterocyclic systems,[13] also gives good yields in coupling with boronic acids under mild conditions (Table).

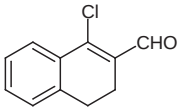
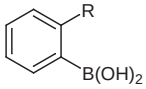
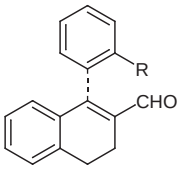
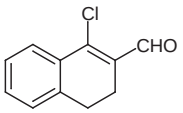
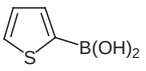
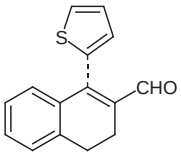
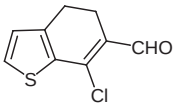
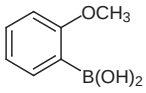
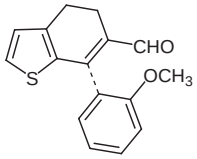
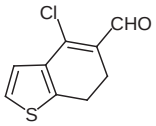
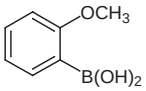
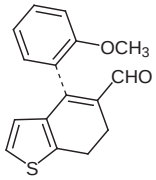
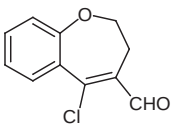
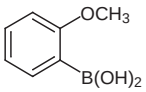
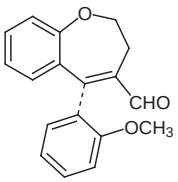
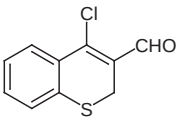
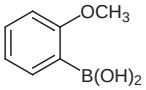
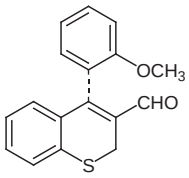
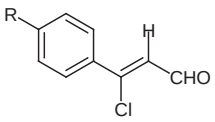
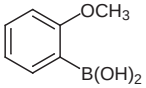
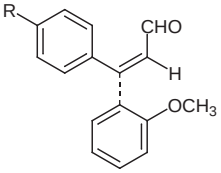
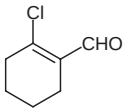
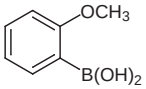
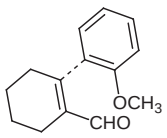
Easy access to β-chloroacroleins and boronic acids may give this methodology a very broad application.

$Pd(OAc)_2$ was purchased from Aldrich and Bu_4NBr from Lancaster. β-Chloroacroleins[12] and boronic acids[14] were prepared according to literature procedures. Melting points were determined on a Kofler bench and are uncorrected. ^1H and ^{13}C NMR spectra were recorded

Synthesis 2001, No. 5, 12 04 2001. Article Identifier:
1437-210X,E;2001,0,05,0755,0758,ftx,en;Z01501SS.pdf.

ISSN 0039-7881

Table Coupling of Aryl Boronic Acids and β-Chloroacroleins in Water in the Presence of Bu_4NBr

Entry	β-Chloroacrolein	Boronic acid	Product	Yield (%)[a]
1a-1c				66 (R = H) 65 (R = CH_3) 75 (R = OCH_3)
2				69
3				62
4				65
5				86
6				87
7a,7b				50 (R = H) 51 (R = OCH_3)
8				59

[a] Isolated yield by column chromatography.

on a AC Bruker 250 MHz spectrometer in $CDCl_3$. Infrared spectra were measured on a Perkin-Elmer 881 spectrometer. Mass spectra were obtained on a Hewlett-Packard 5971 A GCMS instrument with an ionization voltage of 70 eV.

Representative Procedure

β-Chloroacrolein (2.59 mmol, 1 equiv), boronic acid (2.83 mmol, 1.1 equiv), tetrabutylammonium bromide (2.60 mmol, 1 equiv), palladium acetate (0.053 mmol, 2 mol%) and potassium carbonate (6.45 mmol, 2.5 equiv) were added to a 10 mL round-bottom flask.

Deionized H_2O (5 mL) was added, and the reaction was stirred vigorously for 3 h at 45 °C. The reaction mixture became dark and non-homogenous. Then the mixture was diluted with 15 mL H_2O, and the product was extracted with EtOAc (3 × 30 mL). The organic products were separated, and the free floating material as well as the syrupy layer was collected. The organic products were stirred over charcoal for 30 min followed by drying over sodium sulfate. Then the organic products were filtered and concentrated.

