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Ionic Liquid Acceleration of Solid-Phase Suzuki–Miyaura Cross-Coupling Reactions

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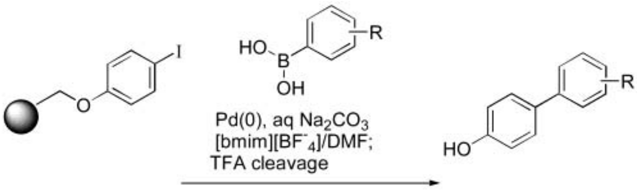
ABSTRACT



Room-temperature ionic liquids promote various transition metal-catalyzed reactions in the solution phase. Here, for the first time, we show that these effects are translatable to solid-phase reactions. The Suzuki–Miyaura cross-coupling of 4-iodophenol immobilized on polystyrene–Wang resin with various arylboronic acids was significantly accelerated by the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ($[bmim][BF_4^-]$).

Ionic liquids that are fluid at room temperature are usually salts of quaternary ammonium species with poorly coordinating ions. The resulting materials have recently attracted considerable attention[1] as solvents and catalysts for a plethora of organic reactions. The highly polar nature of ionic liquids ensures immiscibility with many organic solvents, offering unique opportunities for recycling and phase-switching techniques. On the catalysis front, many reactions ranging from transition metal-mediated processes to Friedel−Crafts reactions, C−C bond-forming condensations, and cycloadditions are dramatically accelerated in ionic liquids.

We set out to examine whether the beneficial effects of ionic liquids were translatable to *solid-phase* reactions. We are unaware of any previous reports combining the potential of ionic liquids and solid-phase synthesis, which continues[2] to be of paramount importance in the preparation of discrete and pooled combinatorial libraries.

Our initial studies focused on the Suzuki−Miyaura[3] palladium(0)-catalyzed coupling of aryl or alkenyl boronic acids with aryl or alkenyl halides. Because of its efficiency and functional group tolerance, this cross-coupling reaction has been intensively employed in the solution phase, and there are numerous examples[4] of solid-phase applications as well. Furthermore, there was a solution-phase precedent[5] of increased turnover frequency in Suzuki−Miyaura reactions carried out in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ($[bmim][BF_4^-]$).

Given the hydrophobicity of cross-linked polystyrene resins popularly used in solid-phase synthesis, we anticipated

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(1) For some reviews, see: (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071−2083. (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772−3789. (c) Sheldon, R. *Chem. Commun.* **2001**, 2399−2407. (d) Olivier-Bourbigou, H.; Magna, L. *J. Mol. Catal. A* **2002**, *182*, 419−437.

(2) For a recent review, see: Ganesan, A. *Drug Discovery Today* **2002**, *7*, 47−55.

(3) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168.

(4) For some recent examples, see: (a) Lutz, C.; Bleicher, K. H. *Tetrahedron Lett.* **2002**, *43*, 2211−2214. (b) Hanazawa, T.; Wada, T.; Masuda, T.; Okamoto, S.; Sato, F. *Org. Lett.* **2001**, *3*, 3975−3977. (c) Barn, D.; Caulfield, W.; Cowley, P.; Dickins, R.; Bakker, W. I.; McGuire, R.; Morphy, J. R.; Rankovic, Z.; Thorn, M. *J. Comb. Chem.* **2001**, *3*, 534−541. (d) Zhang, H.-C.; Ye, H.; White, K. B.; Maryanoff, B. E. *Tetrahedron Lett.* **2001**, *42*, 4751−4754. (e) Park, C.; Burgess, K. *J. Comb. Chem.* **2001**, *3*, 257−266. (f) Pourbaix, C.; Carreaux, F.; Carboni, B. *Org. Lett.* **2001**, *3*, 803−805.

(5) Mathews, C. J.; Smith, P. J.; Welton, T. *Chem. Commun.* **2000**, 1249−1250.

