

Palladium catalysed Suzuki cross-coupling reactions in ambient temperature ionic liquids

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Palladium catalysed Suzuki cross-coupling reactions have been conducted in the ambient temperature ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF₄]), exhibiting unprecedented reactivities in addition to easy product isolation and catalyst recycling.

The continuing depletion of natural resources and growing environmental awareness has necessitated changes in the practices of both the chemical industry and academia. One strategy that addresses these issues is the replacement of deleterious molecular solvents with environmentally more benign, reaction enhancing alternatives. Of the novel solvents that have emerged, ambient temperature ionic liquids consisting of 1,3-dialkylimidazolium cations have shown great promise (Fig. 1).¹ Their negligible vapour pressure, ease of handling and potential for recycling, circumvent many of the problems associated with volatile organic solvents. Furthermore, their high compatibility with transition metal catalysts and limited miscibility with common solvents, enables easy product and catalyst separation with the retention of the stabilised catalyst in the ionic phase. These and related ionic liquids have been successfully employed as the media in a number of reactions, which include hydrogenations,² alkene dimerizations,³ Diels–Alder⁴ and Friedel–Crafts⁵ reactions.

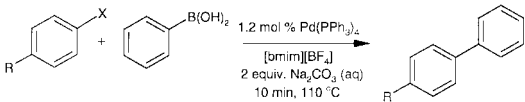
The Suzuki⁶ cross-coupling reaction is an extremely versatile methodology for the generation of new carbon–carbon bonds and is employed most successfully in the synthesis of biaryls.⁷ The reaction, however, suffers from a number of drawbacks such as catalyst loss into the product, catalyst decomposition and poor reagent solubilities. We postulated that these problems might be resolved by the use of ionic liquids. Recently, the closely related Heck⁸ and Trost–Tsuji⁹ coupling reactions have been conducted in ionic liquids with great success. We report herein the first examples of the more complex palladium catalysed Suzuki cross-coupling reactions in the ambient temperature ionic liquid, [bmim][BF₄]. [bmim][BF₄] has a liquid range in the order of 300 °C, it is stable in air and is known to solubilise many organometallic compounds.¹⁰ These properties, in addition to its controllable miscibility with water and immiscibility with ether, make [bmim][BF₄] a potential solvent for Suzuki reactions.

The reaction of 4-bromotoluene with phenylboronic acid in [bmim][BF₄] was initially investigated using the original Suzuki conditions.¹¹ This afforded 4-methylbiphenyl in a 30% yield after 6 h, with catalyst decomposition evidenced by the precipitation of a black solid (Table 1, entry 6). Further investigation revealed that modifying the original conditions significantly boosted yields of the desired products, enhanced

reaction rates and prevented catalyst decomposition. The new conditions involved heating the catalyst with the arylhalide in [bmim][BF₄] at 110 °C with vigorous stirring until complete solution occurred. The catalytic solution is cooled to ambient temperature and the reaction started by the addition of the arylboronic acid and an aqueous solution of Na₂CO₃.¹² Adopting this procedure with a reduced catalyst concentration, Pd(PPh₃)₄ (1.2 mol%, based on arylhalide), afforded 4-methylbiphenyl in a 69% yield after 10 min, without catalyst decomposition (Table 1, entry 7). The reaction can also be achieved with one-tenth the catalyst concentration generally required, Pd(PPh₃)₄ (0.3 mol%, Table 1, entry 8). Once the catalytic solution has been generated the reaction can be conducted under air with analogous results and no catalyst decomposition (Table 1, entry 9).

