A comparative study of hydroxy and carboxylate functionalized imidazolium and benzimidazolium salts as precursors for NHC ligands

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Abstract:
The preparation of imidazolium and benzimidazolium salts with hydroxy or carboxylate functions have been achieved by straightforward synthetic pathways. These salts in combination with palladium(II) acetate give active catalytic systems for Suzuki reaction. A comparative study has been performed, which has revealed that both the heterocycle and the functional group are important in the catalytic activity and stability of the catalyst.

1. Introduction

The study and development of catalytic systems involving transition metals for organic transformations is a field of interest in synthetic organic chemistry. In this context, the use of N-heterocyclic carbenes (NHCs) as ligands for transition metals catalysis has experienced a growing importance during the last decades.[1] This type of ligands is unique due to their tunable steric and electronic properties.[2] Among the different applications for the metal-NHC complexes, metal catalyzed cross-coupling reactions have been widely explored, being palladium the most used metal.[3] The preparation of catalysts within NHC ligands, in many cases, needs inert atmosphere and anhydrous reaction conditions.[4] However, Organ and co-workers have described the preparation of stable Pd-NHC complexes by the indroduction of a pyridine ligand, which are described as PEPPSI (Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation).[5] Otherwise, the active catalysts have been prepared in situ, by mixing a metal source and the corresponding NHC precursor, as an interesting alternative.[6] The main precursor for NHCs are azolium salts, and particularly imidazolium derivatives. Moreover, imidazole can be functionalized by the introduction of functional groups on the side chains (on the nitrogens), generating precursors for functionalized NHCs.[7] On this subject, different functional groups have been included in order to modify the physical and chemical properties of the resulting NHCs.[8]

The coupling between boronic acid derivatives and organic electrophiles (Suzuki-Miyaura reaction) is one of the preferred reaction for the carbon-carbon bond formation, due to the stability and non-toxicity of the boron reagents. Moreover, there are other appeling features of this transformation, such as substrate tolerance and mild reaction conditions. So, the Suzuki coupling can be taken as an easy and typical cross-coupling benchmark reaction,[9] in order to compare the efficiency of the

catalytic systems prepared from palladium together with different functionalized imidazolium and benzimidazolium derivatives. The catalytic activity of NHCs based on imidazole has been typically examined,[3] while benzimidazole-based carbenes have been less considered. In the case of 1,3-dimethylbenzimidazolium derivative, similar versatility and efficiency as ligand compare with the imidazole analogue has been reported.[10] The study of the steric effect of N-substituents has been considered for benzimidazolium derivatives. Thus, Yaşar and co-workers have described the preparation of 1,3-dialkylbenzimidazolium chlorides, bearing different benzyl and phenethyl substituents, as precursors of palladium carbene ligands for catalysis.[11] Additionally, this type of dialkylbenzimidazolium salts has been employed in the preparation of well-defined palladium(II) complexes of PEPPSI type.[12] The use of bulkier substituents, such as N,N-diadamantylbenzimidazolium salts, has been reported by Organ and co-workers, being also considered in the study the influence of substituents (with different electronic properties) in positions C5 and C6 of benzimidazole.[13] Moreover, benzimidazole carbene sulfonamidate from binaphthyl-2,2'-diamine[14] and different bis-benzimidazolium derivatives[15] have been considered as potential carbene and bis-carbene ligands respectively. Regarding functionalized-NHC benzimidazole-based, Huynh and co-workers have described the preparation of different thioether-functionalized benzimidazol-2-ylidene ligands.[16] Furthermore, palladium complexes from imidazolium and benzimidazolium salts bearing alkyl-aryl thioether functions have been compared in the Suzuki reaction, and the thio-ether group is acting as a hemilabile ligand.[17]

The chemical stability of the carbenes and carbene complexes is directly related with the population of the carbon p(π) orbital,[18] so different activities for imidazolium and benzimidazolium derivatives should be expected. Besides, the comparison of the catalytic activity of functionalized imidazolium and benzimidazolium is relevant. Herein, we disclose our findings on the effectiveness of different imidazolium and benzimidazolium salts functionalized with hydroxy and carboxylate moieties as precursors of NHCs. In addtion, the catalytic systems formed in combination with palladium(II) acetate are compared in the Suzuki reaction.

2. Experimental

All commercial available reagents and solvents were purchased (Acros, Aldrich, Fluka) and used without further purification. Ultrasound irradiated reactions were performed using a bath Selecta Ultrasons (6 L, and potency of 150 W). The optimization reactions were carried out in a Carrousel 12 Plus™ Reaction Station. Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at the technical service of the University of Alicante (SSTTI – UA), employing a Bruker AC-300 or a Bruker Advance-400. $CDCl_3$ was employed as solvent, unless otherwise stated, and tetramethylsilane (TMS) as internal reference. Chemical shifts (δ) are given in ppm and the coupling constants (*J*) in Hertzs (Hz). Low-resolution mass spectra (EI) were obtained at 70 eV with an Agilent 5973 Network spectrometer, fragment ions *m/z* with relative intensities (%) in parenthesis. Low-resolution high-performance liquid chromatograph with electrospray ionization (HPLC-ESI) mass spectra were recorded at the technical service of the University of Alicante (SSTTI – UA), employing an Agilent 1100 Series apparatus with the possibility of MS/MS. Infrarred spectra (IR) were recorded with a FT-IR 4100 LE (JASCO – Pike Miracle ATR) spectrometer. Spectra were recorded from neat samples, without further preparation, and results are given in cm^{-1}. Analytical TLC was performed on Merck aluminum sheets with

silica gel 60 F_{254}, 0.2 mm thick. Silica gel 60 (0.04-0.06 mm) was employed for flash chromatography. The conversion of the reactions and purity of the products were determined by GC analysis on a Younglin 6100GC, equipped with a flame ionization detector (FID) and a column Phenomenex ZB-5MS (5% PH-ME siloxane): 30 m (length), 0.25 mm (inner diameter), and 0.25 μm (film).

2.1. Hydroxy-functionalized imidazoles and benzimidazoles

Imidazole or benzimidazole (10 mmol) and the epoxide (10 mmol) were placed into a high-pressure flask. The neat mixture was stirred at 60 ºC for 16 h and the product was purified from the reaction crude by recrystallization with acetone/hexane.

2-(Imidazol-1-yl)-1-phenylethanol (**1**). Off white solid; mp 130-134 ºC (acetone/hexane); R_f 0.72 (MeOH/AcOEt, 2/1); ν 3139, 3118 (CH_2); δ_H (300 MHz, $CDCl_3$): 4.07-4.13 (2H, m, CH_2), 4.91 (1H, dd, *J* = 7.0, 4.6 Hz, C*H*OH); 6.88, 6.92 (2H, 2s, NCHCHN), 7.28-7.40 (6H, m, NCHN, ArH); δ_c (75 MHz, $CDCl_3$): 55.3 (NCH_2), 74.2 (CHO), 121.5, 127.1, 128.4, 129.4, 129.7, 139.0 (ArC, ArCH, NCHCHN), 143.0 (NCHN); *m/z* (HPLC-ESI): 189 $[M]^+$, MS^2 [189]: 69 (100%).

