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Halogenation of organic compounds in ionic liquids

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Abbreviations: Ac, acetate, $MeCOO^-$; AIBN, 2,2′-azobis(isobutyronitrile); BINAP, 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; Bu, butyl, C_4H_9; CAN, ceric ammonium nitrate; CPO, chloroperoxidase; cyc, *cyclo*- or cyclic; DABCO, 1,4-diazobicyclo[2.2.2]octane; DAST, diethylaminosulfur trifluoride, Et_2NSF_3; DBU, 1,8-diazobicyclo-[5,4,0]-7-undecene; DCE, 1,2-dichloroethane; DFI, 2,2-difluoro-1,3-dimethylimidazolidine; DMA, dimethylacetamide; DME, 1,2-dimethoxyethane; DMF, dimethylformamide; DMSO, dimethylsulfoxide; Et, ethyl, C_2H_5; EWG, electron-withdrawing group; FDG, 2-fluoro-2-deoxy-D-glucose; FLT, 3′-deoxy-3′-fluorothymidine; F-TEDA-BF_4, 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); IL, ionic liquid; Me, methyl, CH_3; Ms, mesylate, methanesulfonate, $CH_3SO_3^-$; MW, microwave; NFPy·B_2F_7, 1-fluoropyridinium pyridine heptafluorodiborate; NFTh, 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane; NXS (X=C,B, I), *N*-halo (chloro-, bromo-, iodo-) succinimide; Ph, phenyl; Pr, propyl; PSIL, polymer-supported ionic liquid; $PTMAICl_2$, phenyltrimethylammonium dichloroiodate, $Ph(CH_3)_3N^+ICl_2^-$; PTSA, *p*-toluenesulfonic acid; rt, room temperature; SM, starting material; SPB, sodium perborate, $NaBO_3 \cdot 4H_2O$; TBAA, tetrabutylammonium acetate, [*n*-Bu_4N][OAc]; TBAB, tetrabutylammonium bromide, [*n*-Bu_4N][Br]; TBDMS, *tert*-butyldimethylsilyl; TCICA, trichloroisocyanuric acid; TEMPO, 2,2,6,6-tetramethylpiperidine1-oxyl; Tf, triflate, trifluoromethanesulfonate, $CF_3SO_3^-$; TFA, trifluoroacetate, CF_3COO^-; THP, tetrahydropyranyl; TMS, trimethylsilyl; Ts, tosylate, *p*-toluenesulfonate; TSIL, task-specific ionic liquid; UHP, urea-hydrogen peroxide; [emim], 1-ethyl-3-methylimidazolium; [bmim], 1-butyl-3-methylimidazolium; [pmim], 1-pentyl-3-methylimidazolium; [hmim], 1-hexyl-3-methylimidazolium; [Hmim], 3-methylimidazolium; [omim]=[C_8mim], 1-octyl-3-methylimidazolium; [C_{10}mim], 1-decyl-3-methylimidazolium; [domim]=[C_{12}mim], 1-dodecyl-3-methylimidazolium; [bbim], 1-butyl-3-butylimidazolium; [bm_2im], 1-butyl-2,3-dimethylimidazolium; [bPy]=[C_4Py], *N*-butylpyridinium; [C_5Py], *N*-pentylpyridinium; [hPy]=[C_6Py], *N*-hexylpyridinium; [bmpy], 1-butyl-1-methylpyrrolidinium; [C_8Qui], *N*-octylquinolinium; [Acmim], 1-acetyl-3-methylimidazolium; PS[him-^{t}OH], polymer-supported 1-hexamethyl-3-*tert*-hydroxyl-functionalized imidazolium cation; TBA=[*n*-Bu_4N], tetrabutylammonium; $N_{2226}B_{2226}$, triethyl-*n*-hexyl-ammonium triethyl-*n*-hexylboride; Citr, citrate, $HOC(CH_2COOH)_2COO^-$; OTf, triflate, $CF_3SO_3^-$; NTf_2, bis(trifluoromethylsulfonyl)imide, $N(CF_3SO_2)_2$; OMs, mesylate, $CH_3SO_3^-$; X, halide (Cl^-, Br^-, I^-).