The scope of the reaction in [bmim][BF₄] was investigated with electron-rich and electron-deficient arylhalides (Table 1). The reactivity exhibits dramatic enhancements over the conditions generally employed. For example, conducting the reaction of bromobenzene with phenylboronic acid under the original Suzuki conditions affords biphenyl with an 88% yield in 6 h (5 TON h⁻¹).¹¹ In [bmim][BF₄] a 93% yield is achieved in 10 min (455 TON h⁻¹, Table 1, entry 2), which is over 90 times the original reactivity. Notably, 4-methoxybiphenyl is afforded in a 40% yield in 6 h (2 TON h⁻¹) applying the original conditions.¹¹ In [bmim][BF₄] an 81% yield is afforded in

Table 1 Scope of the Suzuki cross-coupling reaction in [bmim][BF₄]: variation of the arylhalide



Entry	X	R	Yield (%) ^a	TON	TON h ⁻¹
1	I	H	86 (95)	72	430
2	Br	H	93 (95)	78	465
3	Cl	H	1 (1)	1	5
4	Br	Cl	17	14	85
5	Br	COCH ₃	67 (97)	56	335
6	Br	CH ₃	30 ^b	25	150
7	Br	CH ₃	69 (92)	58	345
8	Br	CH ₃	72 ^d	60	360
9	Br	CH ₃	68 ^c	57	340
10.1	Br	OCH ₃	81 (92)	67	401
10.2	Br	OCH ₃	89	73	441
10.3	Br	OCH ₃	77	64	381
10.4	Br	OCH ₃	82	68	406

^a Isolated yields of corresponding cross coupled product based on arylhalide. Purity confirmed by GC, GC-MS and ¹H NMR. Isolated yields after 3 h in parentheses. ^b Suzuki reaction without prior activation of catalyst. Original catalyst concentration employed, Pd(PPh₃)₄ (3 mol%). Catalyst decomposition observed. ^c Reaction performed under air. ^d Lower catalyst concentration, Pd(PPh₃)₄ (0.3 mol%). Reaction time 1 h.

Cationic Components



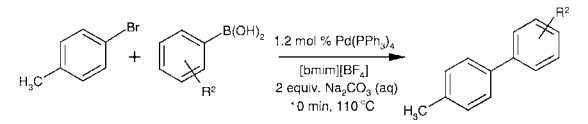
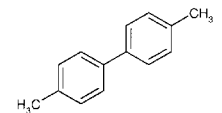
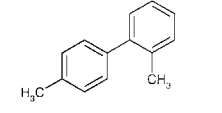
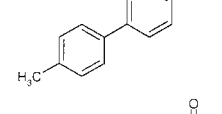
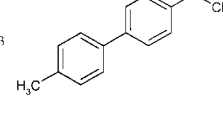
R = "Bu"; R' = Me, 1-*n*-Butyl-3-methylimidazolium, ([bmim]⁺)
R = Et; R' = Me, 1-Ethyl-3-methylimidazolium, ([emim]⁺)

Anionic Components

Cl⁻
[AlCl₄]⁻
[TfO]⁻
[BF₄]⁻
[PF₆]⁻

Fig. 1

Table 2 Scope of the Suzuki cross-coupling reaction in [bmim][BF₄]: variation of the arylboronic acid

				
Entry	R ²	Product	Yield (%) ^a	TON h ⁻¹
1	4-CH ₃		68	57
2	2-CH ₃		68	57
3	4-OMe		81	68
4	4-COCH ₃		45	38

^a Isolated yields of corresponding cross coupled product based on arylhalide. Purity confirmed by GC-MS and ¹H NMR.

10 min (401 TON h⁻¹, Table 1, entry 10.1), which is in the order of 200 times the original reactivity. We are continuing to explore the generality of this result. Despite these enhancements, chlorobenzene was still inactive even after 3 h, with only a trace of biphenyl being detected, presumably due to *homo*-coupling of the arylboronic acid (Table 1, entry 3).¹³

The effect of the arylboronic acid partner on the Suzuki reactions in [bmim][BF₄] was also investigated (Table 2). The results of the functionalised arylboronic acids seem to parallel those obtained with the same functional groups on the arylhalide. This suggests that both the nature of the arylhalide and the arylboronic acid affect the reaction, apparently in an analogous manner. We are continuing to investigate these interesting results.

