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Ionic liquid as an efficient promoting medium for two-phase nucleophilic displacement reactions

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Abstract—The use of the room temperature ionic liquid (RTIL) 1-*n*-butyl-3-methylimidazolium hexafluorophosphate as an efficient catalyst and solvent for several representative nucleophilic substitution reactions under aqueous-RTIL phase transfer conditions was explored. Recycling and reuse of the reaction medium was demonstrated for the azide formation.

1. Introduction

The development of environmentally friendly catalysts and solvents for organic chemistry is an area of considerable importance. From both economical and environmental points of view, the use of non-volatile solvents and non-metallic catalysts is very promising. In the last few years room temperature ionic liquids (RTILs), especially those based on 1,3-dialkylimidazolium cations,[1] have been recognised as a possible environmentally benign alternative to chemical volatile solvents.[2]

The RTILs show useful properties such as thermal stability, high ionic conductivity, negligible vapour pressure and a large electrochemical window. Depending on the anion and alkyl group of the imidazolium cation, the RTILs can solubilize carbonyl compounds, alcohols, alkyl halides, supercritical CO_2 ($scCO_2$), and also transition metal complexes. Furthermore, they can have low miscibility with dialkyl ethers, alkanes, water[2] and can be insoluble in $scCO_2$.[3] The RTILs emerged as an alternative recyclable environmentally benign reaction media for chemical processes[2] including bio-[4] and chemical catalysis.[5] Moreover, RTILs have successfully replaced traditional organic solvents (OS) in aqueous-OS biphasic extraction[6] systems, OS-$scCO_2$ extraction,[7] selective transport using supported liquid membranes,[8] pervaporation,[9] dissolution of cellulose[10] and in CO_2 capture.[11]

Phase-transfer catalysis (PTC) is a powerful methodology for the preparation of numerous classes of non chiral and chiral compounds.[12] Some nucleophilic reactions are frequently carried out in two phases system using PTC. The PTCs are generally quaternary ammonium salts,[12] including immobilised on a polymeric matrix ones[13] or ketiminium salts.[14] The PTC facilitates the reaction between the organic reactant in the organic phase and the nucleophile in the aqueous phase as an inorganic salt. In a conventional reaction using PTC, the OS such as methylene chloride or toluene are environmentally undesirable compounds. The use of RTILs as an alternative media for alkylation[15] and as a reagent for the conversion of alcohols to alkyl halides[16] has been demonstrated. Here we report that the ionic liquid 1-*n*-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6] is an efficient catalyst and solvent for several representative reactions carried out under aqueous-RTIL PTC conditions. Meanwhile, Eckert et al. already recently demonstrated the use of the RTIL [bmim][PF_6] as a catalyst and solvent for the cyanide displacement of benzyl chloride and alkylation of benzyl cyanide under solid-RTIL PTC conditions.[17]

2. Results and discussion

We started to study the alkylation of N-diphenyl methylene glycine esters **1** and **2** as an example of biphasic reaction (Table 1). For comparison, the reported yields of the same reaction promoted by non-chiral catalysts were also presented.[14] Using a catalytic amount of [bmim][PF_6] (50 mol%) in the aqueous/dichloromethane biphasic system or as a solvent, the alkylated product was obtained respectively in 10% and 44% (entries 1 and 2). In case of the alkylation of **1** with methyl iodide and benzyl bromide the obtained yields are similar to the reported examples using ketiminium salt as a PTC (44% versus 35%[14] and 82% versus 78%[14]) nevertheless in shorter reaction times (2.5 h

Keywords: ionic liquids; nucleophilic substitution; Schiff base; aryl alkyl ether; alkyl iodide; alkyl cyanide; alkyl azide; recycling.

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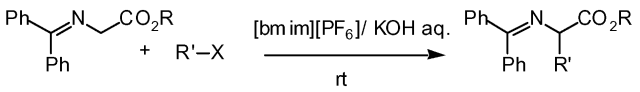
Table 1. Alkylation of Schiff bases **1** and **2** using aqueous-RTIL system



