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Suzuki cross-coupling mediated by tetradentate *N*-heterocyclic carbene (NHC)–palladium complexes in an environmentally benign solvent †

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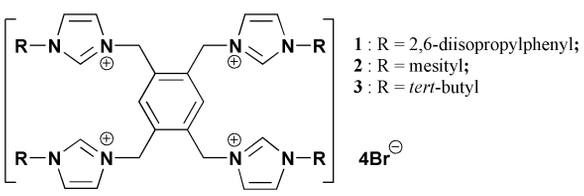
A highly effective, easy to handle and environmentally benign process for palladium mediated Suzuki cross-coupling was developed. By utilizing a solid support based NHC–palladium catalyst, cross couplings of aryl bromides with phenylboronic acid were achieved in neat water under air. A high ratio of substrate to catalyst was also realized.

Since the discovery made by Suzuki and Miyaura in 1981,[1] palladium catalyzed cross-coupling of arylboronic acids with aryl halides, the Suzuki reaction, has been intensively studied for its important applications in biaryl synthesis.[2] In the last five years, much attention had been paid towards the activation of aryl chlorides which are generally less expensive and more accessible substrates.[3] Recent advances in this field have led to the discovery of several effective ligated palladium systems that can effect the cross-coupling between aryl chlorides and arylboronic acids under mild conditions.[4] Although activation of aryl chlorides has been realized by employing these catalytic systems, the usefulness of this process in industry was compromised by the requirement of a relatively high loading of palladium (with 1–3% mol equiv.) and ligand. From the industrial point of view, however, the cost of the aryl halide is only one of the factors contributing to the total cost; as a matter of fact, cheaper ligands that can be used in an environmentally benign solvent while in low concentration for the activation of aryl bromides are also highly desired. In this article, we wish to report an air and water stable, highly effective tetradentate *N*-heterocyclic carbene (NHC) ligated palladium catalyst that can be used in high substrate to catalyst ratio (10^3–10^6) towards the activation of aryl bromides. ‡

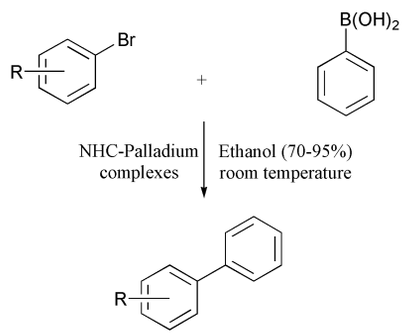
Aiming to find novel ligands for palladium catalyzed transformations, we synthesized a number of tetradentate imidazoliums as depicted in Scheme 1.[5] By coupling with palladium(II) acetate, ligands **1** and **2** are highly effective for the Suzuki reaction. Room temperature cross couplings of aryl bromides with phenylboronic acid were realized in aqueous ethanol (70–95%), a cheaper and environmentally benign solvent (see Table 1). Although numerous non-phosphine ligands have been developed for Suzuki cross-coupling,[6] to the best of our knowledge, synthesis of hindered biaryls has never been reported by utilizing non-phosphine ligands. It is noteworthy that ligand **1** can be used to effect the coupling of sterically hindered aryl bromides. For the synthesis of hindered biaryls, *n*-butanol was the solvent of choice. Other solvents such as 1,4-dioxane or toluene tended to promote self-coupling of arylboronic acids as well as debromination of aryl bromides. Activation of aryl chlorides was also achieved by employing ligand **1** in refluxing *n*-butanol under air (see Table 2).



1 : R = 2,6-diisopropylphenyl;
2 : R = mesityl;
3 : R = *tert*-butyl

Scheme 1 Ligands for Suzuki cross-coupling.