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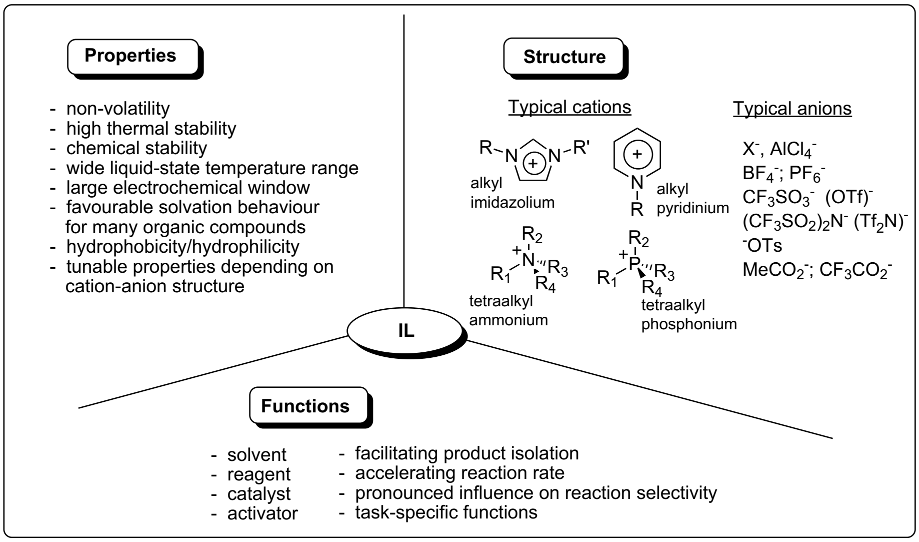
1. Introduction

The term ionic liquid (IL) generally refers to salts with a melting temperature below the boiling point of water. Although considerable interest has been shown in ILs in the last decade, recognizing them as novel solvents, a report on a salt with a melting point of 8 °C appeared as early as 1914,[1] but did not receive much attention in the following decades. Then, in the late 1970s, ILs containing chloroaluminate ions were developed by electrochemists in search of ideal electrolytes for batteries.[2] Increasingly stringent environmental demands created renewed interest in 'molten salts' at the end of the last century, leading to the rediscovery of ILs as potential media for 'greener' reaction protocols.[3] While early emphasis on their 'green' aspect relied on their non-volatility, their unique physico-chemical properties (namely high thermal and chemical stability, wide liquid-state temperature range, large electrochemical window, and favourable solvation behaviour) were also considered to be promising advantages.[4] Increased interest led to an exponential growth of papers reporting on various aspects of ILs,[5] including synthesis of a vast number of new ILs, and their application in synthetic transformations,[6] catalysis,[7] electrochemistry,[8] spectroscopy and extraction and separation processes, in some of which, halogenation reactions have only been partially and briefly discussed.[4a,c,5f,6,7c,8] By a judicious combination of cations and anions, it is possible to generate a huge set of ILs (Scheme 1). The cation is usually bulky with a low degree of symmetry, most commonly used cations being based on the imidazolium and pyridinium substructures, while BF_4^-, PF_6^-, OTf^- and NTf_2^- often constitute the anionic part. The possibility of tuning their properties by varying the nature of the constituent ions has enabled the design of ILs for specific applications, hence the term task-specific ILs (TSILs) or designer solvents.[9] Apart from being applied as non-volatile and potentially reusable solvents, ILs have been shown to serve other important roles, including acting as reagents, catalysts or activators, as generators of novel catalytic species, facilitators of product isolation, accelerators of reaction rates, and often as significant influencers of reaction selectivities. A full understanding of their physical and chemical behaviour is, however, still lacking, especially with regard to toxicity studies, and research on their environmental influence has only just started to appear.[10] The notion of the unusual high stability of ILs has been challenged in recent articles, and the 'non-innocent' nature of some ILs has also been recently highlighted in a review.[11]



Scheme 1. Properties and common functions of ILs.

Table 1
Atomic properties[a] of halogens[12e,13]

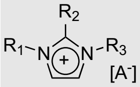
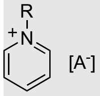
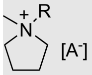
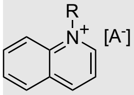
Atom	IP (kcal/mol)	EA (kcal/mol)	α_v (Å^3)	r_v (Å)	χ_p	E_{C-X} (kcal/mol)
H	313.6	17.7	0.667	1.20	2.20	
O	310.4	33.7	0.82	1.52	3.5	
C	240.5	29.0	1.76	1.70	2.55	
F	401.8	79.5	0.557	1.47	3.98	115.7
Cl	299.0	83.3	2.18	1.75	3.16	77.2
Br	272.4	72.6	3.05	1.85	2.96	64.3
I	241.2	70.6	4.7	1.98	2.66	50.7

[a] IP ionisation potential; EA electron affinity; α_v atomic polarisability; r_v van der Waals radius; χ_p Pauling electronegativity; E_{C-X} bond energy.