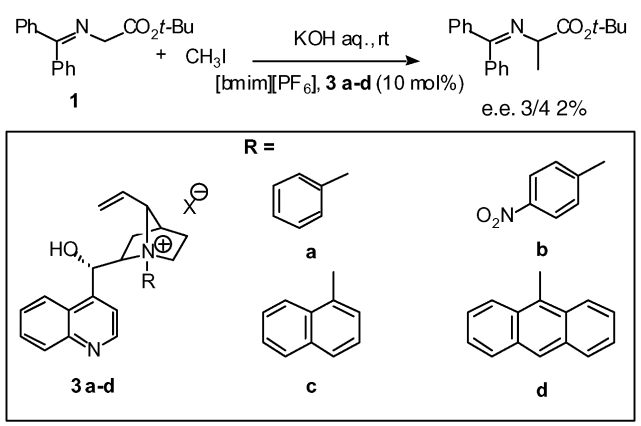
Entry[a]	Substrate	R′-X (eq.)	Time	Yield[b]	Lit. yield
1	1R=*t*-Bu	Mel (1.2)	3.5 h	10%	
2	1R=*t*-Bu	Mel (1.2)	2.5 h	44%	35%[c,d]
3	1R=t-Bu	BnBr (1.2)	40 min	82%	78%[c,e]
4	2R=ET	Mel (1.2)	1.5 h	60%	
5	2R=ET	BnBr (1.2)	20 min	84%	

[a] Reactions were performed in a two phase system containing aqueous KOH solution (50%, 0.5 mL), 1-*n*-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6] (1.0 mL), **1** (0.24 mmol) or **2** (0.26 mmol), alkyl halide (1.2 eq.), rt, vigorous stirring. In case of entry 1 was used [bmim][PF_6] (18 μL, 0.5 eq.) in CH_2Cl_2 (1.7 mL).
[b] Isolated yields, except for entry 1 which corresponds to conversion by ^{1}H NMR.
[c] CH_2Cl_2 (5 mL)/aqueous KOH solution (50%, 1.2 mL), **1** (0.5 mmol), catalyst (ketiminium salt, 10 mol%), alkyl halide (1.4 eq.), rt.[14]
[d] Reaction time of 48 h.
[e] Reaction time of 20 h.

versus 48 h[14] and 40 min versus 20 h[14]) (entries 2 and 3). The examples presented here illustrate the potential use of [bmim][PF_6] for the alkylation of Schiff bases as an alternative method to the reported ones which need the use of volatile OS and PTC.

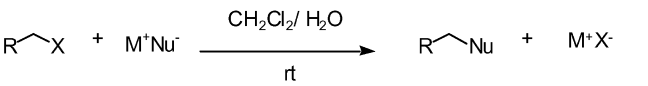
When the transformation was performed under similar reported conditions using the very efficient cinchoninium salts **3**[12] catalysts in [bmim][PF_6] instead of the traditional organic solvent, almost no asymmetric induction on the alkylation was observed (Scheme 1). The very low asymmetric induction observed is in line with the above results, which arise of competitive catalysts by the achiral RTIL that will predominate since the RTIL is present in enormeous excess as being the reaction solvent.

The use of the [bmim][PF_6] as a solvent and PTC to other representative nucleophilic substitution reactions of alkyl halides were also explored as e.g. phenoxide, iodide, cyanide and azide displacement. In a biphasic blank experiment using a system consisting of sodium phenoxide in water and benzyl bromide in dichloromethane without [bmim][PF_6] only 3% of phenyl benzyl ether was observed (Table 2, entry 1). On the other hand, the addition of



Scheme 1.

Table 2. Effect of the ionic liquid [bmim][PF_6] on aqueous-dichloromethane biphasic nucleophilic substitution reactions on benzyl bromide



Entry	M^+Nu^- (eq.)	[bmim][PF_6] (eq.)	Time (h)	Conversion (by ^{1}H NMR)
1[a]	NaOPh (1.0)	None	3	3%
2[a]	NaOPh (1.0)	0.5	3	80%
3[b]	KCN (2.0)	None	16	5%
4[b]	KCN (2.0)	0.5	16	47%
5[b]	NaN_3 (2.0)	None	5	37%
6[b]	NaN_3 (2.0)	0.5	5	90%

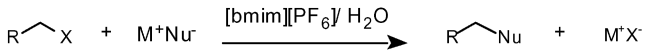
[a] Reaction was performed in a two phase system containing NaOH (6.0 eq.) in H_2O (1.0 mL), phenol (1.0 mmol) and BnBr (1.2 eq.) in dichloromethane (0.5 mL), vigorous stirring.
[b] Reaction was performed in a two phase system containing KCN or NaN_3 (2.0 eq.) in H_2O (1.0 mL), BnBr (1.0 mmol) in dichloromethane (0.5 mL), vigorous stirring.

