



Developing an ionic medium for ligandless-palladium-catalysed Suzuki and Heck couplings

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Abstract

High-melting-point alkylammonium tetrafluoroborates melt with water or toluene to form biphasic mixtures at much lower temperatures than their normal melting points, thus could serve as green reaction media for Suzuki and Heck couplings. Advantages of using the aqueous-ammonium biphasic catalytic system include: (1) working well with a ligandless palladium catalyst, (2) solving the solubility problem of organic substrates and (3) simplifying work-up procedures for both separation of products and recycling of reaction media.

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1. Introduction

Ionic liquids (ILs) have recently attracted much attention as environment friendly media for organic reactions and catalytic processes [1–6]. Almost all kinds of reactions have been successfully carried out in ionic liquids. For an environmental point of view, replacement of traditional organic solvents is often expected to make reactions or processes efficient, clean or practical, in a popular word, green. However, in contrast to a wide variety of traditional organic solvents, the availability of ILs is rather limited. Further, purification of ILs themselves represents a big challenge for chemists since ILs are liquids with little vapour pressure or low-melting-point solids, thus incompatible with the most widely used purifying techniques of distillation for liquids and recrystallization for solid

materials. One way to overcome the purification drawback of conventional ILs is using high-melting-point salts. But this strategy is only suitable for reactions or processes conducted at temperatures above the melting point of the salts [7]. The nature-occurring green solvent, water, is another alternative [8]. However, water has inherent drawbacks as solvent for organic reactions, such as solubility problems of organic materials in water. We report here an aqueous-ionic liquid biphasic reaction medium based on high-melting-point hydrophobic alkylammonium tetrafluoroborates and its application to Suzuki and Heck couplings with a ligandless palladium catalyst.

2. Experimental

2.1. General considerations

All commercial reagents were used without further purification. ^1H and ^{13}C NMR spectra were recorded

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with a Varian 300 instrument and chemical shifts are reported in parts per million relative to the residues of the deuteriated solvents. GC analyses were performed on an SRI instrument with a 15 m MXT-1 column. The Suzuki and Heck couplings were carried out under N₂ atmosphere and other manipulations were conducted in air. Elemental analyses were performed by the Analytical Center of ECNU.

2.2. Representative procedure for the synthesis of alkylammoniums

To a solution of pyrrolidine (7.1 g, 0.1 mol) in toluene (50 ml) was slowly added 2.5 eq. *n*-BuBr (34 g, 0.25 mol), followed by 5 eq. NaOH (20 g in 30 ml H₂O). The resulting mixture was heated at 90 °C until the middle layer (molten salt) stopped increasing. The molten salt was then separated and treated with 2.0 eq. NaBF₄ (22 g, 0.2 mol) in acetone (200 ml) for overnight at RT. Then 500 ml water was added to the mixture and part of acetone was removed in vacuum to give **1** as white crystals 24 g (91%), mp 125–127 °C. Anal. for **1**, C₁₂H₂₆NBF₄ (required): C, 53.24 (53.16); H, 9.80 (9.67); N, 5.22 (5.17). NMR (CDCl₃, 300 MHz, 25 °C), ¹H (δ, ppm): 0.95 (t, *J* = 7.4 Hz, 6H, Me), 1.45 (m, 4H), 1.65 (m, 4H), 2.25 (br. s, 4H), 3.25 (m, 4H), 3.55 (br. s, 4H); ¹³C (δ, ppm): 13.62, 19.72, 21.95, 25.27, 59.76, 62.96.

Compounds **2–4** were prepared and characterised in a similar manner to **1**.

2 (Yield: 85%), Anal. for C₂₀H₄₂NBF₄ (required): C, 62.75 (62.66); H, 11.30 (11.04); N, 3.53 (3.65). NMR (CDCl₃, 300 MHz, 25 °C), ¹H (δ, ppm): 0.90 (t, *J* = 6.8 Hz, 6H, Me), 1.35 (m, 20H), 1.65 (m, 4H), 2.25 (br. s, 4H), 3.20 (m, 4H), 3.55 (br. s, 4H); ¹³C (δ, ppm): 14.17, 21.96, 22.70, 23.42, 26.39, 29.13, 31.76, 59.91, 63.01.