1-Phenyl-3,4-dihydronaphtalene-2-carboxaldehyde (**1a**)
Yellow solid, purified by column chromatography on silica gel using CH_2Cl_2-C_6H_{12} (1:1) as eluent, mp 84 °C.

IR (KBr): ν = 1660 (CO) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.69 (m, 2H), 2.89 (m, 2H), 6.86 (d, 1H, *J* = 7.87 Hz), 7.13 (m, 1H), 7.27–7.34 (m, 4H), 7.45–7.48 (m, 3H), 9.58 (s, CHO).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.29 (CH_2), 27.62 (CH_2), 126.60 (CH), 127.80 (CH), 128.27 (CH), 128.43 (CH), 130.00 (CH), 130.17 (CH), 130.46 (CH), 134.39 (C), 135.10 (C), 135.28 (C), 138.62 (C), 154.37 (C), 193.34 (CHO).

GC-MS: *m/z* (%): 234 (100), 205 (54), 128 (30).

1-(*o*-Tolyl)-3,4-dihydronaphtalene-2-carboxaldehyde (**1b**)
Yellow solid, purified by column chromatography on silica gel using CH_2Cl_2-C_6H_{12} (3:2) as eluent, mp 54 °C.

IR (KBr): ν = 1660 (CO) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.08 (s, 3H, CH_3), 2.62 (m, 1H), 2.79 (m, 1H), 2.94 (m, 2H), 6.74 (d, 1H, *J* = 7.58 Hz), 7.11–7.18 (m, 3H), 7.24–7.36 (m, 4H), 9.48 (s, CHO).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 19.62 (CH_3), 19.84 (CH_2), 27.57 (CH_2), 125.72 (CH), 126.80 (CH), 127.48 (CH), 127.89 (CH), 128.49 (CH), 129.16 (CH), 130.24 (CH), 130.49 (CH), 134.30 (C), 134.39 (C), 134.80 (C), 136.77 (C), 138.43 (C), 154.25 (C), 193.12 (CHO).

GC-MS: *m/z* (%): 248 (30), 233 (100).

1-(*o*-Anisyl)-3,4-dihydronaphtalene-2-carboxaldehyde (**1c**)
Yellow solid, purified by column chromatography on silica gel using CH_2Cl_2 as eluent, mp 82 °C.

IR (KBr): ν = 1660 (CO) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.69 (m, 2H), 2.93 (m, 2H), 3.71 (s, 3H, CH_3O), 6.81 (d, 1H, *J* = 7.76 Hz), 7.01 (d, 1H, *J* = 8.16 Hz), 7.06 (d, 1H, *J* = 7.72 Hz), 7.10–7.17 (m, 2H), 7.26 (m, 2H), 7.44 (ddd, 1H, *J* = 8.06, 7.69 and 1.81 Hz), 9.53 (s, CHO).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.07 (CH_2), 27.56 (CH_2), 55.60 (CH_3O), 110.97 (CH), 120.45 (CH), 124.10 (C), 126.56 (CH), 127.38 (CH), 127.76 (CH), 129.90 (CH), 130.04 (CH), 131.91 (CH), 134.61 (C), 134.86 (C), 138.42 (C), 152.05 (C), 157.51 (C), 193.50 (CHO).

GC-MS: *m/z* (%): 264 (15), 233 (100), 202 (21).

1-(2-Thienyl)-3,4-dihydronaphtalene-2-carboxaldehyde (**2**)
Yellow solid, purified by column chromatography on silica gel using CH_2Cl_2-C_6H_{12} (1:1) as eluent, mp 82 °C.

IR (KBr): ν = 1655 (CO) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.69 (m, 2H), 2.90 (m, 2H), 7.10–7.14 (m, 2H), 7.16–7.35 (m, 4H), 7.52 (dd, 1H, *J* = 4.88 and 1.07 Hz), 9.79 (s, CHO).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.74 (CH_2), 27.39 (CH_2), 126.74 (CH), 127.02 (CH), 127.75 (CH), 128.13 (CH), 130.40 (CH), 130.60 (CH), 130.70 (CH), 134.98 (C), 135.36 (C), 136.91 (C), 138.35 (C), 146.69 (C), 192.87 (CHO).

GC-MS: *m/z* (%): 240 (100), 211 (38), 178 (60), 165 (30), 128 (28).

7-(*o*-Anisyl)-4,5-dihydrobenzo[b]thiophene-6-carboxaldehyde (**3**)
Yellow solid, purified by column chromatography on silica gel using CH_2Cl_2-C_6H_{12} (3:2) as eluent, mp 126 °C.