Due to their distinctive properties, organohalogen compounds have found widespread use in a range of applications, serving as valuable intermediates in organic synthesis, as radiolabelled markers in medical diagnostics and as active substances in the pharmaceutical industry. Halogenated organics are also utilized as agrochemicals, pigments and photographic materials. Consequently, their related chemistry has received a wealth of attention.[12]

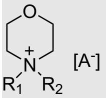
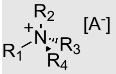
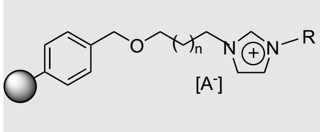
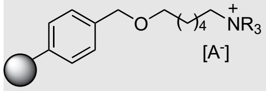
There is a considerable variation in the properties of the halogens (X=F, Cl, Br, I), with fluorine occupying one extreme and iodine the other, resulting in a marked difference in reactivity of the C–X bond and, consequently, in the corresponding synthetic routes that are available for forming carbon–halogen bonds. To illustrate this, it is sufficient to point out that fluorine is the smallest halogen, it is highly electronegative, least polarizable and forms the strongest C–X bond, while for iodine, the opposite characteristics hold true (Table 1).[12e,h,13] Whereas elemental fluorine is too reactive/poorly selective, requiring special handling and safety precautions, elemental iodine is scarcely reactive enough to be effectively introduced into organic molecules. Therefore, numerous approaches and reagents were developed for efficient and selective halogenation. The progress and outcomes of halotransformations proved to be crucially dependent upon the substrate structure, reagent structure and other reaction conditions such as solvent properties, reaction time, source of energy (heat, microwave, pressure) and presence of promoters and/or catalysts (Scheme 2). With the boost of interest in ILs as neoteric solvents in the last decade and the importance of organohalogen compounds, significant attention has been focused on halogenation reactions in these media comprising alternatives to organic solvents (Scheme 3). Since a comprehensive review that systematically focuses on halotransformations in ILs has not yet appeared, it is the aim of this review to fill this knowledge gap.

List of ILs utilized for halotransformations.[a]

IL type	Cationic part				Anionic part	IL abbreviation
	R_1	*R_2*	*R_3*	*Abbreviation*	*A*	
	H	H	Me	[Hmim]	Cl, Br, NO_3, Br_3, HBr_2	[Hmim][Cl], [Hmim][Br], [Hmim][NO_3], [Hmim][Br_3], [Hmim][HBr_2]
	Me	H	Me	[mmim]	$MeSO_4$, Me_2SO_4	[mmim][$MeSO_4$], [mmim][Me_2SO_4]
	Et	H	Me	[emim]	BF_4, PF_6, OTf, NTf_2, $EtSO_4$, $(HF)_{2,3}$	[emim][BF_4], [emim][PF_6], [emim][OTf], [emim][NTf_2], [emim][$EtSO_4$], EMIM$(HF)_{2,3}$ (see Fig. 3)
	*i*Pr	H	Me	[^{i}Prmim]	Br	[^{i}Prmim][Br]
	^{n}Pr	H	Me	[^{n}Prmim]	I	[^{n}Prmim][I]
	(*sec*) C_3H_6OH	H	Me	[$^{2\text{-}OH}C_3$mim]	PF_6	[$^{2\text{-}OH}C_3$mim][PF_6] (IL*), IL*-$OPPh_2$ (see Fig. 6)
	^{n}Bu	H	Me	[bmim]	BF_4, PF_6, OTf, NTf_2, SbF_6, HSO_4, Cl, Br, I, Br_3, IBr_2, CCl_3COO, CF_3COO, $Co(CO)_4$, $Cl\cdot xAlCl_3$, OH	[bmim][BF_4], [bmim][PF_6], [bmim][OTf], [bmim][NTf_2], [bmim][SbF_6], [bmim][HSO_4], [bmim][Cl], [bmim][Br], [bmim][I], [bmim][Br_3], [bmim][IBr_2], [bmim][CCl_3COO], [bmim][CF_3COO], [bmim][$Co(CO)_4$]; [bmim]$Cl\cdot xAlCl_3$ (x=1.27–2.0), [bmim][OH]
	$C_4H_8SO_3H$	H	Me	[bmim(SO_3H)]	OTf	[bmim(SO_3H)][OTf]
	C_5H_{11}	H	Me	[pmim]	Br, BF_4	[pmim][Br], [pmim][BF_4];
	C_6H_{13}	H	Me	[hmim]	BF_4, PF_6, OTf, NTf_2, SbF_6, OAc, ClO_4, Cl, I, ICl_2	[hmim][BF_4], [hmim][PF_6], [hmim][OTf], [hmim][NTf_2], [hmim][SbF_6], [hmim][OAc], [hmim][ClO_4], [hmim][Cl], [hmim][I], [hmim][ICl_2];
	C_8H_{17}	H	Me	[omim]	PF_6, Br, I	[omim][PF_6], [omim][Br], [omim][I];
	$C_{10}H_{21}$	H	Me	[C_{10}mim]	Cl	[C_{10}mim][Cl];
	$C_{12}H_{25}$	H	Me	[C_{12}mim] or [domim]	Br, BF_4	[C_{12}mim][Br], [C_{12}mim][BF_4];
	Ac	H	Me	[Acmim]	Cl, Br, I	[Acmim][Cl], [Acmim][Br], [Acmim][I];
	^{n}Bu	H	^{n}Bu	[bbim]	BF_4	[bbim][BF_4];
	^{n}Bu	Me	Me	[bm_2im]	NTf_2, PF_6, BF_4	[bm_2im][NTf_2], [bm_2im][PF_6], [bm_2im][BF_4]
	R			Cation abbreviation	A	
	^{n}Bu			[C_4Py] or [bPy]	BF_4, NTf_2	[C_4Py][BF_4], [bPy][NTf_2]
	C_5H_{11}			[C_5Py] or [pPy]	Br, Br_3	[C_5Py][Br], [C_5Py][Br_3]
	C_6H_{13}			[C_6Py] or [hPy]	NTf_2	[C_6Py][NTf_2]
	^{n}Bu			[bmpy]	NTf_2, OTf	[bmpy][NTf_2], [bmpy][OTf]
	C_8H_{17}			[C_8Qui]	Br_3	[C_8Qui][Br_3]