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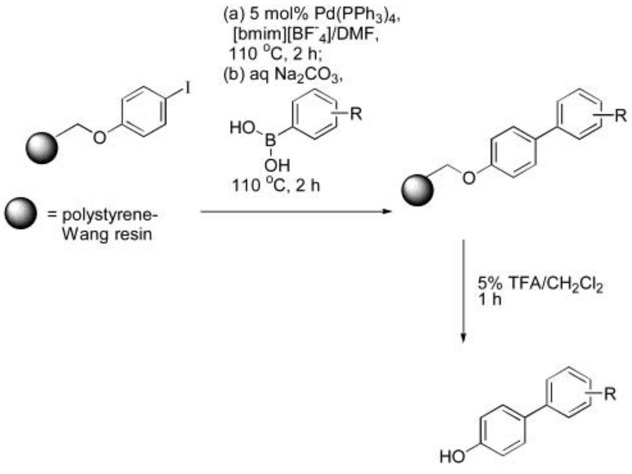
the need for a cosolvent to ensure swelling of beads to the gel phase. The ionic liquid [bmim][BF_4^-] was mixed with four test solvents: dichloromethane, DME, DMF, and dimethyl acetamide. The mixture with dichloromethane rapidly turned cloudy,[6] while those with DME and dimethyl acetamide gradually separated. Only DMF remained miscible with [bmim][BF_4^-] as a homogeneous translucent liquid upon overnight standing and was hence chosen as the cosolvent.

For our solid-phase reactions, 4-iodophenol was immobilized on the polystyrene−Wang resin according to the trichloroacetimidate procedure[7] of Hanessian and Xie. The resin was then swollen in 1:1 [bmim][BF_4^-]/DMF, followed by addition of $Pd(PPh_3)_4$ and catalyst activation by heating to 110 °C for 2 h. The resulting orange-red suspension was heated[8] at 110 °C for a further 2 h after addition of phenylboronic acid and aqueous Na_2CO_3. Upon cooling of the suspension, workup, and resin cleavage, we were pleased to obtain ~70% isolated yield of 4-phenylphenol (Scheme 1, R = H).

Scheme 1. Ionic Liquid-Accelerated Suzuki−Miyaura Reactions of Immobilized 4-Iodophenol



Two control experiments served to highlight the importance of both the ionic liquid and cosolvent. Thus, under identical reaction conditions with neat DMF in the absence of any ionic liquid, only 46% of the biaryl product was isolated. On the other hand, when the solid-phase reaction was carried out with neat ionic liquid in the absence of any DMF, no biaryl was detected. Presumably, this is due to poor penetration of the active catalyst into the unswollen resin beads. A time course of the extent of reaction with 1:1 [bmim][BF_4^-]/DMF versus DMF alone (Table 1) confirms significant rate acceleration in the former case.

Table 1. Rate Acceleration of the Solid-Phase Suzuki−Miyaura Reaction by [bmim][BF_4^-]

reaction time	yield (%) DMF	yield (%) 1:1 [bmim][BF_4^-]/DMF
30 min	19	48
60 min	31	59
90 min	38	67
120 min	46	74
48 h	80	84

The scope of the ionic liquid-accelerated process was investigated with the parallel reactions of the resin-bound aryl iodide with a set of 10 arylboronic acids bearing a range of electron-donating and -withdrawing substituents (Table 2). As can be seen, the ionic liquid efficiently promotes the Suzuki−Miyaura coupling of a variety of arylboronic acids. With some boronic acids, the conversion was lower due to their decreased reactivity. Nevertheless, these reactions are even less efficient without the ionic liquid. For example, the coupling product of 4-(trifluoromethoxy)phenyl boronic acid (entry 6) was obtained in only 26% under control conditions.

Table 2. Examples of Ionic Liquid Promoted Solid-phase Suzuki-Miyaura Cross-coupling

entry	R	yield (%)[a] 1:1 conditions[b]	yield (%)[a] 1:9 conditions[b]
1	H	74	70
2	4-CHO	72	68
3	3-CHO	70	64
4	4-OPh	61	64
5	3-NHAc	40	44
6	4-OCF_3	45	40
7	3,5-diCF_3	42	37
8	4-Et	65	67
9	3,4-OCH_2O-	60	63
10	4-*t*-Bu	73	70

[a] Isolated yield after silica chromatography, average of three experiments. [b] Ratios of 1:1 and 1:9 refer to the proportion (v/v) of [bmim][BF_4^-]/DMF.