IR (KBr) cm^{-1}: 1640 (CO)

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.81 (m, 2H), 2.90 (m, 2H), 3.76 (s, 3H, CH_3O), 6.97 (d, 1H, *J* = 4.81 Hz), 6.96–7.06 (m, 2H), 7.25 (dd, 1H, *J* = 7.14 and 1.68 Hz), 7.36 (d, 1H, *J* = 4.92 Hz), 7.43 (ddd, 1H, *J* = 7.91, 7.69 and 1.59 Hz), 9.47 (s, CHO).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.75 (CH_2), 23.42 (CH_2), 55.61 (CH_3O), 111.15 (CH), 120.40 (CH), 124.31 (C), 127.70 (CH), 128.76 (CH), 130.07 (C), 130.52 (CH), 131.25 (CH), 138.09 (C), 141.32 (C), 146.70 (C), 157.09 (C), 192.22 (CHO).

GC-MS: *m/z* (%): 270 (22), 239 (100), 208 (15).

4-(*o*-Anisyl)-6,7-dihydrobenzo[b]thiophene-5-carboxaldehyde (**4**)
Yellow solid, purified by column chromatography on silica gel using CH_2Cl_2-C_6H_{12} (3:2) as eluent, mp 81 °C.

IR (KBr): ν = 1685 (CO) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.85 (m, 2H), 3.01 (m, 2H), 3.74 (s, 3H, CH_3O), 6.52 (d, 1H, *J* = 5.19Hz), 6.97–7.05 (m, 3H), 7.17 (dd, 1H, *J* = 7.37 and 1.70 Hz), 7.56 (ddd, 1H, *J* = 7.88, 7.71 and 1.73 Hz), 9.49 (s, CHO).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.07 (CH_2), 22.83 (CH_2), 55.53 (CH_3O), 110.98 (CH), 120.35 (CH), 122.06 (CH), 124.37 (C), 126.11 (CH), 130.05 (CH), 130.34 (C), 131.32 (CH), 136.65 (C), 142.35 (C), 147.92 (C), 157.09 (C), 192.84 (CHO).

GC-MS: *m/z* (%): 270 (20), 239 (100).

5-(*o*-Anisyl)-2,3-dihydro-1-benzoxepine-4-carboxaldehyde (**5**)
Yellow solid, purified by column chromatography on silica gel using CH_2Cl_2-C_6H_{12} (1:1) as eluent, mp 77 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.74 (m, CH_2), 3.67 (s, CH_3O), 4.58 (m, CH_2), 6.84 (dd, 1H, *J* = 7.83 and 1.57 Hz), 6.95–7.03 (m, 3H), 7.10–7.15 (m, 2H), 7.31 (ddd, 1H, *J* = 7.68, 7.57 and 1.57 Hz), 7.41 (ddd, 1H, *J* = 7.92, 7.54 and 1.76 Hz), 9.56 (s, CHO).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 25.20 (3-CH_2), 55.65 (CH_3O), 79.46 (2-CH_2O), 111.28 (CH), 120.39 (CH), 122.41 (CH), 123.34 (CH), 126.02 (C), 130.41 (CH), 130.54 (CH), 130.63 (CH), 132.78 (CH), 133.83 (C), 137.42 (C), 153.97 (C), 157.06 (C), 157.61(C), 192.02 (CHO).

GC-MS: *m/z* (%): 280 (10), 249 (100).

4-(*o*-Anisyl)-thiochromen-3-carboxaldehyde (**6**)
Yellow solid, purified by column chromatography on silica gel using CH_2Cl_2 as eluent, mp 112 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.71 (s, CH_3O), 3.76 (s, CH_2S), 6.85 (dd, 1H, *J* = 7.90 and 1.24 Hz), 6.98–7.07 (m, 3H), 7.11 (dd, 1H, *J* = 7.38 and 1.92 Hz), 7.21 (ddd, 1H, *J* = 7.46, 7.62 and 1.57 Hz), 7.38–7.48 (m, 2H), 9.43 (s, CHO).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 22.07 (CH_2S), 55.61 (CH_3O), 111.07 (CH), 120.53 (CH), 124.17 (C), 125.44 (CH), 127.70 (CH), 128.78 (C), 129.58 (CH), 130.06 (CH), 130.49 (CH), 132.03 (CH), 134.44 (C), 136.32 (C), 151.42 (C), 157.50 (C), 191.48 (CHO).