(*continued on next page*)

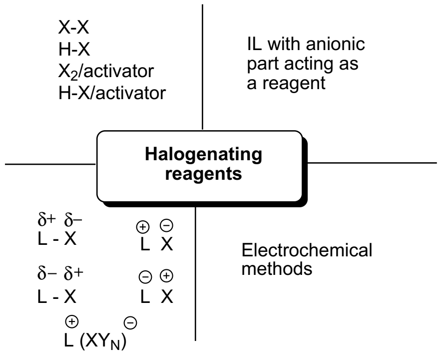
(*continued*)

IL type	Cationic part		Anionic part	IL abbreviation
	R_1=R_2=Me	[Mor$_{11}$]	$MeSO_4$	[Mor$_{11}$][$MeSO_4$]
	R_1=R_2=R_3=R_4=*n*Bu	[*n*-Bu_4N] or [N_{444}] or TBA	Br, Cl, I, IBr_2	[*n*-Bu_4N][Br] (=TBAB), [*n*-Bu_4N][Cl], [*n*Bu_4][I] [*n*-Bu_4N][IBr_2]
	R_1=R_2=R_3=Me, R_4=C_2H_4OH	[N_{1112OH}]	OAc, H_2PO_4, Citrate	[N_{1112OH}][OAc], [N_{1112OH}][H_2PO_4], [N_{1112OH}][Citr]
Polymer-supported ILs		*n*	*R*	
		1	Me	PS[^{n}Prmim][BF_4]
		2	Me	PS[bmim][BF_4]
		4	Me	PS[hmim][A] (A=BF_4, PF_6, OTf, SbF_6, OAc, OMs)
		10	Me	PS[C_{12}mim][BF_4]
		4	*tert*OHC_4H_8	PS[him-^{t}OH][OMs]
		4	Et	PS[hNEt$_3$][OMs]
IL electrolytes			$Et_3N\cdot 3HF$, $Et_3N\cdot 4HF$, $Et_3N\cdot 5HF$, $Et_4N\cdot 4HF$, $Et_4N\cdot 5HF$	