[bmim][PF_6] (0.5 eq.) to the biphasic aqueous/dichloromethane system allows a considerable increase of the conversion (80%, entry 2). Similar effect of the [bmim][PF_6] was observed for the substitution with cyanide (5% versus 47%, entries 3 and 4) and azide (37% versus 90%, entries 5 and 6) anions. These experiments illustrate that the RTIL is an efficient PTC for these transformations.

Then we turned our attention to study the possibility of substitution of the volatile organic solvent by the [bmim][PF_6] (Table 3). By comparison with reported PTC examples the formation of aryl benzyl ethers is extremely effective under these conditions, giving high yields (98% versus 18%[13a]) using shorter reaction times (3 h versus 22 h[13a]) (entries 1–3). While the iodide/bromide exchange also occurs under these conditions, the conversion is lower than for reported PTC methods (44% versus 85%,[13a] entry 4) and only comparable yields were obtaining using KI (solid)/[bmim][PF_6] system (67%, entry 5). On the other hand, for the cyanide/bromide exchange the liquid/liquid system is considerable more effective and under milder conditions than the recent reported KCN (solid)/[bmim][PF_6] system[17] (92% at rt for 16 h versus 59% at 40°C for 200 h, entry 6).

The preparation of primary and secondary alkyl azides by azide/halogen exchange is the most common method.[18] Among several well known methods,[19] the reported procedure using NaN_3 dissolved in DMSO is simple and efficient, needing only mild conditions.[20] We observed that the use of a biphasic system of NaN_3 in water and the alkyl halide in [bmim][PF_6] is also extremely effective for this transformation at room temperature (entries 7 and 9–13). In case of the less reactive benzyl chloride (entry 8), higher temperature (75°C) is necessary. In the particular example of 2-bromoacetophenone was obtained the desired azide quantitatively, while a complex mixture was described in the reported method[20] (entry 10). We also studied the possibility to fulfil the azide displacement using less amount of the ionic liquid [bmim][PF_6]; 1 g of 3-bromoacetophenone dissolved in the minimal amount of [bmim][PF_6] (0.5 mL) was reacted with sodium azide dissolved in water (1.5 mL) for 1.5 h to give the corresponding azide in high

Table 3. Examples of nucleophilic substitution reactions in aqueous-RTIL system



Entry	RCH_2X (eq.)	M^+Nu^- (eq.)	Time (h)	Temp (°C)	Yield[a]
1[b]	BnBr (1.2)	Phenol	3	25	98%[c]
2[b]	BnBr (1.2)	4-Chloro-phenol	3	25	97%
3[b]	BnBr (1.2)	4-Chloro-phenol	12	25	98%
4[d]	1-Bromo-octane	KI (5.0)	12	75	44%[e]
5[f]	1-Bromo-octane	KI (5.0)	12	75	67%
6[d]	BnBr	KCN (2.0)	16	25	92%[g]
7[d]	BnBr	NaN_3 (2.0)	5	25	84%[h]
8[d]	BnCl	NaN_3 (2.0)	1.5	75	69%
9[d]	PhCHBrMe	NaN_3 (2.0)	1	25	63%[h]
10[d]	2-Bromo-acetophenone	NaN_3 (2.0)	1	25	98%[i]
11[d]	2,4′-Dibromo-acetophenone	NaN_3 (2.0)	1	25	95%
12[d]	1-Bromo-octane	NaN_3 (2.0)	3	75	27%[j]
13[k]	2-Bromo-acetophenone	NaN_3 (2.0)	1.5	25	95%

[a] Isolated yield, except for entries 4 and 5 corresponds to the observed conversion by ^{1}H NMR.
[b] Reaction was performed in a two phase system containing NaOH (6.0 eq.) in H_2O (1.0 mL), 1-*n*-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6] (0.5 mL), vigorous stirring.
[c] Reported yield of 18% using CH_2Cl_2/NaOH 0.1M in H_2O; catalyst (supported quaternary ammonium salt, 1 mol%); 22 h, 25°C.[13a]
[d] Reaction was performed in a two phase system containing H_2O (1.0 mL) and [bmim][PF_6] (0.5 mL), vigorous stirring.
[e] Reported yield of 85% using H_2O (no organic solvent was added); 8 h, 85°C.[13a]
[f] Reaction was performed in a two phase system containing solid KI and [bmim][PF_6] (0.5 mL), vigorous stirring.
[g] Reported yield of 59% using 1 M of BnBr in ionic liquid, 3 M KCN, 200 h, 40°C, HPLC conversion (59%).[17]
[h] Reported yield of 98% using NaN_3 (0.5 M, 1.1 eq.) in DMSO, rt, 1 h.[20]
[i] Reported formation of complex mixture using NaN_3 (0.5 M, 1.1 eq.) in DMSO, rt, 1 h.[20]
[j] Reported yield of 99% using NaN_3 (0.5 M, 1.1 eq.) in DMSO, rt, 4 h.[20]
[k] Reaction was performed in a two phase system containing H_2O (1.5 mL), and 2-bromoacetophenone (5.0 mmol) in [bmim][PF_6] (0.5 mL), vigorous stirring.

