4-Dimethylaminopyridine, an efficient ligand for the Heck reaction in aqueous media

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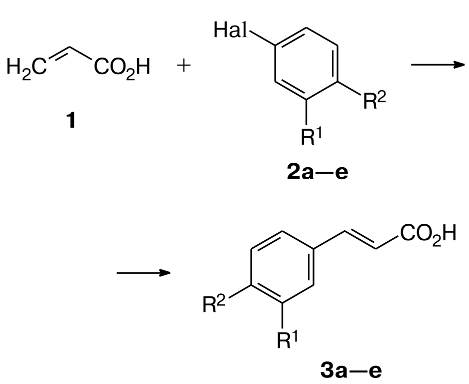
The Heck reaction, a palladium-catalyzed cross-coupling of olefins with aryl and vinyl halides,[1,2] is widely employed in modern organic synthesis for preparation of alkenes containing virtually any functional groups.[3] The reaction is usually carried out in organic solvents with prolonged heating in the presence of palladium complexes with phosphine ligands (1—5 mol.%) and an appropriate base. In recent years, catalysts based on phosphorus-,[4] sulfur-,[5] and nitrogen-containing[6] palladacycles and carbene ligands[7] have been proposed instead of palladium complexes with phosphine. However, even in the presence of new, more efficient catalysts, the reaction is completed at 100—150 °C in 24—90 h (see Ref. 8). For this reason, a search for active palladium catalysts is still among the most important tasks in the study of catalytic reactions.[9] Another promising line (from the practical standpoint) in this area is the use of water instead of toxic and difficult-to-recover organic solvents, because water is the most accessible, safe, and ecologically pure solvent.[10]

Here we showed for the first time, with reactions of acrylic acid **1** with aryl halides **2** as examples (Scheme 1), that a complex of palladium dichloride with 4-dimethylaminopyridine (DMAP) $PdCl_2(DMAP)_4$ is an efficient catalyst for the Heck reaction in water and aqueous ethylene glycol. The catalytic activity of the complex was so high that reactions of water-soluble (in the presence of a base) 4-iodobenzoic (**2a**) and 5-iodosalicylic acids (**2b**) in water were completed at 100 °C in 4 and 2 min, respectively, the catalyst concentration being 0.1 mol.%. Bromobenzoic acids (*e.g.*, **2c**) reacted with acrylic acid under analogous conditions; however, the reaction duration was 50 min. In addition, sodium formate (4.3 mol.%) should be used as a promoter.

The reactions with water-insoluble aryl bromides **2d,e** were carried out in aqueous ethylene glycol ($HOCH_2CH_2OH : H_2O = 1 : 1$) at 111 °C. The reaction with 4-bromoacetophenone **2d** containing a strong electron-withdrawing substituent in the presence of the catalyst (0.4 mol.%) was completed in 10 min, producing (*E*)-3-(4-acetylphenyl)prop-2-enoic acid **3d** in 93% yield as the sole product, while in the case of 4-bromoanisole **2e** with an electron-donating methoxy group, the reaction time increased to 1.4 h (the yield of product **3e** was 91%).

Scheme 1



Reagents and conditions: $PdCl_2(DMAP)_4$ (0.1—0.4 mol.%), K_2CO_3, H_2O or $H_2O—HOCH_2CH_2OH$ (1 : 1), 100 or 111 °C

2, 3	R^1	R^2	Hal	Yield of **3** (%)
a	H	CO_2H	I	86
b	CO_2H	OH	I	97
c	CO_2H	H	Br	85
d	H	Ac	Br	93
e	H	OMe	Br	91

According to the literature data,[11] a comparable catalytic activity in the Heck reaction is exhibited by a complex of $Pd(OAc)_2$ with *N*-phenylurea (DMF, 0.1 mol.% Pd, 130 °C, 2—6 h, 81—99%). However, the reaction time is absolutely independent of the nature of the substituent in the aromatic ring of aryl halide and in some cases, aryl iodides are substantially less reactive than the corresponding aryl bromides.

Tetrakis(4-dimethylaminopyridine)palladium(II) dichloride. A solution of 4-dimethylaminopyridine (1.2 g, 9.8 mmol) in MeCN (50 mL) was added to $PdCl_2(MeCN)_2$ (0.572 g,