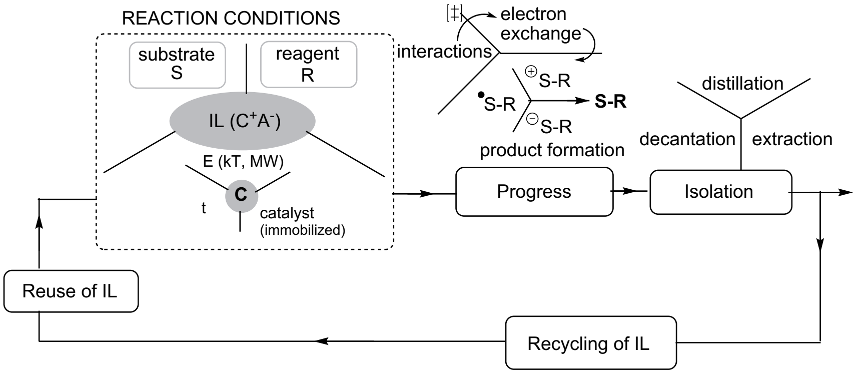
[a] For abbreviations, see abbreviations list.

2. Fluorofunctionalization of organic compounds in ILs

Owing to its unique properties and reactivities, fluorine is regarded as being totally different in its chemistry from that of the other halogens. The dramatic change in physical, chemical and biological properties of many organic compounds upon incorporation of fluorine into the molecule stems from fluorine's unique combination of properties (see discussion earlier). An increased demand for fluorinated compounds for diverse applications such as pharmaceuticals, agrochemicals, solvents, liquid crystals, dyestuffs, polymers and novel materials has been notable in recent decades. Consequently, the selective fluorination of organic molecules has become a very important target in various sectors, ranging from pharmaceuticals to electronics. Much effort has been placed in developing methods for the selective introduction of fluorine into target molecules, but, nevertheless, mild, selective and environmentally more acceptable fluorination still continues to remain a significant challenge for organofluorine chemists. The synthetic strategies can be divided into two groups, namely the 'building-block' approach utilizing a starting material already containing the needed C–F bond(s) and direct methods of C–F bond formation. The latter methods will be discussed in this section and can be further subdivided based on the electronic nature of the reaction system. Fluorine can be incorporated into organic molecules in a nucleophilic manner, an electrophilic manner, or electrochemically. The outcome of fluorotransformations performed in ILs will be compared to that in methods initially developed in organic solvents, highlighting the advantages and/or disadvantages of ILs. Attention will also be given to the practical utilization of fluorination methods in ILs, especially for radiochemical applications.

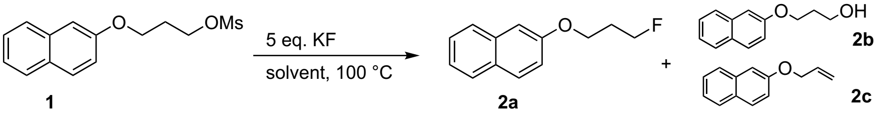


Scheme 3. Types of reagents for halogenation in ILs.



Scheme 2. Various steps of a transformation performed in IL.

Table 2
Fluorination of mesylate (**1**) with KF under various ionic liquids and cosolvents[a]



Entry	IL (ml)	MeCN (ml)	H_2O (μl)	Reaction time (h)	Yield[b] (%)			
					1	**2a**	**2b**	**2c**
1	—	5	—	24	86	Trace	—	—
2	[bmim][BF_4] (5)	—	—	2	—	85	—	10
3	[bmim][BF_4](5)	—	90[c]	1.5	—	92	—	—
4	[bmim][BF_4] (1.6)	3.2	90	1.5	—	94	—	—
5	[bmim][PF_6] (1.6)	3.2	90	2	—	90	Trace	—
6	[bmim][SbF_6] (1.6)	3.2	90	2	—	93	—	—
7	[bmim][OTf] (1.6)	3.2	90	4	—	79	15	—
8	[bmim][NTf_2] (1.6)	3.2	90	5	61	35	Trace	—

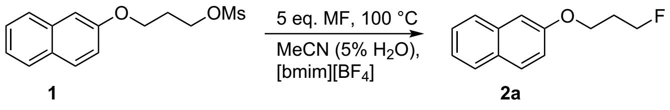
[a] Reactions carried out on 1.0 mmol reaction scale of mesylate **1** using 5 mmol KF.
[b] Isolated yield.
[c] 5 equiv.