2-(Imidazol-1-yl)cyclohexanol (**2**). White solid; mp 120-124 ºC (acetone/hexane); R_f 0.67 (MeOH/AcOEt, 2/1); ν 1500 (C=N); δ_H (300 MHz, $CDCl_3$): 1.26-1.51, 1.58-1.76, 1.76-1.90, 1.98-2.10, 2.11-2.22 (3H, 1H, 2H, 1H, 1H, 2H, 5m, CH_2 ring), 3.53-3.76 (2H, m, NCHCHO), 6.86, 6.91 (1H, 1H, 2s, NCHCHN), 7.35 (1H, s, NCHN); δ_c (75 MHz, $CDCl_3$): 24.5, 25.2, 32.4, 34.3 (CH_2 ring), 64.0 (CHN), 73.0 (CHO), 117.3, 128.6 (NCHCHN), 136.3 (NCHN); *m/z* (HPLC-ESI): 167 $[M]^+$, MS^2 [167]: 69 (100%).

1-(Benzo[d]imidazol-1-yl)-3-phenoxypropan-2-ol (**5**). Brown solid; mp 139-141 ºC (acetone/hexane); R_f 0.79 (MeOH/AcOEt, 2/1); ν 1494 cm^{-1}(C=N); δ_H (300 MHz, CD_3OD): 3.93 (2H, qd, *J* = 9.8, 5.3 Hz, NCH_2), 4.24-4.35 (1H, m, CHO), 4.36-4.46, 4.53 (1H, 1H, m, dd, *J* = 14.4, 3.8, CH_2O), 6.86-7.02 (3H, m, ArH), 7.19-7.33 (4H, m, ArH) 7.53-7.61 (1H, m, ArH), 7.62-7.70 (1H, m, ArH), 8.13 (1H, s, NCHN); δ_c (75 MHz, CD_3OD): 48.8 (NCH_2), 69.4 (CHOH), 70.1 (CH_2O), 111.6, 115.6, 120.0, 122.2, 123.4, 124.2, 130.6 (ArCH), 135.4, 143.8 (ArC), 145.6 (NCHN), 159.9 (ArC-Ph); *m/z* (HPLC-ESI): 269 $[M]^+$, MS^2 [269]: 159 (20%), 119 (100).

2-(Benzo[d]imidazol-1-yl)cyclohexanol (**6**). Off white solid; mp 156-158 ºC (acetone/hexane); R_f 0.74 (MeOH/AcOEt, 2/1); ν 1496 cm^{-1}(C=N); δ_H (300 MHz, $CDCl_3$): 1.32-1.63, 1.67-1.95 (3H, 3H, 2m, CH_2 ring), 2.01 (1H, d, *J* = 12.8 Hz, CH_2 ring), 2.15-2.30 (1H, m, CH_2 ring), 3.87-4.06 (2H, m, NCHCHO), 5.70 (1H, s, OH), 7.09 (1H, t, *J* = 7.6 Hz, ArH), 7.20 (1H, t, *J* = 7.6 Hz, ArH), 7.37-7.49 (3H, m, ArH and NCHN); δ_c (75 MHz, $CDCl_3$): 24.6, 25.4, 32.0, 34.6 (CH_2 ring), 62.6 (*C*HNCHO), 72.3 (CHO), 110.8, 119.5, 122.2, 122.7 (ArCH), 133.9, 140.8 (ArC), 142.9 (NCHN); *m/z* (HPLC-ESI): 217 $[M]^+$, MS^2 [217]: 119 (100%).

2.2. Hydroxy-functionalized imidazolium and benzimidazolium chlorides

In a round-bottom flask, the hydroxy-functionalized imidazolium (**1** or **2**) or benzimidazolium (**5** or **6**) (5 mmol), acetonitrile (10 mL), and benzyl chloride (1.1 eq, 5.5 mmol) were added. The mixture was refluxed with stirring for 16 h. Finally the solvent was removed under reduced pressure and the product was purified by recrystallization with acetone.

1-Benzyl-3-(2-hydroxy-2-phenylethyl)imidazolium chloride (**3**). White solid; mp 190-192 ºC (acetone); R_f 0.48 (AcOEt/MeOH, 1/1); ν 1561 (C=N); δ_H (400 MHz, CD_2Cl_2): 4.34 (1H, dd, *J* = 13.7, 7.1 Hz, NC*H*HCH), 4.72 (1H, dd, *J* = 13.7, 3.1 Hz, NCH*H*CH), 5.05-5.16 (1H, m, C*H*OH), 5.27 (2H, s, NCH_2Ph), 6.58 (1H, d, *J* = 5.7 Hz, OH), 6.93 (1H, t, *J* = 1.8 Hz, C*H*CH), 7.00 (1H, t, *J* = 1.7 Hz, CHC*H*), 7.16-7.38 (10H,

m, ArH), 9.94 (s, 1H, NCHN); δ_C (100 MHz, $CDCl_3$): 53.3, 56.9 (N*C*H_2Ph; NCH_2CHOH), 70.9 (CHOH), 120.6, 123.5, 126.0, 127.8, 128.5, 128.7, 129.4 (ArC), 132.7, 137.4 (N*C*HCHN, NCH*C*HN), 140.0 (NCHN).

1-Benzyl-3-(2-hydroxycyclohexyl)imidazolium chloride (**4**). White solid; mp 153-155 ºC (acetone); R_f 0.56 (AcOEt/MeOH, 2/1); ν 1557 (C=N); δ_H (300 MHz, $CDCl_3$): 1.20-1.60, 1.65-1.95, 2.00-2.20 (3H, 3H, 2H, 3m, 4xCH_2 ring), 2.75-3.10 (1H, br s, OH), 3.60-3.80, 4.22-4.37 (1H, 1H, 2m, NC*H*CO, C*H*OH), 5,45 (1H, d, *J* = 14.5 Hz, PhC*H*H), 5,52 (1H, d, *J* = 14.5 Hz, PhCH*H*), 7.22-7.29, 7.31-7.39, 7.39-7.51 (1H, 3H, 3H, 3m, ArH and NCHCHN), 10.06 (1H, s, NCHN); δ_C (75 MHz, $CDCl_3$): 24.2, 24.7, 31.5, 34.5 (CH_2 ring), 53.3 (CH_2Ph), 66.1 (N*C*HCHOH), 72.1 (HOCH), 120.9, 121.4 (NCHCHN), 129.1, 129.3(5), 129.4(1) (ArCH), 133.3 (ArC), 136.6 (NCHN); *m/z* (HPLC-ESI): 257 $[M\text{-}Cl]^+$, MS^2 [257]: 159 (100%), 91 (60).

1-Benzyl-3-(2-hydroxy-3-phenoxypropyl)benzimidazolium chloride (**7**). Off white solid; mp 97-100 ºC (acetone); ν 1551 cm^{-1}(C=N); δ_H (300 MHz, $CDCl_3$): 3.86 (1H, t, *J* = 9.1 Hz, NC*H*HCHOH), 4.19 (1H, dd, *J* = 9.6, 4.5 Hz, NCH*H*CHOH), 4.59 (1H, m, C*H*OH), 4.87-5.01 (2H, m, OCH_2), 5.78 (2H, s, NCH_2Ph), 6.48 (1H, d, *J* = 6.7 Hz, OH), 6.87 (2H, dd, *J* = 8.7, 0.9 Hz, ArH), 6.96 (1H, t, *J* = 7.4 Hz, ArH), 7.20-7.55 (10H, m, ArH), 7.63-7.80 (1H, m, ArH), 10.94 (1H, s, NCHN); δ_C (75 MHz, $CDCl_3$): 50.1, 51.7 (NCH_2), 67.0 (CHOH), 68.3 (OCH_2), 113.2, 113.7, 114.6, 121.3, 126.9, 127.0, 128.2, 129.2, 129.4, 129.6 (ArCH), 131.0, 132.2, 132.7 (ArC), 143.9 (NCHN), 158.0 (ArC-O); *m/z* (HPLC-ESI): 359 $[M\text{-}Cl]^+$, MS^2 [359]: 265 (18%), 249 (24), 222 (100), 221 (25), 209 (53), 207 (21), 145 (18), 133 (12), 132 (15), 131 (78), 119 (40).