Isolation of the biaryl products from the [bmim][BF₄] reaction mixture can be achieved by extraction with diethyl ether, sublimation or precipitation by the addition of water, all without any apparent leaching of palladium species into the product. Extraction with diethyl ether was found to be a generally applicable method for all biaryls and led to the highest yields. Biphenyl, mono-, and di-functionalised biaryls can easily be sublimed from the reaction mixture by heating at 80 °C *in vacuo*. With water insoluble products, isolation and catalytic solution recovery and recycling was most effective with water. Typically, the reaction mixture was allowed to cool to *ca.* 60 °C, warm water was added and the mixture left to cool to ambient temperature whereupon the biaryl products crystallised out. These were collected by filtration and washed with cold water to afford the desired product with a purity >98% (determined by GC). The only impurity being the *homo*-coupled product. The negligible amount of *homo*-coupled products detected in the reactions can be avoided by adding the phenylboronic acid to the reaction mixture over a period of an hour.

The by-products (NaHCO₃ and Na[XB(OH)₂]) generated in the reaction modify the miscibility of water with [bmim][BF₄] such that two phases are formed at ambient temperature. The by-products are preferentially soluble in the large excess of added water. This enables the removal of the by-products with

the water, affording the cleaned, ionic liquid, catalytic solution. The ability to isolate product and recover the catalytic solution permits repetitive catalytic runs. The catalytic solution was re-used three times without loss of activity in the reaction of 4-bromoanisole with phenylboronic acid (Table 1, entries 10.2–10.4). Once the catalytic solution has been prepared in the first run, it can be re-used with no further modification. The product was extracted with diethyl ether and the catalytic solution washed with water after each run.

In summary, we have demonstrated that Suzuki cross-coupling reactions can be successfully conducted in the ambient temperature ionic liquid, [bmim][BF₄], with a number of advantages: (i) The reactions show a significant increase in reactivity at reduced catalyst concentration, especially with respect to non-activated arylbromides. (ii) *Homo*-coupled products can be eliminated, affording isolated products in high purity avoiding laborious purification procedures. (iii) The reactions can be performed under air without loss of yield or catalyst decomposition. (iv) The procedures developed permit repetitive catalytic runs without loss of catalyst activity. Further investigations concerning the nature of the active catalytic species and the mechanism of reaction are currently in progress.

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- The original Suzuki conditions employ: arylhalide (2.5 mmol, 1 equiv.); arylboronic acid (2.75 mmol, 1.1 equiv.); Pd(PPh₃)₄ (3 mol%, based on arylhalide); Na₂CO₃ (5.3 mmol, 2 equiv.) and toluene–H₂O–EtOH 4:2:1, heated at 110 °C for 6 hours. N. Miyaura, T. Yanagi and A. Suzuki, *Synth. Commun.*, 1981, **11**, 513.
- Typical procedure for the Suzuki reaction in [bmim][BF₄]: aryl halide (2.5 mmol, 1 equiv.) was added to a suspension of Pd(PPh₃)₄ (34.7 mg, 0.03 mmol, 1.2 mol%) in degassed [bmim][BF₄] (5 cm³) at ambient temperature under nitrogen. The mixture was slowly heated to 110 °C with vigorous stirring affording a yellow–orange solution. The solution was cooled to ambient temperature and the arylboronic acid (2.75 mmol, 1.1 equiv.) and a solution of Na₂CO₃ (560 mg, 5.28 mmol, 2.1 equiv.) in water (2.5 cm³) was added. The mixture was reheated at 110 °C with vigorous stirring for a further 10 min, then cooled and extracted with diethyl ether (3 × 15 cm³). The combined extracts were washed first by brine (2 × 10 cm³), then water (2 × 10 cm³) and dried (MgSO₄). Filtering through a silica pad and evaporation to dryness afforded the Suzuki biaryl product as characterised by GC-MS, ¹H-NMR and IR spectroscopy. The reaction mixture was washed with water (2 × 10 cm³) and dried *in vacuo* to recover the catalytic solution.
- The low reactivity of aryl chlorides in cross-coupling reactions is well documented. For discussions, see V. V. Grushin and H. Alper, *Chem. Rev.*, 1994, **94**, 1047.