2.1. Nucleophilic fluorination in ILs

Introduction of a single fluorine into aliphatic organic compounds has been typically carried out by nucleophilic substitution of sulfonates and halides utilizing alkali-metal fluorides as reagents. Their limited solubility and low nucleophilicity in organic solvents require generally vigorous conditions. Moreover, in addition to behaving as a nucleophile, fluoride anion can act as a base, causing the formation of undesired byproducts. In 2002, Kim et al. reported a highly efficient method for the synthesis of fluoroalkanes from alkyl mesylates or alkyl halides using KF in various ILs.[14] Whereas the fluorination of 2-(3-methanesulfonyloxypropoxy)naphthalene (**1**) with KF in acetonitrile at 100 °C hardly occurred, even after 24 h (Table 2, entry 1), the same reaction performed in [bmim][BF_4] was completed within 2 h (Table 2, entry 2), giving **2a** along with the formation of significantly smaller amounts of alkene **2c** as byproduct, which could, however, be completely eliminated by the addition of 5 equiv of water (Table 2, entries 3 and 4). Under optimized reaction conditions, other imidazolium-based ionic liquids, namely [bmim][PF_6], [bmim][SbF_6], [bmim][OTf] and [bmim][NTf_2], were investigated in the presence of various cosolvents for this transformation.

Similar to [bmim][BF_4], high yields of the fluorinated alkyl product were also obtained in [bmim][PF_6] and [bmim][SbF_6] ILs, while in [bmim][OTf], the yield was slightly lower and in [bmim][NTf_2] the yield was rather poor (Table 2, entries 5–8). The same authors further reported that fluorination using 5 equiv of KF in [bmim][BF_4] as the solvent provided good yields of the fluorinated products from primary mesylato-, chloro-, bromo- and iodoalkanes, while secondary mesylates or halides predominantly underwent elimination. Based on their experimental results, the authors stated that the IL–water system significantly enhanced the reactivity of KF and reduced the formation of byproducts such as alkenes **2c** and alcohols **2b**. As a continuation of this study, Chi et al. studied the fluorination of mesylate **1** with various metal fluorides in [bmim][BF_4] (Table 3, entries 1–7) and found that CsF was the most reactive among alkali-metal fluorides, while fluorination using alkaline-earth and transition-metal fluorides under the same set of conditions hardly occurred or did not proceed.[15]

Table 3
Fluorination of mesylate **1** with various metal fluorides in [bmim][BF_4][a]

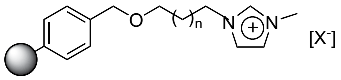


Entry	MF	Reaction time (h)	Yield[b] (%)
1	LiF	48	
2	NaF	48	
3	KF	1.5	93
4	RbF	0.5	93
5	CsF	20 min	95
6	CaF_2	24	
7	AgF	48	5[c]

[a] Reactions carried out on 1.0 mmol reaction scale of mesylate **1** using 5 mmol MF in 3 ml [bmim][BF_4] and 3 ml MeCN (5% H_2O) at 100 °C.
[b] Isolated yield.
[c] Determined by ^1H NMR.

In the same year, Murray et al. reported Halex fluorination, utilizing CsF in a hydrophobic IL [bmim][PF_6] for substitution of bromine or chlorine by fluorine located at various sp^2 and sp^3 carbon sites.[16] The fluorination of highly activated systems such as benzoyl chloride or benzyl bromide occurred efficiently at room temperature, while less reactive substrates, namely bromoalkanes, gave lower yields of the corresponding fluoroalkanes, due to the elimination reaction as a competing process. The authors also demonstrated the reusability of the IL over a limited number of reaction cycles.

To overcome the problems that were noted during the isolation step of highly polar fluorinated compounds containing many heteroatoms after fluorination with an alkali-metal fluoride in IL, Kim et al. developed a polymer-supported IL (PSIL), based on imidazolium salts (Fig. 1).[17,18] These proved to be highly efficient catalysts for nucleophilic fluorination, which converted various haloalkanes and sulfonyloxyalkanes into their corresponding fluorinated products. In particular, PS[hmim]BF_4 showed a significantly higher catalytic activity as compared to free IL. Moreover, these workers were able to demonstrate catalyst recovery and its practical reuse. Product isolation and purification of polar substrates, which, due to their high solubility can be extracted from ILs with great difficulty,

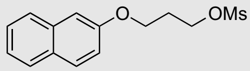
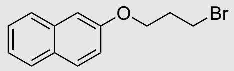
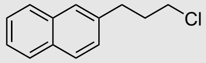
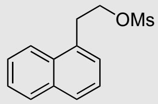


X = BF_4, n = 1: PS[pmim][BF_4]
X = BF_4, n = 4: PS[hmim][BF_4]
X = BF_4, n = 10: PS[domim][BF_4]
X = PF_6, n = 4: PS[hmim][PF_6]
X = SbF_6, n = 4: PS[hmim][SbF_6]
X = OTf, n = 4: PS[hmim][OTf]
X = OAc, n = 4: PS[hmim][OAc]

Figure 1. Different structurally modified polymer-supported ILs: PS[alkylmim][A].