Table 4. Reuse of the ionic liquid [bmim][PF_6] for the azide substitution of 2-bromo-acetophenone

Cycle[a]	Yield[b]	Cycle[a]	Yield[b]	Cycle[a]	Yield[b]
1	94%	6	Quant.	11	Quant.
2	Quant.	7	Quant.	12	Quant.
3	Quant.	8	Quant.	13	Quant.
4	Quant.	9	Quant.	14	Quant.
5	Quant.	10	Quant.	15	Quant.

[a] All cycles were carried out using 2-bromo-acetophenone (2 mmol scale) in [bmim][PF_6] (2 mL)—water (4 mL) at room temperature for 1.5 h.
[b] Complete reaction by TLC; yield of isolated 2-azide-acetophenone after flash chromatography.

yield (95%) (entry 13). The use of this biphasic aqueous-RTIL procedure, in opposition to the reported method seems particularly appealing, since it avoids the use of less friendly solvent DMSO.

One important feature of the use of ionic liquids as reaction medium is the possibility of its recycle and reuse, for the same as well as for different types of reactions. We found that the recycling and reuse of the [bmim][PF_6] is feasible for the azide formation: using 2-bromo-acetophenone as a representative substrate, all reactions were performed for 1.5 h using biphasic water-[bmim][PF_6] system at room temperature (Table 4). After each cycle, the aqueous phase was removed and the ionic liquid phase was extracted with diethyl ether.† Then, more 2-bromo-acetophenone and aqueous phase containing NaN_3 was added to the ionic liquid. It is noteworthy that for the maximum of 15 cycles tested no starting bromide was detected by TLC and the isolated yield was high (>94%) for each cycle. The only observed limitation to this recycling procedure is the overall reduction of the ionic liquid phase to 40% of the initial volume, which arise from some solubility of the [bmim][PF_6] in water[1h] and in diethyl ether.[5f] This problem could be minimised by using supercritical CO_2 ($scCO_2$) extraction[7] or pervaporation.[9]

The stability of the ionic liquid under the reaction conditions is also an important issue. Due to the acidic nature of the proton H–C(2) of the imidazolium cation being more acidic (pK_a=22.7 in DMSO),[21] in case of the experiments performed under basic conditions, some alkylation on the carbon C(2) could eventually occur.‡ Additionally, the stability of the anion PF_6^- of the RTIL in the presence of water under acidic conditions has been also questioned, due to the occurrence of some decomposition reactions producing HF.[7c,22] However, the recovered [bmim][PF_6] from displacement reactions of benzyl bromide by phenoxide and azide (Table 3, entries 1 and 7) and the remained sample from the last cycle of the recycling experiments (Table 4) presented identical spectroscopic data (^{1}H, ^{13}C and ^{31}P NMR) to the initial sample allowing the conclusion that both imidazolium and PF_6 ions are stable under these conditions.

† Comparable results were obtained by extraction the reaction mixture with methyl *t*-butyl ether (MTBE) or di-*iso*-propyl ether.

‡ In the course of the ongoing studies on the use of ionic liquids as a reaction media for the Baylis-Hillman reaction (condensation between aldehydes and acrylates) catalysed by DABCO[5f] we observed more recently that under these conditions the base DABCO promotes the reaction between carbon (C2) of the imidazolium cation [bmim] and benzaldehyde to give the [bmim]-CH(OH)Ph adduct as a side reaction. While this reaction is minimised using [bmim][PF_6], the replace of the PF_6^- anion by the more polar BF_4^- or Cl^- considerably increases this side reaction (order of reactivity: [bmim][Cl]>[bmim][BF_4]>[bmim][PF_6]).