3 (Yield: 94%), Anal. for C₁₃H₂₈NBF₄ (required): C, 54.76 (54.75); H, 10.08 (9.90); N, 4.87 (4.91). NMR (CDCl₃, 300 MHz), ¹H (δ, ppm): 1.00 (t, *J* = 7.3 Hz, 6H, Me), 1.45 (m, 4H), 1.65 (m, 4H), 1.75 (br. s, 2H), 1.90 (br. s, 4H), 3.25 (m, 4H), 3.55 (br. s, 4H); ¹³C (δ, ppm): 13.65, 19.75, 19.81, 20.90, 23.43, 58.44, 59.32.

4 (Yield: 87%), Anal. for C₂₁H₄₄NBF₄ (required): C, 63.50 (63.47); H, 11.40 (11.16); N, 3.38 (3.52). NMR (CDCl₃, 300 MHz), ¹H (δ, ppm): 0.90 (t, *J* = 7.1 Hz, 6H, Me), 1.35 (m, 20H), 1.65 (br. s, 4H), 1.75 (m, 2H), 1.90 (br. s, 4H), 3.20 (m, 4H), 3.35 (m, 4H);

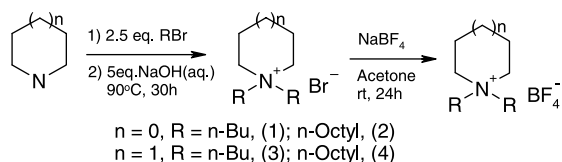
¹³C (δ, ppm): 14.18, 19.86, 20.93, 21.57, 22.71, 26.42, 29.15, 31.77, 58.61, 59.39.

2.3. Representative procedure for cross-coupling in the aqueous-alkylammonium tetrafluoroborate biphasic system

To a suspension of alkylammonium tetrafluoroborate (5 g) in water (5 g) (1:1 (w/w)) was added phenylhalide (3 mmol), K₂CO₃ (9.0 mmol, ~3 eq.), PdCl₂ (11 mg, 0.06 mmol, 0.02 eq.) and *p*-tolylboronic acid (3.3 mmol, 1.1 eq.) for the Suzuki coupling and butyl acrylate (3.5 mmol, 1.2 eq.) for the Heck coupling under nitrogen. Then the mixture was heated at 90 °C (bath temperature) for 8–10 h. Conversion of the substrates was determined by GC. After being cooled to room temperature, the suspension was extracted with hexane (3 × 5 ml) and crude product was purified by recrystallization or passing a short pad of column of silica gel. Yields were compiled in Tables 2 and 3.

3. Results and discussion

Although there is theoretically unlimited possibility to make ionic liquids by combination of different cations and anions, the practically used ones are limited to a few sorts of compounds, such as alkylammonium, alkylphosphonium, *N*-alkylpyridinium and *N,N'*-dialkylimidazolium salts, at present. In fact, only alkylimidazolium salts have enjoyed the widest use. However, alkylimidazoliums are intrinsically unstable under basic conditions or when being subjected to metal salts due to the formation of stable carbenes or carbene complexes [9,10]. Saturated alkylammoniums are expected to be more stable than imidazoliums. To search for base-tolerant ILs, we prepared two alkylpiperidiniums [C₅H₁₀NRMe]⁺BF₄⁻ (R = Bu or octyl) by quarterisation of the amine followed by simple metathesis of alkylammonium halides with NaBF₄ in acetone. The resulting *N*-methyl-*N*-octylpiperidinium tetrafluoroborate is a low-melting-point solid or viscous liquid at room temperature if not totally dried. Not surprisingly, we encountered the problem to purify the 'ionic liquid' satisfactorily since it resisted distillation, recrystallization and routine chromatography. *N*-methyl-*N*-butylpiperidinium is water-soluble and has disappointingly high melting



Scheme 1. Synthesis of alkylammonium tetrafluoroborates.

point of 155 °C. To further screen for proper ammoniums, *N,N*-dialkylpyrrolidiniums (**1** and **2**) and *N,N*-dialkylpiperidiniums (**3** and **4**) were prepared (Scheme 1).