Table 4

Synergistic effect of PS[hmim][BF_4] and *tert*-amyl alcohol for fluorination with CsF

Entry	Compound	Method[a]	T (°C)	t (h)	Yield[b] (%)	Comment
1		A	80	6	93	5% Ether[c]
2		B	80	12	89	9% SM[d]
3		C	80	1	96	2% Ether[c]
4		A	90	2	18[c]	81% SM
5		B	90	12	40	52% Alkene
6		C	90	2	84	11% Alkene
7		A	100	24	Trace	90% SM
8		C	100	24	92	Trace alkene
9		B	90	12	24	73% Alkene
10		C[e]	90	1	87	9% Alkene

[a] Method A: in *tert*-amyl alcohol, B: with 0.5 equiv PS[hmim][BF_4] in MeCN, C: with 0.5 equiv PS[hmim][BF_4] in *tert*-amyl alcohol.

[b] Isolated yield.

[c] Determined by NMR spectroscopy.

[d] Starting material (SM) determined by NMR.

[e] PS[hmim][BF_4] (0.25 equiv) was used.

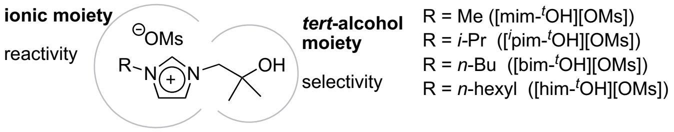


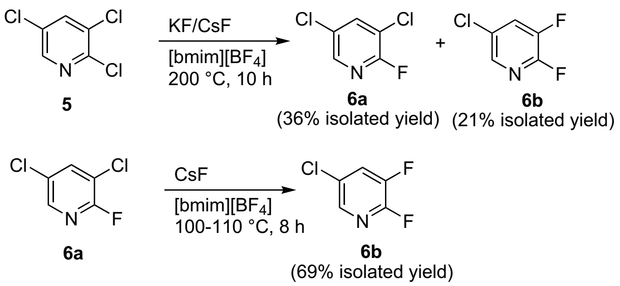
Figure 2. ILs functionalized with *tert*-alcohols.

became simpler in the polymer-supported version. In examining the relationship between catalytic activity and the length of the alkyl chain linker, the counteranion and the loading level of the IL portion on the resin, they found that a longer alkyl linker had superior catalytic activity, which was ascribed to the longer distance between the polystyrene backbone and the IL moiety.[18] Tetrafluoroborate (BF_4^-) as the counteranion showed the best catalytic activity as compared to PSIL systems with other counteranions. Furthermore, the PSIL system with a higher ionic portion exhibited improved catalytic performance in fluorination reactions, which can be explained by the matrix effect.[18] Kim et al. also reported the synergistic effect of the PSIL as a catalyst and *tert*-amyl alcohol as a non-polar protic solvent for nucleophilic fluorination employing various metal fluorides (CsF, RbF or KF).[19]

The PS[hmim][BF_4]/*tert*-alcohol system not only enhanced the reactivity of metal fluorides significantly, but, remarkably, also suppressed side reactions (Table 4, entries 1–10). This was explained by the weak F–H hydrogen bond that maintained the inherent nucleophilicity and reduced the basicity of the fluoride anion. Other practical merits of this protocol as compared with the conventional method, employing the use of a *tert*-alcohol solvent or a PSIL system alone, include easy purification, recyclability and reusability, without any loss of the catalytic activity for 10 cycles in the case of PS[hmim][BF_4]. These findings were applied to the synthesis of functionalized ILs with a *tert*-alcohol moiety (Fig. 2), which were then utilized for nucleophilic fluorine substitution as both the solvent and the catalyst.[20] They provided better conversion and selectivity than conventional ILs, with the highest yield obtained in the case of [mim-^{t}OH][OMs]. By demonstrating the synergistic effect of functionalized ILs possessing a *tert*-alcohol functionality, the authors illustrated the possibility of solvent engineering for a specific reaction. Furthermore, such a functionalized IL was loaded onto a polystyrene backbone, forming a polymer-supported protic functionalized IL for nucleophilic substitution reactions.[21] The *tert*-alcohol-containing PSIL resin displayed superior reactivity and chemoselectivity, as compared to unfunctionalized PSIL, and this was rationalized by the synergism between the imidazolium salt and the *tert*-alcohol hydroxyl group. Subsequently, the PS[mim-^{t}OH][OMs]-catalyzed fluorinations of mesylate **1** using CsF (3 equiv) were conducted in several solvents, and MeCN was found to be the solvent of choice, as it gave no byproducts.