3. Conclusion

In summary, we have demonstrated, that the ionic liquid [bmim][PF_6] can be used as a useful media for nucleophilic substitution reactions, which traditionally needs the use of aqueous-organic biphasic systems by replacement of the volatile solvent reaction and the phase transfer catalyst. The possibility to recycle and reuse the [bmim][PF_6] for the azide formation was also demonstrated. Additionally, because of the peculiar properties of the RTILs, the reaction product can be potentially recovered by more environmentally friendly methods such as using supercritical CO_2 ($scCO_2$) extraction or pervaporation.

4. Experimental Section

4.1. General remarks

^{1}H NMR spectra were recorded on a Bruker AMX 400 spectrometer. Chemical shifts are reported downfield in parts per million (ppm) from a tetramethylsilane reference. IR spectra were recorded on a Mattson Instruments model Satellite FTIR as thinly dispersed films. Melting points (uncorrected) were determined on a Electrothermal Mod. IA 6304 capillary melting point apparatus. Flash chromatography column was carried out using MN Kieselgel 60M (40–63 μm, Art. 815381). All eluents were distilled prior to use. Preparative and analytical thin layer chromatography (TLC) was carried out using, respectively MN Kieselgel G/UV_{254} (Art. 816320) glass backed plates and MN Alugram® SIL G/UV_{254} (Art. 818133). The plates were visualised using ultraviolet light (254 nm). HPLC analysis were performed using Merck & Hitachi components L-600A, L-4250, T-6300, D-6000 using Chiralcel OD column (0.46 cm, 25 cm) at 25°C and λ=254 nm. Commercially supplied reagents were used as supplied. All aqueous solutions were prepared using distilled water. The room temperature ionic liquid (RTIL) 1-n-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6][1a,1f,23] and the cinchoninium salts **3b–d**[24] were prepared following reported procedures.

4.2. Typical procedure for the alkylation of *N*-diphenyl methylene glycine esters 1 (R=*t*-Bu) and 2 (R=Et)

Aqueous KOH solution (50%, 0.5 mL) was added to a vigorous stirred solution (approx. 1200 rpm) of Schiff base **1**[25] (70 mg, 0.24 mmol) or **2**[25] (70 mg, 0.26 mmol) and methyl iodide (1.2 eq.) or benzyl bromide (1.2 eq.) in 1-*n*-butyl-3 methylimidazolium hexaflurophosphate [bmim][PF_6] (1.0 mL) at room temperature in a glass vial of 10 mL. The course of the reaction was followed by TLC (eluent: *n*-hexane/ethyl acetate, 90:10). The reaction mixture was extracted with diethyl ether (5×5 mL) and the combined organic phases were dried over Na_2SO_4, filtered and evaporated in vacuo. Purification of the residue by preparative chromatography (eluent: *n*-hexane ethyl acetate/triethylamine, 89.5:10:0.5) gave the alkylated product. For the experiments performed in the presence of cinchoninium salts **3a–d** (10 mol%), the catalyst was added to the ionic liquid prior to the addition of the aqueous KOH solution. The enantiomer excess was determined by HPLC (Chiralcel OD column), eluent: *n*-hexane/2-propanol 99.5:0.5; 1.0 mL/min, t_R=11.8 min and t_g=12.6 min.

4.3. Typical procedure for the benzylation of phenol

NaOH (6.0 eq.) in water (1.0 mL) was added to a vigorous stirred solution (approx. 1200 rpm) of benzyl bromide (1.2 eq.) and the corresponding phenol (100 mg) [phenol (1.06 mmol); 4-chlorophenol (0.78 mmol); 4-nitrophenol (0.72 mmol)] in [bmim][PF_6] (0.5 mL) at room temperature in a glass vial of 10 mL. The course of the reaction was followed by TLC (eluent: *n*-hexane/ethyl acetate, 90:10). The reaction mixture was extracted with diethyl ether (5×3 mL) and the combined organic phases were dried over $MgSO_4$, filtered and evaporated in vacuo and the residue was passed through a small flash chromatography (pipette size, eluent: diethyl ether). After partial evaporation of the solvent, the aryl benzyl ether precipitated from the ether solution; phenyl benzyl ether (191.5 mg, 98%), mp 37–38°C (diethyl ether) reported[26] mp 37°C; 4-cholorophenyl benzyl ether (172.1 mg, 97%), mp 70–71°C (diethyl ether), reported[27] mp 69–70°C; 4-nitrophenyl benzyl ether (161.7 mg, 98%), mp 106–107°C (diethyl ether), reported[28] mp 105–107°C (ethanol).