GC-MS: *m/z* (%): 282 (34), 251 (100).

3-(*o*-Anisyl)-3-phenyl-propenal (**7a**)
Orange solid, purified by column chromatography on silica gel using CH_2Cl_2 as eluent, mp 87 °C.

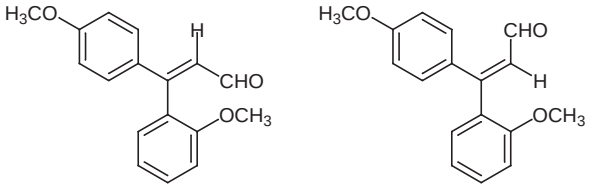
^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.69 (s, 3H, CH_3O), 6.65 (d, 1H, *J* = 8.05 Hz), 7.02–7.08 (m, 2H), 7.19 (dd, 1H, *J* = 5.75 and 1.70 Hz), 7.36 (s, 5H), 7.45 (m, 1H), 9.45 (d, CHO, *J* = 8.05 Hz)

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 55.62 (CH_3O), 111.30 (CH), 120.49 (CH), 125.43 (C), 127.39 (CH), 128.52 (CH), 130.13 (CH), 130.61 (CH), 131.92 (CH), 139.20 (C), 157.26 (C), 158.71 (C), 193.69 (CHO).

GC-MS: *m/z* (%): 237 (10), 207 (100).

3-(*o*-Anisyl)-3-(*p*-anisyl)-propenal (**7b**)
Orange solid, purified by column chromatography on silica gel using CH_2Cl_2 as eluent, mp 80 °C.

The two isomers could not be separated neither by column chromatography on silica gel nor by gas chromatography, but they can be distinguished by NMR.



A (18%) **B** (82%)

Figure

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.69 (s, CH_3O, **A**), 3.71 (s, CH_3O, **B**), 3.83 (s, CH_3O, **B**), 3.86 (s, CH_3O, **A**), 6.49 (d, 1H, *J* = 7.97 Hz, **A**), 6.62 (d, 1H, *J* = 7.98 Hz, **B**), 6.86 (d, 2H, *J* = 9.02 Hz, **B**), 6.92–7.23 (m, 3H **B** + 6H **A**), 7.31–7.35 (m, 2H **B** + 2H **A**), 7.44 (m, 1H, **B**), 9.38 (d, CHO, *J* = 8.16 Hz, **B**), 9.65 (d, CHO, *J* = 8.15 Hz, **A**).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 55.30 (CH_3O, **A**), 55.33 (CH_3O, **B**), 55.61 (CH_3O, **A**), 55.64 (CH_3O, **B**), 111.21 (CH, **B**), 111.71 (CH, **A**), 113.45 (CH, **A**),113.99 (CH, **B**), 120.44 (CH, **B**), 120.47 (CH, **A**), 125.52 (CH, **B**), 129.11 (CH, **B**), 129.90 (CH, **A**), 130.43 (CH, **B**), 130.55 (C, **B**), 130.93 (CH, **A**), 131.27 (C, **B**), 131.44 (CH, **A**), 131.75 (CH, **A**), 131.78 (CH, **B**), 157.21 (C, **B**), 157.59 (C, **A**), 158.35 (C, **B**), 160.01 (C, **A**), 161.46 (C, **B**), 193.72 (CHO, **B**), 193.88 (CHO, **A**).

GC-MS: *m/z* (%): 268 (14), 237 (100).

2-(*o*-Anisyl)-cyclohexen-1-carboxaldehyde (**8**)
Orange oil, purified by column chromatography on silica gel using C_6H_{12}-EtOAc (8:2) as eluent.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.77 (m, 5H), 2.34 (m, 3H), 3.79 (s, 3H, CH_3O), 6.90–6.98 (m, 2H), 7.06 (dd, 1H, *J* = 7.32 and 1.78 Hz), 7.32 (ddd, 1H, *J* = 8.20, 7.51 and 1.82 Hz), 9.39 (s, CHO).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.52 (CH_2), 21.93 (CH_2), 22.28 (CH_2), 32.95 (CH_2), 55.38 (CH_3O), 110.77 (CH), 120.18 (CH), 128.28 (C), 129.27 (CH), 130.11 (CH), 135.54 (C), 156.23 (C), 157.18 (C), 193.57 (CHO).

GC-MS: *m/z* (%): 216 (5), 185 (100).

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