Table 1 Room temperature Suzuki cross-coupling of aryl bromides[a]



ArBr	Time/h	mol% Pd	Yield (%)
4-Bromoanisole	4	0.1	98
4-Bromoanisole	48	0.01	98
4-Bromoveratrole	10	0.1	65
2-Bromobenzaldehyde	2	0.1	98
3-Bromoquinoline	22	0.1	84
9-Bromophenanthrene	22	0.1	97
3-Bromotoluene	15	0.1	98
3-Bromopyridine	15	0.1	71
5-Bromopyrimidine	24	0.1	98

[a] For reaction conditions see Notes and references. Reaction conditions and time are not optimized. Yields represent isolated yield based on aryl halides.

There has recently been considerable interest in the application of water as a solvent for the Suzuki reaction.[6e,7] Due to a solubility problem, however, the catalyst generated by directly mixing NHC ligand **1** with palladium(II) acetate under the above reaction conditions failed to afford good Suzuki cross-coupling in neat water with palladium black formation being observed. We reckoned that a preformed solid support based catalyst might be suitable for reactions in water. Thus NHC ligand **1** (0.055 mmol, 75 mg) and palladium(II) acetate

† Electronic supplementary information (ESI) available: general experimental procedures and characterization data. See http://www.rsc.org/suppdata/ob/b3/b302646a/

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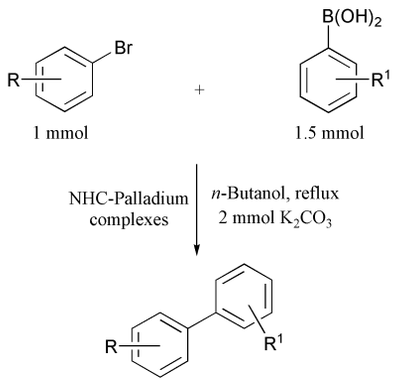
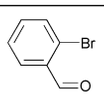
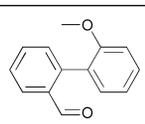
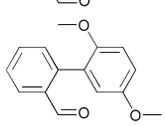
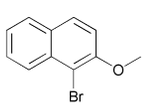
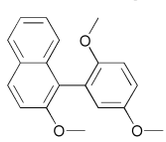
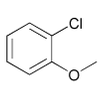
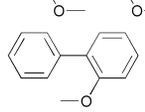
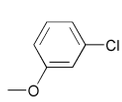
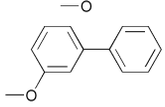
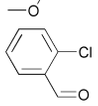
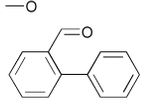
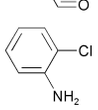
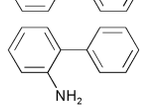
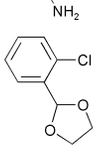
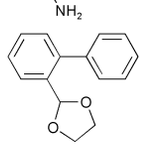
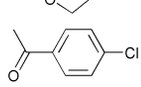
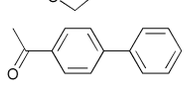
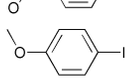
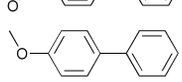
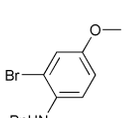
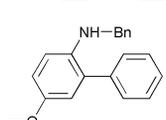
Table 2 Suzuki reaction of aryl halides in *n*-butanol[a]