4.4. Typical procedure for the bromide/iodide exchange

KI (187 mg, 5.0 eq.) in water (1.0 mL) was added to a vigorous stirred solution (approx. 1200 rpm) of 1-bromooctane (100 μl, 0.52 mmol) in [bmim][PF_6] (0.5 mL) at 75°C (oil bath) in a glass vial of 10 mL. The reaction mixture was extracted with diethyl ether (5×3 mL), the combined organic phases were dried over $MgSO_4$, filtered and evaporated in vacuo. The obtained crude mixture showed, by ^{1}H NMR, bromooctane and iodooctane respectively in 56:44. In case of entry 5, KI (187 mg, 5.0 eq.) was added as a solid to the solution of 1-bromooctane (100 μl, 0,52 mmol) in [bmim] [PF_6] (0.5 mL). The obtained crude mixture showed, by ^{1}H NMR, bromooctane and iodooctane respectively in 33:67.

4.5. Typical procedure for the bromide/cyanide exchange

Potassium cyanide (130 mg, 2.0 eq.) in water (1.0 mL) was added to a vigorous stirred solution (approx. 1200 rpm) of benzyl bromide (119 μl, 1 mmol) in [bmim][PF_6] (0.5 mL) at room temperature, in a glass vial of 10 mL. The course of the reaction was followed by TLC (eluent; *n*-hexane/ethyl acetate, 90:10). The reaction mixture was extracted with diethyl ether (5×3 mL), the combined organic phases were dried over $MgSO_4$, filtered and evaporated in vacuo Purification was made by flash chromatography (eluent: *n*-hexane/ethyl acetate, 90:10) to give 108,3 mg (92%) of benzyl cyanide as a oil.

4.6. Typical procedure for the preparation of azides

Sodium azide (130 mg, 2.0 eq.) in water (1.0 mL) was added to a vigorous stirred solution (approx. 1200 rpm) of alkyl halide (1 mmol scale) in [bmim][PF_6] (0.5 mL) at rt, in a glass vial of 10 mL. The course of the reaction was followed by TLC (eluent; *n*-hexane/ethyl acetate, 90:10).

The reaction mixture was extracted with diethyl ether (5×3 mL) and the combined organic phases were dried over $MgSO_4$, filtered and evaporated in vacuo. The obtained residue showed by ^1H NMR only the azide for entries 7, 10 and 11 and a mixture of azide and alkyl halide for entries 8 (98:2), 9 (80:20) and 12 (27:73), respectively; 2-azido-4′-bromo-acetophenone; IR (film): 2107, 1700, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25°C): δ 7.78, (2H, d J=8.4 Hz), 7.65 (2H, d J=8.4 Hz), 4.53 (2H,s), unstable in pure form. Spectral data (IR and ^1H NMR) of BnN_3[29,30] $PhCHN_3Me$,[29,31] 1-azido-octane[29] and 2-azido-acetophenone[32] identical to those reported. For the formation of 2-azido-acetophenone (entry 10), the reaction mixture was extracted (5×3 mL) with different solvents giving the following yields: methyl *t*-butyl ether (99%), di-*iso*-propyl ether (99%) and *n*-hexane (44%). In case of entry 13 was used sodium azide (653.9 mg, 2.0 eq.) in water (1.5 mL) and 2-bromoacetophenone (1.00 g, 5.0 mmol) in [bmim][PF_6] (0.5 mL).

4.7. Recycling assays

Sodium azide (267 mg, 2.0 eq.) in water (4 mL) was added to a vigorous stirred solution (approx. 1200 rpm) of 2-bromo-acetophenone (400 mg, 2.1 mmol) in [bmim][PF_6] (2 mL) at rt, in a glass vial of 20 mL. After 1.5 h (complete reaction by TLC) the aqueous phase was removed using a pipette and the remained ionic liquid phase was extracted with diethyl ether (4×10 mL). The combined organic phases were dried over $MgSO_4$, filtered, evaporated in vacuo and the residue was passed through a small flash chromatography (pipette size, eluent: diethyl ether) to give 2-azido-acetophenone; spectral data (IR and ^1H NMR) identical to the above sample. For the next cycle was added successively 2-bromo-acetophenone, a solution of sodium azide in water and repeated the previous procedure. After 15 cycles the volume of the ionic liquid [bmim][PF_6] was 0.8 mL; spectral data (IR, ^1H, ^{13}C and ^{31}P NMR) identical to the initial [bmim][PF_6] sample.

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