1-Benzyl-3-(2-hydroxycyclohexyl)benzimidazolium chloride (**8**). Off white solid; mp 211-214 ºC (CH_3CN/Et_2O); R_f 0.69 (AcOEt/MeOH, 2/1); ν 1555 (C=N); δ_H (300 MHz, $CDCl_3$): 1.36-1.72, 1.74-1.99, 2.15-2.35 (3H, 3H, 2H, 3m, 4×CH_2 ring), 4.37-4.53 (2H, m, CH_2), 5.73 (1H, d, *J* = 15.2 Hz, PhC*H*H), 5.75 (1H, s, OH), 5.84 (1H, d, *J* = 15.2 Hz, PhCH*H*), 7.31-7.40 (3H, m, ArH), 7.43-7.58 (5H, m, ArH), 7.78 (1H, d, *J* = 8.1 Hz, ArH), 11.32 (1H, s, NCHN); δ_C (75 MHz, $CDCl_3$): 24.1, 24.9, 32.3, 34.7 (CH_2 ring), 51.6 (CH_2Ph), 64.7 (N*C*HCHOH), 69.9 (CHOH), 113.6, 113.7, 126.6, 126.7, 128.4, 129.1, 129.3 (ArCH), 131.2, 131.9, 132.9 (ArC), 142.6 (NCHN); *m/z* (HPLC-ESI): 307 $[M\text{-}Cl]^+$, MS^2 [307]: 289 (12%), 209 (100), 131 (18), 91 (39).

2.3. 1-Methoxycarbonylmethyl-3-methylimidazolium and -benzimidazolium chlorides

1-Methylimidazole or 1-methylbenzimidazole (10 mmol) and methyl chloroacetate (10 mmol) were added to a high-pressure flask, and the mixture was placed into an ultrasound bath during 1 h (for imidazole) or 2 h (for benzimidazole). The resultant solid was washed with diethyl ether.

1-(Methoxycarbonylmethyl)-3-methylimidazolium chloride (**9**). White solid; mp 123-126 ºC (Et_2O); R_f 0.5 (MeOH); ν 1755 cm^{-1}(C=N); δ_H (300 MHz, $CDCl_3$): 3.73 (3H, s, NCH_3), 4.03 (3H, s, OCH_3), 5.54 (2H, s, CH_2), 7.59, 7.79 (1H, 1H, 2t, *J* = 1.7 Hz, CHCH), 10.27 (1H, s, NCHN); δ_c (75 MHz, $CDCl_3$): 36.8 (NCH_3), 50.1 (CH_2), 53.4 (OCH_3), 123.1, 124.1 (CHCH), 138.7 (NCHN), 166.9 (COOMe); *m/z* (HPLC-ESI): 155 $[M\text{-}Cl]^+$, MS^2 [155]: 95 (100%).

1-(Methoxycarbonylmethyl)-3-methylbenzimidazolium chloride (**10**). White solid; mp 149-152 ºC (dec., Et_2O); R_f 0.46 (MeOH); ν 1741 cm^{-1}(C=N); δ_H (400 MHz, D_2O): 3.91 (3H, s, CH_3O), 4.18 (3H, s, CH_3N), 5.54 (2H, s, CH2), 7.72-7.79, 7.83-7.89, 7.89-7.95 (2H, 1H, 1H, 3m, ArH); δ_c (100 MHz, D_2O): 33.8 (NCH_3), 48.0 (CH_2), 54.3 (OCH_3), 113.5, 113.8, 127.8, 128.0 (ArCH), 131.9, 132.3 (ArC), 142.9 (NCHN), 169.0 (CO_2H); *m/z* (HPLC-ESI): 205 $[M\text{-}Cl]^+$, MS^2 [205]: 145 (100%).

2.4. 1-Carboxymethyl-3-methylimidazolium and -benzimidazolium chlorides

In a high-pressure flask, the methyl acetate derivative **9** or **10** (10 mmol) and concentrated HCl (37%, 0.8 mL, 10 mmol) were added, and the resulting mixture was refluxed during 1 h. The resultant solid was washed with acetone and diethyl ether.

1-Carboxymethyl-3-methylimidazolium chloride (**11**). White solid; mp 184-187 ºC (CH_2Cl_2); R_f 0.44 (MeOH); ν 1721 cm^{-1}(C=N); δ_H (300 MHz, $CDCl_3$): 3.93 (3H, s, CH_3), 5.11 (2H, s, CH_2), 7.48 (1H, t, *J* = 1.8 Hz, C*H*CH), 7.50 (1H, t, *J* = 1.8 Hz, CHC*H*), 8.79 (1H, s, NCHN); δ_c (75 MHz, $CDCl_3$): 35.9 (CH_3), 49.9 (CH_2), 123.4 (CHCH), 137.3 (NCHN), 170.0 (COOH); *m/z* (HPLC-ESI): 141 $[M\text{-}Cl]^+$, MS^2 [141]: 95 (100%).

1-Carboxymethyl-1-methylbenzimidazolium chloride (**12**). White solid; mp 225 ºC (dec., CH_2Cl_2); R_f 0.36 (MeOH); ν 1720 cm^{-1}(C=N); δ_H (300 MHz, D_2O): 4.07 (3H, s, CH_3), 5.36 (2H, s, CH_2), 7.59-7.68 (2H, m, ArH), 7.71-7.77 (1H, m, ArH), 7.71-7.84 (1H, m, ArH), 9.28 (1H, s, NCHN); δ_c (75 MHz, D_2O): 33.2 (CH_3), 47.5 (CH_2), 112.8, 113.1, 127.0, 127.2 (ArCH), 131.3, 131.6 (2xArC), 142.4 (NCHN), 169.7 (COOH); *m/z* (HPLC-ESI): 191 $[M\text{-}Cl]^+$, MS^2 [191]: 145 (100%).

2.5. Zwitterionic imidazolyl and benzimidazolyl acetates

The imidazole and benzimidazole derivative **11** or **12** (10 mmol), dichloromethane (15 mL), and triethylamine (10 mmol) were added to a reaction tube. The mixture was stirred during 1 day at room temperature. The resultant solid was filtered and washed with dichloromethane (3×10 mL) and then dried under vacuum.

2-(3-Methylimidazol-3-ium-1-yl)acetate (**13**). White solid; mp 250-260 ºC (dec., CH_2Cl_2); R_f 0.51 ($MeOH/H_2O$, 4/1); ν 1618 (C=N); δ_H (300 MHz, D_2O): 3.89 (3H, s, CH_3), 4.81 (2H, s, CH_2), 7.41, 7.40 (2H, 2s, NCHCHN), 8.68 (1H, s, NCHN); δ_C (75 MHz, D_2O): 36.6 (CH_3), 52.4 (CH_2), 124.0, 124.2 (NCHCHN), 137.8 (NCHN), 172.9 (COO^-); *m/z* (HPLC-ESI): 141 $[M\text{-}Cl]^+$, MS^2 [141]: 123 (100%), 95 (69).

2-(Methylbenzimidazol-3-ium-1-yl)acetate (**14**). White solid; mp 250-260ºC (dec., CH_2Cl_2); R_f 0.58 ($MeOH/H_2O$, 4/1); ν 1608 (C=N); δ_H (300 MHz, D_2O): 4.15 (3H, s, CH_3), 5.04 (2H, s, CH_2), 7.65-7.73 (2H, m, ArH), 7.82-7.89 (1H, m, ArH), 7.90-7.96 (1H, m, ArH), 9.44 (1H, s, NCHN); δ_c (75 MHz, D_2O): 32.6 (CH_3), 49.0 (CH_2), 112.4, 112.6, 126.4, 126.6 (ArCH), 131.0, 131.4 (ArC), 141.7 (NCHN), 171.5 (COO^-); *m/z* (HPLC-ESI): 191 $[M\text{-}Cl]^+$, MS^2 [191]: 173 (39%), 146 (67), 145 (100), 133 (22), 132 (12), 121 (20), 119 (13).