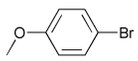
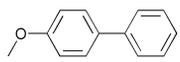
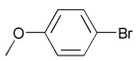
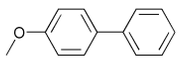
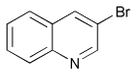
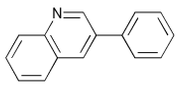
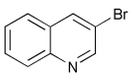
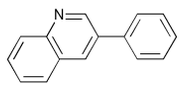
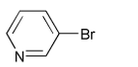
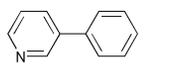
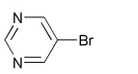
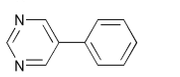
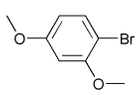
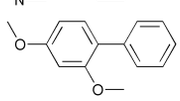
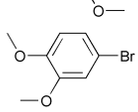
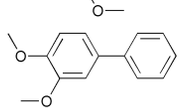
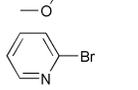
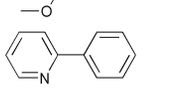
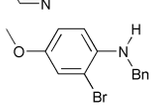
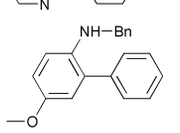
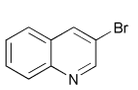
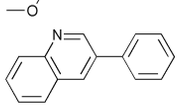
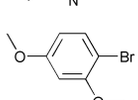
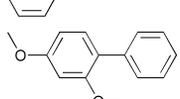
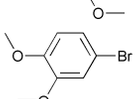
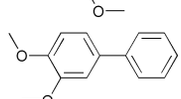


ArBr	Time/h	mol% Pd	Product	Yield
	4	0.5		98%
	8	0.5		83%
	3	0.5		55%
	20	0.5		50%
	20	0.5		77%
	10	0.5		85%
	5	0.5		74%
	3	0.5		78%
	2	0.1		98%
	24	0.0001		98%
	3	0.1		98%

[a] Reactions were carried out in *n*-butanol at reflux under air. Yields represent isolated yield based on aryl halides.

(0.1 mmol, 22.49 mg) were stirred in 1,2-dichlorethane (20 mL) for 24 hours then silica gel or alumina (200–300 mesh, 2.505 g) was added. After 2 hours, the solvent was removed under vacuum to yield the solid support based catalyst. By variation of the amount of silica gel or alumina added, the NHC–palladium catalyst absorbed on an inorganic solid surface in different concentrations can be obtained very conveniently. To our delight, the catalytic system prepared in this way was also effective towards the activation of aryl bromides. It is of industrial importance that the cross-coupling reaction mediated by solid support based NHC–carbene palladium could be carried out in neat water with no presence of a phase transfer catalyst such as *n*-Bu_4NBr (see Table 3, Method A).[8] The results summarized in Table 3 are the only examples of a Suzuki cross-coupling mediated solely by an NHC ligated palladium catalyst in water. The solid support based NHC–palladium complex can be stored for more than two months without significant loss of activity and can be reused (2–3 times) in refluxing water under

Table 3 Suzuki cross-coupling mediated by solid support based catalysts in neat water[a]

ArBr	Time (h)	mol% Pd	Product	Yield[method]
	4	0.1		98%[A]
	48	0.0001		70%[A]
	8	0.1		90%[A]
	48	0.0001		76%[A]
	48	0.0001		55%[A]
	24	0.1		80%[A]
	8	0.1		70%[A]
	8	0.1		61%[A]
	48	0.1		52%[A]
	28	0.5		87%[A]
	8	0.1		92%[B]
	8	0.1		75%[B]
	8	0.1		78%[B]

[a] For general procedure see reference 8. Reaction conditions and time are not optimized. Yields represent isolated yield based on aryl halides.

air. A high ratio of substrate to catalyst (10^6) was realized in aqueous solvent (Entries 2,4,5 in Table 3).

In order to determine the effect of adding silica gel or alumina, Suzuki cross-couplings of 4-bromoanisole with phenylboronic acid in ethanol (95%) were carried out both at room temperature and at reflux in the presence of NHC ligand **1**, palladium(II) acetate and silica gel (or alumina). No reaction rate enhancement or yield improvement was observed in either case. For the NHC–palladium mediated Suzuki reaction in neat water, however, putting silica gel or alumina in the reaction system[8] (Method B) did have a good effect towards the stabilization of the catalyst and afforded similar results to those reactions which were conducted by using a preformed solid support based catalyst. It was observed that without NHC ligand **1**, palladium(II) acetate alone on silica gel or alumina was less effective towards the same cross-coupling reaction. In the absence of palladium(II) acetate and NHC ligand, silica gel or alumina alone were unable to promote Suzuki cross-coupling in neat water as well as in ethanol (95%).