When *N,N*-dibutylpyrrolidinium **1** was heated in a dry state it melted at 125 °C. However, we noticed that the salt melted in water forming a biphasic mixture, aqueous and molten organic salt (ionic liquid) phases, at significantly lower temperature of about 50 °C, which falls in the range of temperatures for a variety of organic reactions. Further, the dioctylammonium tetrafluoroborate **2** melted at only 41 °C in water to form a biphasic mixture (Table 1). The corresponding piperidinium analogues have slightly higher melting points: 159 °C (67 °C in water) for **3** and 75 °C (55 °C in water) for **4**, respectively. Even the commercially available ammonium $[\text{Bu}_4\text{N}]^+\text{BF}_4^-$ turns into liquid at around 80 °C in water although its normal melting point is as high as 160 °C.

It has been known that some ionic liquids are actually mixtures of corresponding salts and water or in the form of hydrates. To test if hydrates formed in the presence of water, the salts **1**, **3** and $[\text{Bu}_4\text{N}]^+\text{BF}_4^-$ were recrystallized in hot water. Their melting points remained unchanged after drying with filter paper at room temperature. A rationale for the

water-promoted phase-transition of these alkylammonium tetrafluoroborates probably lies in their extremely strong freezing-point-depression by a small amount of dissolved water. In fact, we noticed that other ‘impurities’, such as reaction substrates, have also helped to reduce melting points of these alkylammonium tetrafluoroborates [11]. This prompted us to investigate the freezing-point-depression effect of other inert organic substances, such as toluene, since there are many chemical processes sensitive to moisture. We found that these high-melting-point salts **1**, **3** and $[\text{Bu}_4\text{N}]^+\text{BF}_4^-$ also turned into liquid at lower temperatures than their normal melting points in toluene to form a biphasic mixture, ionic liquid and organic phases, respectively. It is common to use co-solvents in chemical processes, especially in transition-metal catalysed organic reactions, so we envisioned that the aqueous-alkylammonium tetrafluoroborate biphasic system should find wide applications in transition-metal-promoted organic reactions or catalytic processes.

Application of the system was first investigated using a palladium-catalysed C–C bond-forming reaction, Suzuki coupling, as a model reaction. Suzuki coupling has become one of the most popular protocol for construction of conjugated aryl moieties due to its excellent tolerance of functional groups and moisture [12,13]. Welton first reported Suzuki coupling in ionic liquids using $\text{Pd}(\text{PPh}_3)_4$ as catalyst, but a special procedure had to be taken, otherwise the phosphine palladium catalyst would deactivate at the early stage of the reaction [14]. Recently, phosphonium has been also reported to serve as an ionic medium for Suzuki reaction [15]. Using our water–ammonium tetrafluoroborate biphasic system the Suzuki coupling of *p*-tolylboronic

Table 1
Alkylammoniums showing strong freezing-point-depression

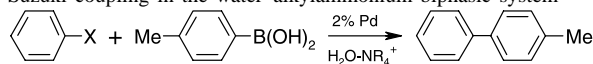
	Compound				
	1	2	3	4	$[\text{Bu}_4\text{N}]^+\text{BF}_4^-$
Melting point ^a	125–127	63–65	159–161	75–77	160–164
Melting point in H ₂ O	~50	~41	~67	~55	~80
Solubility in H ₂ O ^b	158.1	10.0	165.4	9.1	30.3
Melting point in toluene	~78	^c	~95	^c	~55
Solubility in toluene ^b	3.1	^c	1.2	^c	7.6

^a Melting point in °C.

^b Measured in g/l at 80 °C.

^c Very soluble.

Table 2

Suzuki coupling in the water–alkylammonium biphasic system^a

Entry	Halide	Catalyst	Ammonium	Yield (%)	Recycle
1	C ₆ H ₅ I	PdCl ₂	[Bu ₄ N] ⁺	92	1
2	C ₆ H ₅ I	PdCl ₂	[Bu ₄ N] ⁺	76 (84) ^b	2
3	C ₆ H ₅ I	PdCl ₂	[Bu ₄ N] ⁺	(52) ^b	3
4	C ₆ H ₅ I	PdCl ₂	[C ₅ H ₁₀ NBu ₂] ⁺	93	1
5	C ₆ H ₅ I	PdCl ₂	[C ₅ H ₁₀ NOct ₂] ⁺	90	1
6	C ₆ H ₅ I	(dppf)PdCl ₂	[Bu ₄ N] ⁺	93	1
7	C ₆ H ₅ I	(PPh ₃) ₂ PdCl ₂	[Bu ₄ N] ⁺	89	1
8	C ₆ H ₅ Br	PdCl ₂	[Bu ₄ N] ⁺	84 (90) ^b	1
9	C ₆ H ₅ Cl	PdCl ₂	[Bu ₄ N] ⁺	(6) ^b	1