2.6. Cross-coupling reaction. Typical procedure

In a vessel, the aryl bromide (3 mmol) was added to a solution of the boronic acid (3.6 mmol), palladium(II) acetate (0.003 mmol), the corresponding azolium salt (0.003 or 0.006 mmol) and the base (12 mmol) in MeOH (6 mL). The resulting mixture was refluxed for 3 h, and after allowing the reaction mixture to cool down to room temperature, it was extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and then organic solvent was removed under reduced pressure. The crude products were purified by column chromatography (silica gel, mixture of EtOAc and hexane). For physical, spectroscopic, and analytical data, as well as literature references, see Supporting Information.

3. Results and Discussion

3.1 Preparation of imidazolium and benzimidazolium salts

The regioselective ring opening of epoxides constitutes one of the most general methods for the synthesis of hydroxi-functionalized imidazoles and benzimidazoles.

Based on this methodology,[19] imidazole was reacted with styrene oxide or cyclohexene oxide producing the corresponding functionalized imidazoles **1** and **2** with 76% and 60% isolated yield. These imidazoles were subsequently reacted with benzyl chloride, in MeCN at 80 ºC, yielding the imidazolium chlorides **3** and **4** in 54% and 93% isolated yield, respectively (Scheme 1). Likewise, benzimidazole produced the corresponding benzimidazole derivatives **5** and **6** and the hydroxi-functionalized salts **7** and **8** by ring-opening of 2-(phenoxymethyl)oxirane or cyclohexene oxide and subsequent quaternization with benzyl chloride (Scheme 1). Both benzimidazolium salts were obtained with better overall isolated yields than the imidazolium ones.

<<Scheme 1>>

The preparation of carboxylate-functionalized salts was performed following another strategy starting from 1-methylimidazole and 1-methylbenzimidazole. Their reaction with methyl chloroacetate, in an ultrasound bath, produced the expected imidazolium and benzimidazolium chlorides **9** and **10**, which were finally hydrolyzed to the zwitterionic compounds **13** and **14** by subsequent acid treatment (HCl 37% aq. producing salts **11** and **12**), and basic treatment with triethylamine (Scheme 2).

<<Scheme 2>>

3.2 Comparative study of the different imidazolium and benzimidazolium salts

The coupling reaction between 1-bromonaphthalene and phenylboronic acid was chosen as model reaction in order to evaluate the different catalytic systems, and palladium(II) acetate was selected as palladium source. The parameters, which are presented in Table 1, were selected to study the best reaction conditions, different levels being selected for each variable. (1) Solvent: a variety of solvents were considered, such as toluene (apolar solvent), *N*,*N*-dimethylacetamide (DMA, polar aprotic solvent), water and methanol (polar protic solvents), and also we considered the reaction without solvent (neat conditions). (2) Amount of palladium: palladium(II) acetate was considered as source of palladium based on our previous experience,[20] and 3 levels were tested (i.e. 0.1, 0.2 and 0.5 mol% of palladium). (3) Ratio Pd/azolium salt: the ratios 1:1, 1:2 and 1:5 were taken into consideration, besides the no-use of azolium salt was employed as control. (4) Base: three inorganic bases (i.e. K_2CO_3, $KHCO_3$, K_3PO_4), and an organic base (triethylamine) were used in the study, and additionally the use of no-base was considered as an additional level for this parameter. (5) Additive: the use or not of an additive was included in the study, being tetra-*n*-butylammonium bromide (TBAB) and cetyltrimethylammonium bromide (CTAB) selected.

<<Table 1>>

For the comparative study, we decided to conduct a ‘Design of Experiments (DoE) approach,[21] what allowed to check the maximum range of variables in a minimum set of assays providing valuable information concerning the critical factors and best combinations to obtain the hightest yield of 1-phenylnaphthalene (**15**). The selection of experiments was carried out according to a Taguchi L25 array. Table 2 collects the obtained results for the azolium salts **3**, **7** and **13**. Those azolium salts were chosen, at the outset, to cover the ligand diversity in this work, thus salts **3** and **13** present an

imidazole ring in comparison with salt **7** within a benzimidazole ring, and salts **3** and **7** bear a hydroxy functional group versus salts **13** having a carboxy moiety.

<<Table 2>>

In general, there is enough dispersion among the results so the optimal conditions could be quite dependent on the catalytic system employed, as well as on the other factors, or also, some parameters could interact. However, the experiments without solvent or base gave poor results independently to the other factors (Figure 1). Additionally, the use of an organic base, such as triethylamine, produced low yields in any case (Figure 1).

<<Figure 1>>

Following our plan, the study was completed employing the rest of azolium salts synthesized, imidazolium derivative **4** and benzimidazolium salts **8** and **14**. A new set of 18 experiments with salts **4**, **8** and **14** was carried out, excluding the assays with the conditions that lead to bad results systematically (i.e. solvent free, base free or the use of an organic base). The results are presented in Table 3. The reaction is better performed employing 0.1 mol% of $Pd(OAc)_2$ in the presence of an azolium salt (0.1 or 0.2 mol%), employing an inorganic base in MeOH.

<<Table 3>>

With all the results obtained after both set of experiments, we observed a positive effect employing an azolium salt in comparison with the reactions performed only with palladium(II) acetate (Figure 2). Apparently, there are no significant differences between the inorganic bases considered (Figure 2), being possible to obtain good results with any of them. Regarding the solvents, methanol seems to be the best choice (Figure 3), although employing certain conditions, good results can be achieved with other solvents. Moreover, the employ of an additive seems not to have a possitive effect on the outcome of the reaction (Figure 3). Taking a look in more detail, there is an interaction between the use of an additive and the solvent employed (Figure 4). Thus, the use of an additive gains relevance only when performing the reaction in water although the yields are lower when comparing with other solvent in the absence of additive (Figure 4).

<<Figure 2>>

<<Figure 3>>

<<Figure 4>>

Finally, a general trend related to the influence of the different azolium salts in the coupling reaction cannot be concluded from the data,[22] so both, the heterocycle and the functional group at the substituent could play a role in the catalytic system. In order to obtain a better picture of this feature, the coupling between 1-bromonaphthalene and phenylboronic acid was carried out in the presence of K_2CO_3 (4 equiv.) in refluxing methanol, employing 0.1 mol% of $Pd(OAc)_2$ in combination with 0.1 or 0.2 mol% of the corresponding salt (**4**, **8**, **13** and **14**; Scheme 3). Comparable

results or slightly lower, for some of the salts, were obtained when performing these experiments in the presence of 20 mol% of TBAB (Scheme 3). Certainly for any azolium salts, the use of TBAB has no positive effect in methanol, being even detrimental for some catalytic systems. Comparing azolium salts with same functional group and substituent, better results are achieved with benzimidazolium derivatives (Scheme 3). Furthermore, the study shows up that ratio 1:1 works better when a carboxy-functionalized azolium salt is employed, and in contrast a 1:2 ratio is preferable when using hydroxy-functionalized derivatives. This could be related with the fact that carboxylate functionality is less labile, as ligand, than the corresponding hydroxyl. Lastly, it is worthy to comment that under the optimal conditions described in Scheme 3, but in the absence of any azolium salt, the yield decreased to 49%. Consequently, active complex, formed by palladium and any of the salts, improves finely the outcome of the reaction.