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2.2 mmol). The mixture was refluxed for 10 min. Then ethanol (10 mL) was added and reflux was continued for an additional 10 min. The solvent was removed in a rotary evaporator. The solid residue was washed with acetonitrile (5×10 mL) on a Schott glass filter and dried in air. Tetrakis(4-dimethylaminopyridine)palladium(II) dichloride was obtained as a white powder. The yield was 1.409 g (96%), decomp. at 295—300 °C. Found (%): C, 50.84; H, 6.21; N, 16.67. $C_{28}H_{40}Cl_2N_8Pd$. Calculated (%): C, 50.50; H, 6.05; N, 16.83. ^{1}H NMR (400 MHz, D_2O), δ: 2.19 (br.s, 6 H, Me); 6.10 (br.s, 2 H, H(3), H(5)); 8.72 (br.s, 2 H, H(2), H(6)). ^{13}C NMR (100 MHz, D_2O), δ: 37.88 (Me); 108.52 (C(3), C(5)); 149.03 (C(2), C(6)); 154.16 (C(4)), DMAP. ^{1}H NMR (400 MHz, D_2O), δ: 2.66 (s, 6 H, Me); 6.25 (dd, 2 H, H(3), H(5), J = 5.1 Hz, J = 1.6 Hz); 7.81 (dd, 2 H, H(2), H(6), J = 5.1 Hz, J = 1.5 Hz). ^{13}C NMR (D_2O, 100 MHz), δ: 38.01 (Me); 106.57 (C(3), C(5)); 147.87 (C(2), C(6)); 154.66 C(4)).

(*E*)-3-(4-Acetylphenyl)prop-2-enoic acid (3d). An aqueous solution of K_2CO_3 (c = 3 mol L^{-1}, 5 mL, 15 mmol), ethylene glycol (5 mL), acrylic acid (0.91 mL, 13.3 mmol), EtOH (0.5 mL), sodium formate (30 mg, 0.44 mmol, 4.3 mol.%), and $PdCl_2(DMAP)_4$ (26.4 mg, 0.04 mmol) were added to 4-bromoacetophenone **2d** (2.02 g, 10.15 mmol). The mixture was carefully stirred for 5 min and refluxed until palladium black precipitated. The cooled solution was acidified to pH 1. The precipitate that formed was filtered off, washed with water (30 mL), and dried. (*E*)-3-(4-Acetylphenyl)prop-2-enoic acid **3d** was obtained as a white powder. The yield was 1.79 g (93%), m.p. 224—225 °C (*cf.* Ref. 12: m.p. 223—225 °C). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.53 (s, 3 H, Me); 6.59 (d, 1 H, C(8)H, J = 16.2 Hz); 7.59 (d, 1 H, C(7)H, J = 16.2 Hz); 7.73 (d, 2 H, C(2)H, C(6)H, J = 8.1 Hz); 7.90 (d, 2 H, C(3)H, C(5)H, J = 8.1 Hz); 12.55 (br.s, 1 H, OH).

4-[(*E*)-2-Carboxyvinyl]benzoic acid (3a) was obtained analogously in water at 100 °C, without addition of sodium formate or ethanol. The yield was 86%, m.p. 358—360 °C (*cf.* Ref. 13: m.p. 363 °C). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 6.61 (d, 1 H, C(8)H, J = 16.2 Hz); 7.62 (d, 1 H, C(7)H, J = 16.2 Hz); 7.76 (d, 2 H, C(2)H, C(6)H, J = 8.3 Hz); 7.94 (d, 2 H, C(3)H, C(5)H, J = 8.3 Hz); 12.82 (br.s, 2 H, OH).

5-[(*E*)-2-Carboxyvinyl]-2-hydroxybenzoic acid (3b) was obtained analogously in water at 100 °C, without addition of sodium formate or ethanol. The yield was 97%, m.p. 275—277 °C (*cf.* Ref. 14: m.p. 279 °C). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 6.37 (d, 1 H, C(8)H, J = 15.9 Hz); 6.96 (d, 1 H, C(5)H, J = 8.6 Hz); 7.53 (d, 1 H, C(7)H, J = 15.9 Hz); 7.84 (dd, 1 H, C(6)H, J = 8.8 Hz, J = 2.3 Hz); 7.99 (d, 1 H, C(2)H, J = 2.0 Hz); 12.11 (br.s, 2 H, OH).

3-[(*E*)-2-Carboxyvinyl]benzoic acid (3c) was obtained analogously in water at 100 °C, without addition of ethanol. The yield was 85%, m.p. 284—286 °C (*cf.* Ref. 15: m.p. 278—280 °C). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 6.57 (d, 1 H, C(8)H, J = 16.2 Hz); 7.52 (m, 1 H, C(5)H, J = 7.8 Hz); 7.64 (d, 1 H, C(7)H, J = 15.9 Hz); 7.93 (m, 2 H, C(4)H, C(6)H); 8.14 (s, 1 H, C(2)H); 12.80 (br.s, 2 H, OH).

(*E*)-3-(4-Methoxyphenyl)prop-2-enoic acid (3e) was obtained analogously. The yield was 91%, m.p. 176—177 °C (*cf.* Ref. 15: m.p. 174 °C). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 3.76 (s, 3 H, Me); 6.36 (d, 1 H, C(8)H, J = 15.9 Hz); 6.94 (d, 2 H, C(3)H, C(5)H, J = 8.6 Hz); 7.55 (d, 1 H, C(7)H, J = 16.2 Hz); 7.60 (d, 2 H, C(2)H, C(6)H, J = 8.8 Hz); 12.22 (br.s, 1 H, OH).

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