The nature of the ionic liquid catalysis is likely to be twofold. Besides solvent effects due to the dissolving power of this polar medium, the formation of N-heterocyclic carbene complexes by active participation of the ionic liquid with the transition metal has been suggested and experimentally demonstrated[9,10] for Pd(0)-catalyzed reactions. In all our reactions, we have found that the yields are very similar when the ionic liquid concentration is only 10% of the solvent volume (Table 2, column 4). Further reduction to 5:95 [bmim][BF_4^-]/DMF led to a partial increase in yield compared to the ionic liquid-free conditions, while 1:99 [bmim][BF_4^-]/DMF resulted in practically no acceleration over the control.

We have attempted recycling of the ionic liquid, which should contain the catalytically active species, after the solid-

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[6] A reviewer points out that this may be due to NaCl present as an impurity in the ionic liquid. Our [bmim][BF_4^-] was purchased from Fluka and used without further purification.

[7] Hanessian, S.; Xie, F. *Tetrahedron Lett.* **1998**, *39*, 733−736.

[8] Recently, ionic liquid-promoted Suzuki reactions were carried out at ambient temperature with the aid of ultrasound: Rajagopal, R.; Jarikote, D. V.; Srinivasan, K. V. *Chem. Commun.* **2002**, 616−617.

[9] Xu, L.; Chen, W.; Xiao, J. *Organometallics* **2000**, *19*, 1123−1127.

[10] Mathews, C. J.; Smith, P. J.; Welton, T.; White, A. J. P.; Williams, D. J. *Organometallics* **2001**, *20*, 3848−3850.

phase reaction. The supernatant was filtered off and DMF evaporated from the solvent mixture, followed by aqueous washing to remove excess boronic acid and inorganic salts. When the resulting ionic liquid was recycled without addition of Pd(0), the cross-coupling of immobilized 4-iodophenol and phenylboronic acid proceeded in 29% yield. In these solid-phase reactions, we observe deposition of palladium black suggesting a significant loss of the metal. Repeating the cross-coupling with recycled ionic liquid and fresh addition of 5 mol % Pd(0) catalyst afforded 4-phenylphenol in 69%, virtually indistinguishable from the yield in Table 1.

In summary, we have shown that the rate-accelerating properties of ionic liquids observed in solution-phase Suzuki−Miyaura reactions can be extended to solid-phase conditions[11] with standard hydrophobic cross-linked resins. The ionic liquid can be recovered and recycled after the reaction. Work is in progress to examine the influence of ionic liquids on a variety of other solid-phase reactions.

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(11) **General Procedure for Ionic Liquid-Promoted Solid-Phase Suzuki−Miyaura Reactions.** The aryl iodide resin (1.00 g, 0.68 mmol) was partially swollen in a degassed mixture of [bmim][BF_4^-] and DMF (either 1:1 or 1:9, total of 6 mL). Tetrakis(triphenylphosphine)palladium(0) (5.0 mol %, 0.034 mmol, 39 mg) was added with rapid stirring under argon and the reaction mixture heated to 110 °C (oil bath temperature) with rapid stirring for 2 h. After cooling to ambient temperature, to the orange/red suspension was added with stirring the arylboronic acid (2.5 mol equiv, 1.7 mmol) followed by aqueous 1 M Na_2CO_3 (2 mol equiv, 1.36 mmol). The reaction mixture was again heated to 110 °C with rapid stirring for 2 h. After cooling, the resulting black suspension was filtered. For recycling of the ionic liquid, the supernatant was washed with DMF (2 × 5 mL) and the combined washings were filtered through Celite. The DMF was evaporated in vacuo and the orange/red ionic liquid washed with water (5 × 20 mL), ether (3 × 20 mL), and dried under vacuum for 2 h. The resin was washed with water (1 × 10 mL), diethyl ether (5 × 10 mL), and THF (5 × 20 mL), and dried. The resin was then suspended in 5% TFA/CH_2Cl_2 (15 mL) with agitation for 1 h. The supernatant was neutralized with excess solid K_2CO_3 (∼500 mg), and the resulting dark-colored mixture was filtered, concentrated, and dried. The crude product was taken up in 15 mL of 1:1 EtOAc/hexanes, adsorbed onto silica (2 g), loaded on a short silica plug (2 g), and eluted. Pure product fractions were combined and concentrated.