<<Scheme 3>>

In order to broaden the comparison to other aryl halides, the coupling reactions were performed employing the best reaction conditions for the azolium salts: **4**, **8**, **13** and **14** (Table 4). The use of a more sterically hindered bromide, such as 1-bromo-2-methylnaphthalene, resulted in the formation of the expected product **16** with lower yields (Table 4, entries 5-8). The yield did not be improved by prolonging the reaction time, as it was observed employing imidazolium salt **8** (Table 4, entry 6, footnote [c]). Additionally, the use of a more reactive aryl bromide (i.e. 4-bromoacetophenone) resulted in the quantitative formation of the biaryl **17** in all the cases (Table 4, entries 9-12). On the contrary, the electron-rich 1-bromo-4-methoxybenzene reacted slower and the yields were ranging from 55 to 80% after 3 h, albeit the yields got better by lengthening the time to 8 h (Table 4, entries 13-16, and footnote [c]). Indeed, the catalytic systems seem to be sensitive to the electronic properties, so the less deactivated 1-bromo-4-*tert*-butylbenzene gave good yields after 3 h (Table 4, entries 17-20). Additionally, the catalytic systems produced the 3-phenylpyridine **20** in moderate yields (Table 4, entries 21-24). The reaction did not react further for the 3-bromopyridine, with any of the catalytic systems, probably due to deactivation of the active catalyst by substrate and/or product coordination. Finally, the reaction of 1-chloronaphthalene gave no formation of product **15** without any of the studied azolium salts. For the coupling between 4-chloroacetophenone and phenylboronic acid, the product **17** was formed within yields below 12% in all cases, and the formation of the product could not be improved by extending the reaction time.

<<Table 4>>

The catalytic systems described have similar activity in comparison to sulfonamide-[14] and thioether-functionalized[17] NHC from imidazole and benzimidazole derivatives reported in the literature, although the reaction conditions are not the same regarding solvent, temperature and palladium loading. In relation to the catalyst the complexes bearing thioether functions are employed with a palladium loading 10-fold higher than those presented herein (1 mol% instead of 0.1 mol%). The catalyst based on thioether-functionalized NHC are well defined complexes with two or one NHC ligands, so the complexes have to be previously prepared and isolated, while the catalytic systems described with hydroxy- and carboxy-functionalized NHC are prepared in situ. For activated aryl bromides, such as 4-

bromoacetophenone, the coupling product has been obtained quantitatively with thioether-, hydroxy- and carboxy-functionalized, but the sulfur-based NHC complexes worked at room temperature (instead of 65 ºC) with a 1 mol% of Pd (instead of 0.1 mol%). On the other hand for less activated electrophiles, such as 4-bromoanisole, higher temperatures (85 ºC), longer reaction times (21 h) and a palladium loading of 1 mol% are needed when using sulfur-functionalized NHC ligands. The reaction using 4-chloroacetophenone produced slightly better yields (10-30% higher) with the sulfur-containing complexes. However, better activity has been described for a thiolate-functionalized benzimidazolin-2-ylidene palladium complex[16a] when comparing with the catalytic systems described in this work. The palladium loading for thiolate-functionalized NHC-Pd complex could be reduced to 0.001 or 0.0025 mol% for 4-bromoacetophenone and 4-bromoanisole, respectively.

*3.3 Mercury poisoning test for imidazolium salts **4** and **13** and benzimidazolium salts **8** and **14***

The ability of Hg(0) to form amalgam with metal-particles can be employed as an easy test to differenciate between homogeneous and heterogeneous catalysis. The supression of catalysis by Hg(0) is evidence for a heterogeneous catalyst. On the contrary if Hg(0) does not suppress catalysis, that is evidence for a homogeneous catalyst.[23] A large excess of Hg(0), compare with the amount of the metal to be poisoned, should be employed in order to avoid incomplete poisoning.[24] We considered to perform this type of experiment for catatlytic systems formed by $Pd(OAc)_2$ and salts **4**, **8**, **13** and **14**, since palladium is one of the metal which mercury forms easily amalgam with. Thus, in a representative experiment under standard conditions employing the catalytic mixtures formed by palladium(II) acetate/salt (**4**, **8**, **13** or **14**), the reaction between 1-bromonaphthalene and phenylboronic acid was carried out in the presence of a large excess of elemental mercury (in a molar ratio of 300-330/1: Hg/Pd) which was added after 5 minutes. Table 5 collects the yields of product **15**, by GC analysis (using tridecane as internal standard), after 5 minutes of reaction, before adding the Hg(0), and after 3 hours with the mercury. In contrast, parallel mercury-free experiments gave yields comparable to entries 1-4 in Table 4. For the functionalized salts with a hydroxy group (i.e. **4** and **8**), the catalytic activity almost is completely stopped after addition of the mercury (Table 5, entries 1-2 and 3-4). Consequently, **4** and **8** in combination with palladium seem not to form very stable active catalysts or they only work to stabilize nanoparticles formed in the reaction media. On the contrary, the salts containing a carboxylate group on the substituent form a more stable homogeneous palladium catalyst which continues the reaction after the addition of mercury (Table 5, entries 5-6 and 7-8), as previously observed.[20] Particularly, the catalytic system formed with salt **14** gave homogeneous catalysis after the addition of mercury, producing **15** with a yield of 85%. Even though, the formation of small amounts of nanoparticles cannot be completely ruled out in any case.

<<Table 5>>

Looking in more detail, benzimidazole derivatives seem to form more active catalyst than the imidazole ones, giving higher yields after 5 minutes (Table 5, compare entry 1 with 3, and entry 5 with 7). Actually, the analysis of the results for both factors (i.e. heterocyclic ring of the salt and functional group in the side chain) reveals that the heterocycle is more important in terms of activity than the functional

group, being the benzimidazole derivatives more actives,[22] and the hydroxy substituent is better in terms of activity (after 5 minutes).[22] However for longer reaction times (i.e. results in Table 4) the functional group has less importance, being the carboxylate slightly better for almost all the substrates.[22] Accordingly, carboxylate binds stronger the metal center giving a more robust complex, whereas hydroxyl group is a more labile ligand producing initially a more active complex which decomposes when mercury is added.

Conclusions

Imidazolium and benzimidazolium salts with hydroxy and carboxylate functional group have been easily obtained, starting from imidazole and benzimidazole. These salts in combination with $Pd(OAc)_2$ (0.1 mol%) give catalytic systems that promote the cross-coupling between boronic acids and aryl bromides. The optimization process for the different salts (via a Design of Experiments) showed that reaction is better performed in MeOH as solvent, in the presence of K_2CO_3 (4 equiv.) as base, and that the use of a surfactant as additive is not improving the outcome of the reaction. Furthermore, the ratio between palladium and salt can be 1:1 for carboxylate-functionalized, or 1:2 for hydroxy-functionalized. Although under different reaction conditions the catalytic systems based on hydroxy- and carboxy-functionalized NHC have comparable activity to other sulfur-functionalized NHC-ligands, except for the thiolate-derivatives.

The information derived from the study of different substrates and the mercury poisoning tests for four different salts (**4**, **8**, **13** and **14**) pointed out the catalytic system palladium/salt **14** (i.e. carboxylate-functionalized benzimidazole derivative) as the most robust among the studied. Consequently, both the heterocycle ring and the functional group play a role in the formation of the active catalyst, albeit the heterocyclic system influence is a bit more significant.

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[22] For further details, see Supporting Information.