^a Reactions run in 3 mmol scale and isolated yields.^b Conversion by GC.

acid with iodobenzene was carried out satisfactorily with 2% eq. (dppf)PdCl₂ or (Ph₃P)₂PdCl₂ as catalysts (Table 2, Entries 6 and 7).

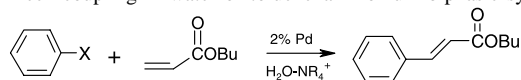
According to the widely accepted mechanism of the Suzuki coupling, the real catalyst is palladium(0) species. Phosphine ligands are only to support the active palladium(0) species, thus preventing it from deactivation. However, most phosphine ligands are toxic and expensive. It is always attractive to use ligandless-catalysts or catalyst precursors in transition-metal-catalysed organic reactions. With this in mind, we tested PdCl₂ as a catalyst precursor to promote the Suzuki coupling in our water–ammonium biphasic system. The same amount of PdCl₂ (2% eq.) gave similar results to the above phosphine palladium complexes (Table 2, Entries 1, 4 and 5). Palladium black was observed in the reactions and during recovering the ammoniums by recrystallization in acetone–water (1:10 (v/v)). So, it is reasonable to conclude the true catalytic species is palladium metal, which is stabilised in the molten alkylammoniums. Different ammoniums displayed similar performance, so the commercially available [Bu₄N]⁺BF₄[−] was suggested for use. Bromobenzene also gave the desired product in a good yield (Table 2, Entry 8) while chlorobenzene was only slightly converted. Reuse of the catalyst was also explored, but its catalytic activity decreased in subsequent runs possibly due to the loss of palladium in work-up (Table 2, Entries 1–3). Separation of the products could be effected by routine purifying procedures: extraction of the reaction mixture with

hexane followed by filtration and removal of solvents. The dialkylammonium tetrafluoroborates could be recycled with almost no loss.

Encouraged by the success for Suzuki coupling, we further extended the application of the aqueous-ammonium biphasic system to Heck coupling, which is another most important palladium-catalysed C–C bond-forming reaction and often requires polar solvents, such as DMF, and organic bases, such as Et₃N, etc. which often lead to tedious work-up procedures. Unlike Suzuki coupling, inorganic palladiums, such as Pd(OAc)₂, nano-palladium metal and Pd/C have been used for Heck coupling, even in ionic liquids [16]. Recently, molten [Bu₄N]⁺Br[−] has been used as a green solvent for Heck coupling with advanced palladium catalysts at elevated temperature (>130 °C) [17–19]. In our water–ammonium biphasic system the Heck coupling of iodobenzene with butylacrylate proceeded smoothly with 2% eq. PdCl₂ as catalyst (Table 3).

Although Pd(OAc)₂ had been used as catalyst for the Heck coupling in alkylimidazolium ionic liquids, the real catalytic species was believed to be carbene complexes generated in situ [20]. In our cases, any palladium carbene complex could be excluded, so the palladium(0) metal should be responsible for the catalysis. Again, different alkylammoniums showed similar performance. However, bromobenzene was almost inactive in the Heck coupling although it gave a satisfactory yield in the Suzuki coupling using the same system. Considering that Heck reaction is often

Table 3
Heck coupling in water or toluene–ammonium biphasic system^a



Entry	Halide	Ammonium	Base	Cosolvent	Yield (%)
1	C ₆ H ₅ I	[Bu ₄ N] ⁺	K ₂ CO ₃	H ₂ O	93
2	C ₆ H ₅ I	[Bu ₄ N] ⁺	NEt ₃	Toluene	84
3	C ₆ H ₅ I	[C ₅ H ₁₀ NBu ₂] ⁺	K ₂ CO ₃	H ₂ O	90
4	C ₆ H ₅ Br	[Bu ₄ N] ⁺	K ₂ CO ₃	H ₂ O	3 ^b
5	C ₆ H ₅ Br	[Bu ₄ N] ⁺	NEt ₃	Toluene	20 ^b

^a Reactions run in 3 mmol scale and isolated yields.