It is noteworthy that all cross-couplings listed in Table 1, Table 2 and Table 3 were carried out under air and no visible palladium black formation was observed during the catalytic process.

In summary, we have developed a highly effective, easy to handle and environmentally benign process for palladium mediated Suzuki cross-coupling. By utilizing a solid support based NHC–palladium catalyst, cross coupling of aryl bromides, including highly electron rich substrates, were realized in neat water. The ligands are comparatively inexpensive and very easily synthesized. The process described herein has the potential for large-scale industrial application. Further utilization of these NHC–palladium complexes is currently under investigation.

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Notes and references

‡ *Reaction conditions*: palladium(II) acetate (0.1 mmol%), NHC ligand **1** (0.05 mmol%), K_2CO_3 (2 mmol), aryl bromide (1 mmol) and phenylboronic acid (1.5 mmol) in ethanol (70–95%, 5 mL) were stirred at room temperature under air. The reaction was monitored by thin-layer chromatography. After removal of the solvent, the residue was diluted

with water (50 mL) and extracted with diethyl acetate (3 × 15 mL). The organic phases were combined, washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel to afford the pure products. All new compounds were characterized by ^{1}H-NMR, ^{13}C-NMR and GC-MS. Yield represents isolated yield based on aryl bromide.

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5 The ligands were prepared by refluxing 1,2,4,5-tetrabromomethylbenzene with the corresponding 1-substituted imidazole in toluene for 24 hours. Compound **1**: IR: ν_{max} (KBr)/cm^{-1}: 3436 (s), 3119 (m), 3071 (m), 2966 (s), 2931 (m), 2871 (m), 1619 (w), 1546 (m), 1467 (m), 1460 (m), 1404 (w), 1388 (w), 1368 (m), 1313 (w), 1183 (m), 1145 (w), 1104 (w), 1069 (w), 1002 (w), 1018 (w), 958 (w), 936 (w). ^{1}H-NMR (300 MHz, DMSO): δ 10.15 (4H, s, $H_{imidazole}$-5), 8.29 (4H, t, J = 1.3 Hz, $H_{imidazole}$-3), 8.23 (4H, t, J = 1.3 Hz, $H_{imidazole}$-2), 7.99 (2H, s, $H_{benzene}$), 7.63 (4H, t, J = 7.8 Hz, $H_{2,6\text{-diisopropylbenzene}}$-4), 7.45 (8H, d, J = 7.8 Hz, $H_{2,6\text{-diisopropylbenzene}}$-3,5), 5.99 (8H, s, H_{benzyl}), 2.29 (8H, septet, J = 6.6 Hz, Me_2CH), 1.14 (24H, d, J = 6.6 Hz, CH_3), 1.12 (24H, d, J = 6.6 Hz, CH_3). ^{13}C-NMR (75 MHz, DMSO): δ 145.44, 138.42, 135.02, 134.30, 131.91, 130.81, 125.70, 124.80, 123.84, 49.35, 28.47, 24.21, 24.18. MS (FAB$^+$) *m/z*: 1280 (1.5%), 1202 (0.5), 1066 (0.3), 667 (1), 583 (1), 517 (1), 437 (3), 357 (6), 321 (12), 229 (100). HRMS (ESI$^+$) *m/z* Found: 1281.4978 [M + 2H − Br]$^{3+}$, $C_{70}H_{92}Br_3N_8$ requires 1281.4995. Compound **2**: IR: ν_{max} (KBr)/cm^{-1}: 3414 (s), 3123 (s), 2979 (m), 1659 (m), 1609 (m), 1548 (s), 1484 (m), 1447 (m), 1402 (m), 1330 (w), 1290 (w), 1199 (m), 1156 (m), 1108 (s), 1069 (w), 1036 (w), 987 (w), 935 (w). ^{1}H-NMR (300 MHz, DMSO): δ 9.77 (4H, s, $H_{imidazole}$-5), 8.14 (4H, t, J = 1.6 Hz, $H_{imidazole}$-3), 8.04 (4H, t, J = 1.6 Hz, $H_{imidazole}$-2), 7.81 (2H, s, $H_{benzene}$), 7.14 (8H, s, $H_{mesitylene}$-3,5), 5.88 (8H, s, H_{benzyl}), 2.33 (12H, s, CH_3), 2.02 (24H, s, CH_3). ^{13}C-NMR (75 MHz, DMSO): δ 140.60, 138.26, 134.92, 134.69, 133.49, 131.46, 129.62, 124.41, 123.74, 49.27, 21.01, 17.76. MS (FAB$^+$) *m/z*: 1116 (2%), 1034 (0.5), 848 (1), 661 (1), 583 (1.5), 499 (3), 314 (16), 279 (4), 187 (100), 146 (10). HRMS (ESI$^+$) *m/z* Found: 1115.3267 [M + 4H − Br]$^{5+}$, $C_{58}H_{70}Br_3N_8$ requires 1115.3273. Compound **3**: IR: ν_{max} (KBr)/cm^{-1}: 3497 (m), 3425 (m), 3288 (m), 3129 (m), 3039 (s), 2980 (m), 1630 (w), 1563 (m), 1478 (w), 1446 (w), 1376 (w), 1349 (w), 1319 (w), 1292 (w), 1234 (w), 1209 (s), 1137 (m), 1017 (w). ^{1}H-NMR (300 MHz, DMSO): δ 9.68 (4H, s, $H_{imidazole}$-5), 8.07 (4H, t, J = 1.8 Hz, $H_{imidazole}$-3), 7.88 (4H, t, J = 1.8 Hz, $H_{imidazole}$-2), 7.62 (2H, s, $H_{benzene}$), 5.72 (8H, s, H_{benzyl}), 1.62 (36H, s, CH_3). ^{13}C-NMR (75 MHz, DMSO): δ 135.47, 134.53, 132.16, 123.10, 120.89, 60.27, 48.75, 29.39. MS (FAB$^+$) *m/z*: 867 (4%), 785 (1), 662 (4), 537 (2), 458 (3), 309 (3), 252 (11), 217 (14), 195 (7), 125 (100), 69 (35). HRMS (ESI$^+$) *m/z* Found: 867.2659 [M + 4H − Br]$^{5+}$, $C_{38}H_{62}Br_3N_8$ requires 867.2647.

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8 *General method for Suzuki cross-coupling in neat water*: **Method A**: Aryl bromide (1 mmol), phenylboronic acid (1.5 mmol), K_2CO_3 (2 mmol) and the solid support based catalyst (0.1 mmol%, 25 mg), which was preformed by mixing palladium(II) acetate (22.5 mg) with ligand **1** (75 mg) in 1,2-dichloroethane (20 mL) overnight and then absorbed on alumina or silica gel (2.505 g), were stirred in neat water (5 mL) at reflux. The reaction mixture was extracted with ethyl acetate (3 × 10 mL). The organic phases were combined and washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel to afford the products. **Method B**: Palladium(II) acetate (0.1 mmol%), NHC ligand **1** (0.05 mmol%), K_2CO_3 (2 mmol), silica gel or alumina (25 mg), aryl bromide (1 mmol) and phenylboronic acid (1.5 mmol) in neat water (5 mL) were stirred at reflux under air for 8 hours. The reaction mixture was extracted with ethyl acetate (3 × 10 mL). The organic phases were combined and washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel to afford the products. All compounds were characterized by ^{1}H-NMR, ^{13}C-NMR and GC-MS.