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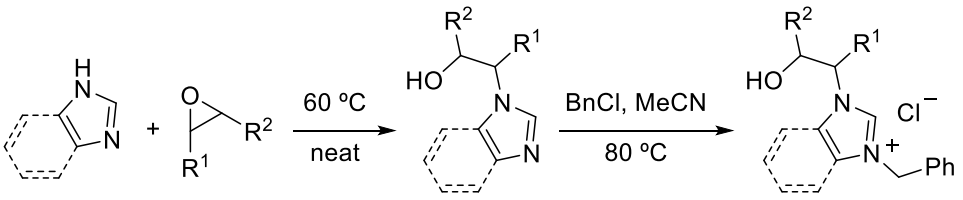
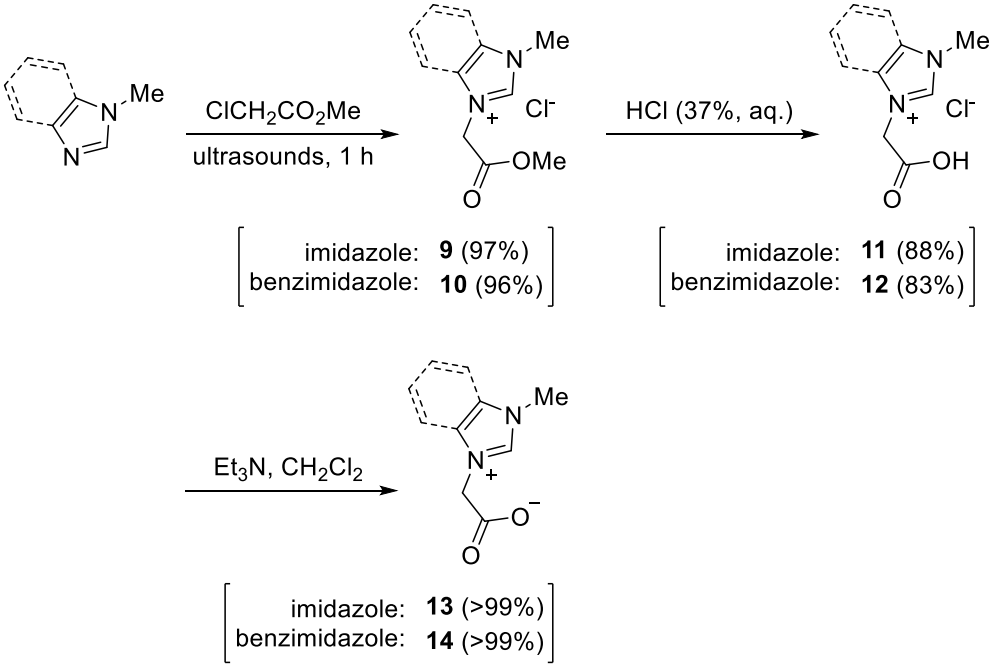
Schemes, Figures and Tables



R^1 = H, R^2 = Ph; imidazole:	**1** (76%)
R^1-R^2 = -$(CH_2)_4$-; imidazole:	**2** (60%)
R^1 = H, R^2 = CH_2OPh; benzimidazole:	**5** (70%)
R^1-R^2 = -$(CH_2)_4$-; benzimidazole	**6** (87%)
	3 (55%)
	4 (93%)
	7 (88%)
	8 (80%)

Scheme 1. Hydroxi-functionalized imidazolium and benzimidazolium derivatives synthesis.



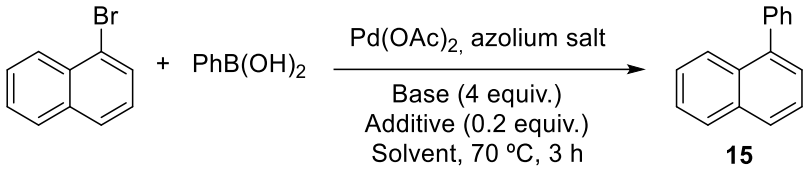
imidazole:	**9** (97%)
benzimidazole:	**10** (96%)
imidazole:	**11** (88%)
benzimidazole:	**12** (83%)
imidazole:	**13** (>99%)
benzimidazole:	**14** (>99%)

Scheme 2. Preparation of carboxylate-functionalized imidazole and benzimidazole zwitterions.

Table 1. Parameters and levels for the DoE.

	Parameters				
Levels	Solvent	$Pd(OAc)_2$ (% molar)	Ratio Pd/Azolium salt	Base	Additive
1	Neat	0.1	Only Pd	None	None
2	Toluene	0.2	1:1	K_3PO_4	TBAB
3	Water	0.5	1:2	$KHCO_3$	CTAB
4	Methanol		1:5	K_2CO_3	
5	DMA			TEA	

Table 2. Comparative study for salts **3**, **7** and **13** using Suzuki-Miyaura reaction.[a]



Entry	Solvent	Pd (% mol)	Ratio Pd/Salt	Base	Additive	Yield (%)[b]		
						3	**7**	**13**
1	Toluene	0.1	1:1	K_3PO_4	CTAB	46	56	50
2	Toluene	0.2	1:2	$KHCO_3$	TBAB	3	37	24
3	Toluene	0.5	1:5	K_2CO_3	No Addit.	69	77	87
4	Toluene	0.1	1:2	TEA	CTAB	1	8	8
5	Toluene	0.2	No salt	No base	TBAB	2	5	5
6	Neat	0.5	1:2	K_3PO_4	TBAB	71	55	42
7	Neat	0.1	No salt	$KHCO_3$	No Addit.	9	8	9
8	Neat	0.2	1:1	K_2CO_3	CTAB	17	20	22
9	Neat	0.1	1:2	TEA	TBAB	6	9	8
10	Neat	0.2	1:5	No base	CTAB	5	4	7
11	H_2O	0.2	1:2	K_3PO_4	No Addit.	16	20	5
12	H_2O	0.1	1:5	$KHCO_3$	CTAB	2	80	43
13	H_2O	0.2	1:2	K_2CO_3	TBAB	50	46	44
14	H_2O	0.5	No salt	TEA	CTAB	38	37	38
15	H_2O	0.1	1:1	No base	TBAB	6	13	15
16	MeOH	0.2	No salt	K_3PO_4	CTAB	55	51	52
17	MeOH	0.5	1:1	$KHCO_3$	TBAB	43	80	77
18	MeOH	0.1	1:2	K_2CO_3	CTAB	45	60	74
19	MeOH	0.2	1:5	TEA	TBAB	7	10	14
20	MeOH	0.1	1:2	No base	No Addit.	7	4	6
21	DMA	0.1	1:5	K_3PO_4	TBAB	58	57	27
22	DMA	0.2	1:2	$KHCO_3$	CTAB	41	73	57
23	DMA	0.1	No salt	K_2CO_3	TBAB	41	42	50
24	DMA	0.2	1:1	TEA	No Addit.	8	11	13
25	DMA	0.5	1:2	No base	CTAB	2	4	5

[a] Reaction conditions: 1-bromonaphthalene (1 mmol), phenylboronic acid (1.2 mmol), additive (0.2 mmol), base (4 mmol), and 2 mL of solvent. [b] Yield obtained by GC analysis, employing tridecane as internal standard.