^b Conversion by GC.

carried out with organic amine bases and under anhydrous conditions, we also investigated the Heck reaction of arylhalides with butyl acrylate in the toluene–ammonium biphasic system (Table 3, Entries 2 and 5). Iodobenzene could be converted smoothly but bromobenzene still gave the desired product in a very low yield.

Compared with the currently used reaction media for Suzuki and Heck couplings, such as conventional organic solvents and ionic liquids, our aqueous–ammonium biphasic system has a couple of advantages. Obviously, our system is environment-friendly compared with those using volatile organic solvents. Secondly, the high-melting-point alkylammonium tetrafluoroborates, which served as liquid reaction media during reaction stage due to their strong freezing-point-depression, could not only be readily separated from products but also be readily purified and recycled in the solid state by recrystallization, thus do not cause the purification problem of conventional ILs. Most importantly, cheap and non-toxic ligandless-palladium compound PdCl₂ could be successfully used as the catalyst for both of the Suzuki and Heck couplings in our aqueous–ammonium biphasic system.

4. Conclusion

In summary, we have developed a green and efficient ionic medium for ligandless-palladium-catalysed C–C bond forming reactions based on high-melting-point dialkylammonium tetrafluoroborates through a solute-promoted phase transition. Using our system the simple palladium compound PdCl₂ displayed

comparable activity to toxic phosphine palladium catalysts that were normally required in Suzuki and Heck couplings. Application of the aqueous–ammonium biphasic system to other organic transformations is in progress in our laboratory.

Acknowledgements

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References

- [1] J. Dupont, R.F. Souza, P.A.Z. Suarez, *Chem. Rev.* 102 (2002) 3667.
- [2] H.O. Bourbigou, L. Magna, *J. Mol. Catal. A* 182–183 (2002) 419.
- [3] R. Sheldon, *Chem. Commun.* (2001) 2399.
- [4] P. Wasserscheid, W. Keim, *Angew. Chem. Int. Ed.* 39 (2000) 3773.
- [5] T. Welton, *Chem. Rev.* 99 (1999) 2071.
- [6] H. Olivier, *J. Mol. Catal. A* 146 (1999) 285.
- [7] R.M. Pagni, *Adv. Molten Salt Chem.* 6 (1987) 211.
- [8] U.M. Lindström, *Chem. Rev.* 102 (2002) 2751.
- [9] W.A. Herrmann, C. Köcher, *Angew. Chem. Int. Ed.* 36 (1997) 2162.
- [10] A.J. Arduengo III, *Acc. Chem. Res.* 23 (1999) 913.
- [11] S.G. Kazarian, N. Sakellarios, C.M. Gordon, High-pressure CO₂ was reported to reduce the melting point of ionic liquids, *Chem. Commun.* (2002) 1314.
- [12] A. Suzuki, *J. Organomet. Chem.* 576 (1999) 147.
- [13] N. Miyaura, A. Suzuki, *Chem. Rev.* 95 (1995) 2457.
- [14] C.J. Mathews, P.J. Smith, T. Welton, *Chem. Commun.* (2000) 1249.

- [15] J. McNulty, A. Capretta, J. Wilson, J. Dyck, G. Adjabeng, A. Robertson, *Chem. Commun.* (2002) 1986.
- [16] H. Hagiwara, Y. Shimizu, T. Hoshi, T. Suzuki, M. Ando, K. Ohkubo, C. Yokoyama, *Tetrahedron Lett.* 42 (2001) 4349, and references therein.
- [17] V.P.W. Böhm, W.A. Herrmann, *Chem. Eur. J.* 6 (2000) 1017.
- [18] S. Bouquillon, B. Ganchegui, B. Estrine, F. Henin, J. Muzart, *J. Organomet. Chem.* 634 (2001) 153.
- [19] V. Calo, A. Nacci, A. Monopoli, L. Lopez, A. Cosmo, *Tetrahedron* 57 (2001) 6071.
- [20] L. Xu, W. Chen, J. Xiao, *Organometallics* 19 (2000) 1123.