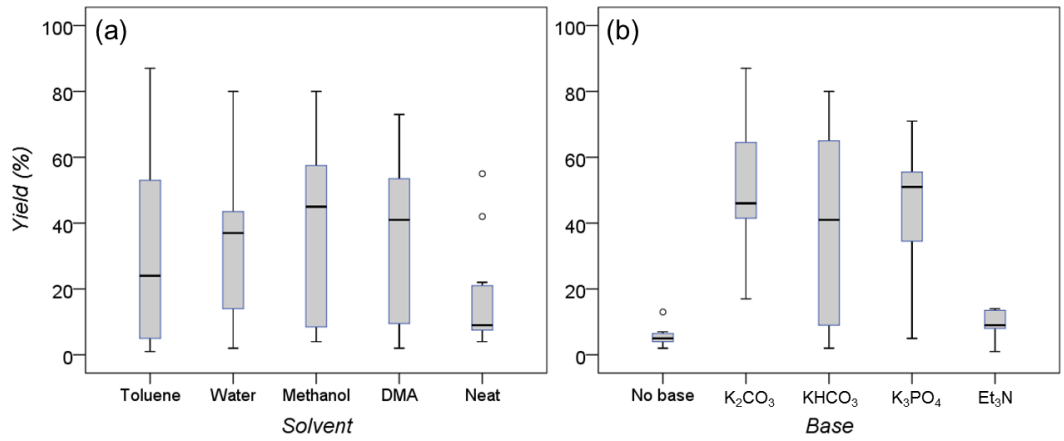
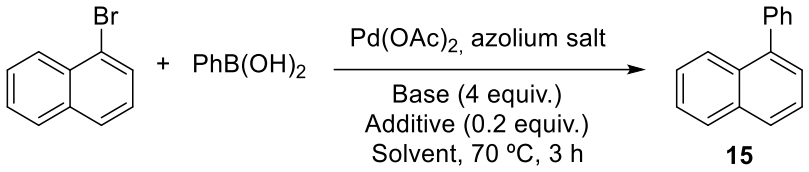


Figure 1. Boxplot of experimental data from Table 2 as function of (a) solvent, and (b) base.

Table 3. Study of the optimal conditions for salts **4**, **8** and **14** using Suzuki-Miyaura reaction.[a]



Entry	Solvent	Pd (% mol)	Ratio Pd/Salt	Base	Additive	Yield (%)[b]		
						4	**8**	**14**
1	Toluene	0.1	1:1	K_3PO_4	CTAB	51	49	48
2	Toluene	0.2	1:2	$KHCO_3$	TBAB	17	15	14
3	Toluene	0.5	1:5	K_2CO_3	No Addit.	61	50	49
4	Toluene	0.1	1:2	K_3PO_4	CTAB	45	49	41
5	Toluene	0.2	No salt	K_2CO_3	TBAB	25	25	20
6	H_2O	0.2	1:2	K_3PO_4	No Addit.	91	72	55
7	H_2O	0.1	1:5	$KHCO_3$	CTAB	46	44	51
8	H_2O	0.2	1:2	K_2CO_3	TBAB	61	44	59
9	H_2O	0.1	1:1	K_2CO_3	TBAB	39	54	55
10	MeOH	0.5	1:1	$KHCO_3$	TBAB	84	89	81
11	MeOH	0.1	1:2	K_2CO_3	CTAB	67	73	78
12	MeOH	0.2	1:5	K_3PO_4	TBAB	66	21	37
13	MeOH	0.1	1:2	K_2CO_3	No Addit.	79	80	88
14	DMA	0.1	1:5	K_3PO_4	TBAB	18	21	31
15	DMA	0.2	1:2	$KHCO_3$	CTAB	52	29	40
16	DMA	0.1	No salt	K_2CO_3	TBAB	45	41	41
17	DMA	0.2	1:1	K_3PO_4	No Addit.	68	51	54
18	DMA	0.5	1:2	K_2CO_3	CTAB	59	38	53

[a] Reaction conditions: 1-bromonaphthalene (1 mmol), phenylboronic acid (1.2 mmol), additive (0.2 mmol), base (4 mmol), and 2 mL of solvent. [b] Yield obtained by GC analysis, employing tridecane as internal standard.

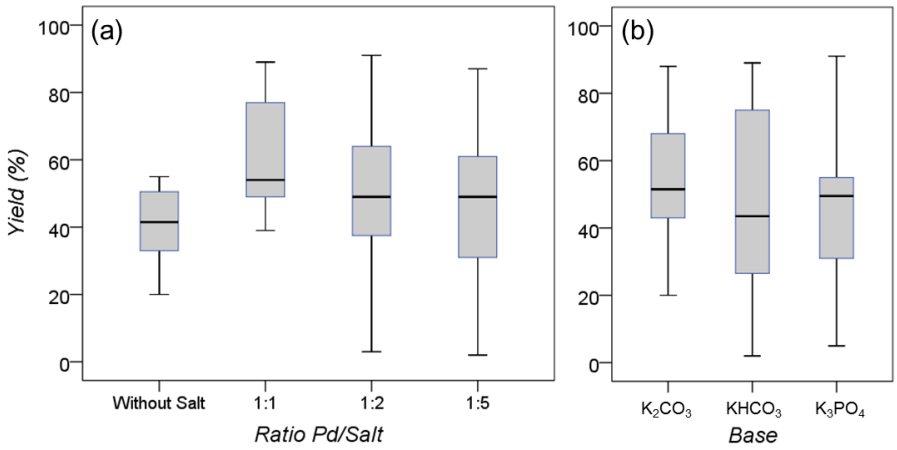


Figure 2. Boxplot of experimental data from Tables 2 and 3 as function of (a) ratio Pd/salt, and (b) base.

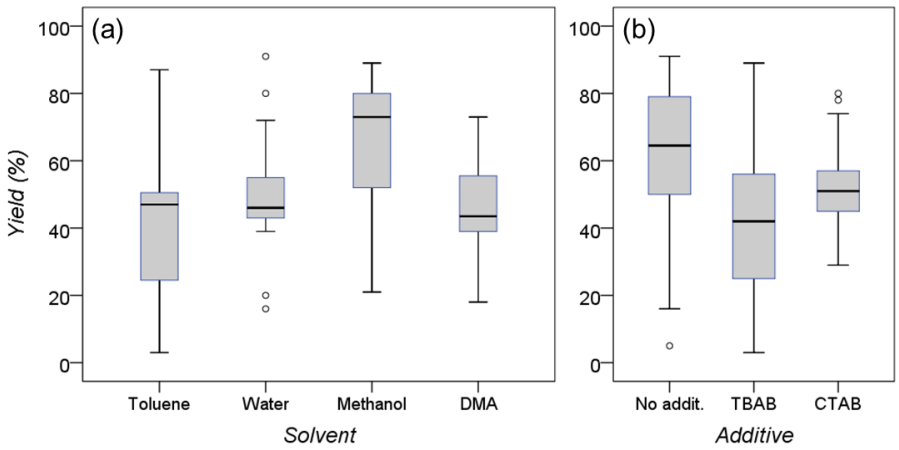


Figure 3. Boxplot of experimental data from Tables 2 and 3 as function of (a) solvent, and (b) additive.

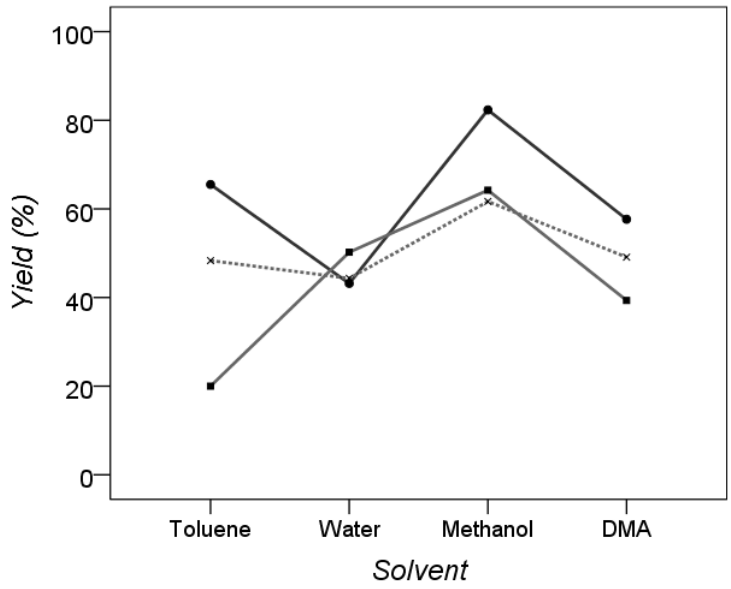
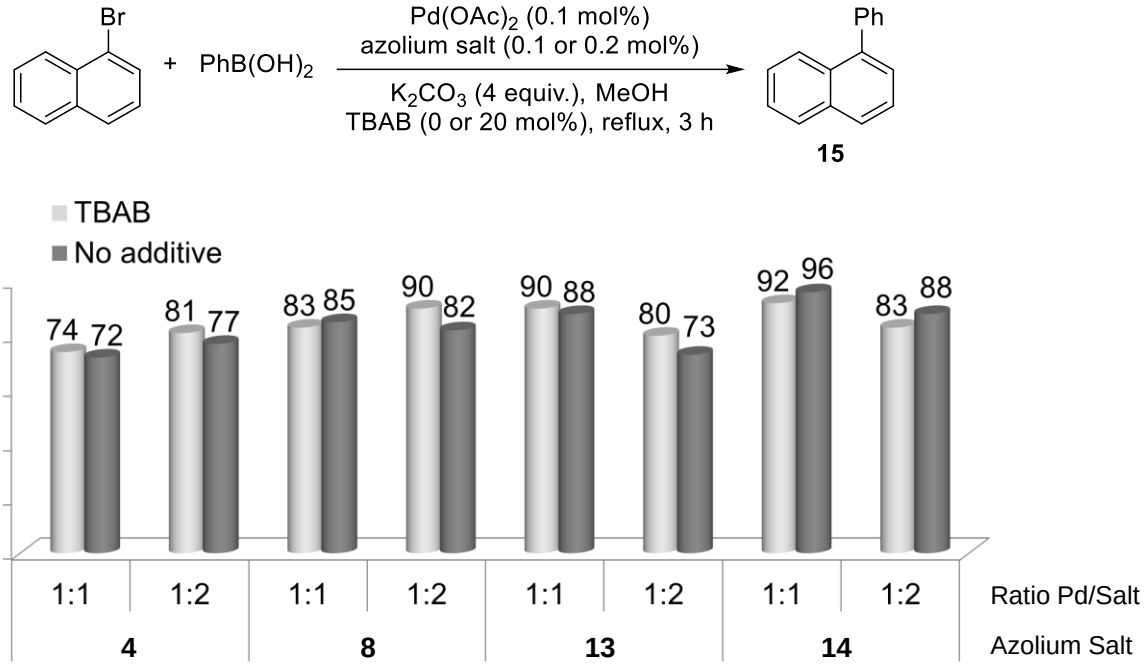
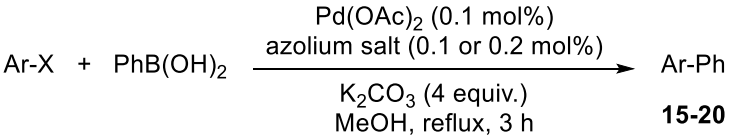


Figure 4. Interaction graph between the solvent and the additive: (•) without additive; (■) 20 mol% of TBAB; (×) 20 mol% of CTAB.



Scheme 3. Yield of 1-phenylnaphthalene with the different azolium salts, employing 2 different Pd/azolium salt ratios.

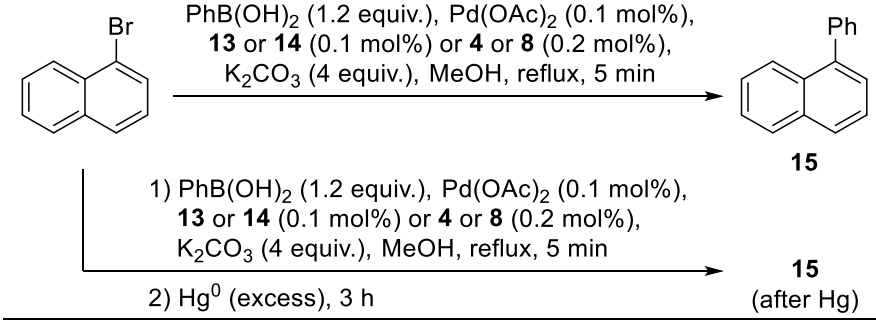
Table 4. Comparative of azolium salts **4**, **8**, **13** and **14** for different aryl halides.[a]



Entry	Ar-X	Azolium salt (mol%)	Product	
			no.	Yield (%)[b]
1	1-Bromonaphthalene	**4** (0.2)	**15**	86
2		**8** (0.2)		89
3		**13** (0.1)		84
4		**14** (0.1)		93
5	1-Bromo-2-methylnaphthalene	**4** (0.2)	**16**	23
6		**8** (0.2)		34 (37)[c]
7		**13** (0.1)		22
8		**14** (0.1)		26
9	4-BrC_6H_4COMe	**4** (0.2)	**17**	99
10		**8** (0.2)		>99
11		**13** (0.1)		97
12		**14** (0.1)		>99
13	4-$MeOC_6H_4Br$	**4** (0.2)	**18**	66 (87)[c]
14		**8** (0.2)		55 (89)[c]
15		**13** (0.1)		57 (85)[c]
16		**14** (0.1)		80 (92)[c]
17	4-*t*-BuC_6H_4Br	**4** (0.2)	**19**	89
18		**8** (0.2)		92
19		**13** (0.1)		87
20		**14** (0.1)		94
21	3-Bromopyridine	**4** (0.2)	**20**	65
22		**8** (0.2)		68
23		**13** (0.1)		67
24		**14** (0.1)		70

[a] Reaction conditions: 1-bromonaphthalene (3 mmol), phenylboronic acid (3.6 mmol), $Pd(OAc)_2$ (0.003 mmol), imidazolium salt (**4**, 0.006 mmol or **13**, 0.003 mmol) or benzimidazolium salt (**8**, 0.006 mmol or **14**, 0.003 mmol), MeOH (6 mL). [b] Isolated yield of pure product after recrystallization or column chromatography (>95% GC or 1H-NMR analysis). [c] Isolated yield for the reaction performed during 8 h instead of 3 h.

Table 5. Mercury-poisoning test for catalytic systems of $Pd(OAc)_2$ and azolium salts **4**, **8**, **13** and **14**.[a]



Entry	Azolium salt (mol%)	Conditions[b]	Yield (%)[c]
1	**4** (0.2)	5 min	26
2		5 min then Hg(0) + 3 h	32
5	**8** (0.2)	5 min	42
7		5 min then Hg(0) + 3 h	46
9	**13** (0.1)	5 min	22
11		5 min then Hg(0) + 3 h	40
13	**14** (0.1)	5 min	31
15		5 min then Hg(0) + 3 h	85

[a] Reactions performed employing: 1-bromonaphthalene (1 mmol), phenylboronic acid (1.2 mmol), $Pd(OAc)_2$ (0.001 mmol), imidazolium salt (**4**, 0.002 or **13**, 0.001 mmol) or benzimidazolium salt (**8**, 0.002 or **14**, 0.001 mmol), MeOH (2 mL). [b] Reaction quenched after 5 min, or Hg(0) (300-330 mol% refer to palladium) was added after 5 min continuing the reaction for an additional 3 h. [c] Yield obtained by GC analysis, employing tridecane as internal standard.