Anguille et al.[22] studied the reaction of KF with trichlorotoluene (**3**) in different imidazolium-derived ILs to form **4a**–**c** (Scheme 4). The reaction was faster in ILs than in regular organic solvents, but was strongly dependent upon the nature of the anion. These workers also established that substoichiometric amounts of bromide salts strongly activated nucleophilic fluorination in [bmim][PF_6], while KPF_6 was a potent activator of nucleophilic fluorination in [bmim][PF_6], [bmim][NTf_2] and sulfolane.

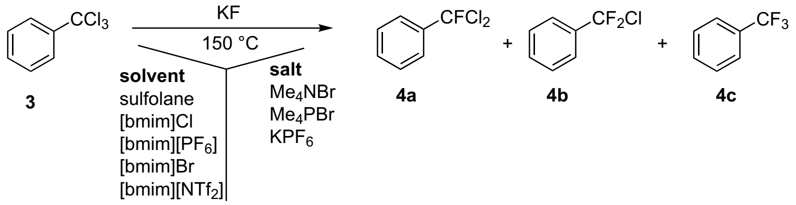
One of the first nucleophilic displacement reactions of a heterocyclic aromatic compound in an IL was reported for the preparation of 3,5-dichloro-2-fluoropyridine (**6a**) and 5-chloro-2,3-difluoropyridine (**6b**) from 2,3,5-trichloropyridine (**5**), with KF or CsF in [bmim][BF_4] at an elevated temperature and under substantially anhydrous conditions, requiring the removal of the difluoropyridine product essentially as it was formed (Scheme 5).[23]



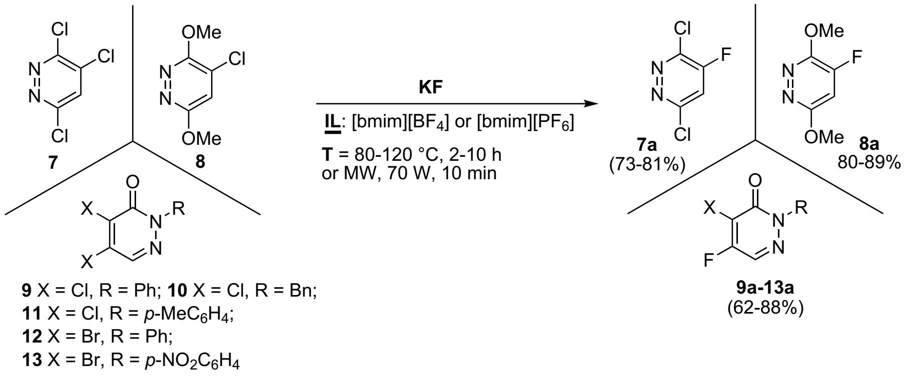
Scheme 5. Fluorination of heterocycles by nucleophilic displacement reaction.

Fluorination of various chloro- and bromo-substituted pyridazine derivatives **7**–**13** was investigated in [bmim][BF_4] and [bmim][PF_6] employing KF as the reagent under conventional heating (80–120 °C) or under MW irradiation.[24] Fluoropyridazines **7a**–**13a** were formed efficiently, while the MW-assisted fluorination reactions decreased the reaction time (Scheme 6).

Kitazume and Ebata used 2,2-difluoro-1,3-dimethylimidazolidine (DFI) as a nucleophilic source of fluorine in the fluorination of

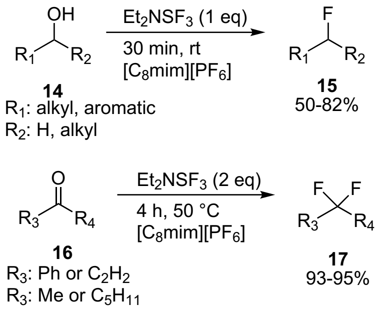


Scheme 4. Fluorination of trichlorotoluene with KF in ILs.



Scheme 6. Fluorination of halopyridazine derivatives in ILs.

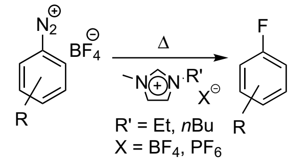
alcohols and α,β-epoxy carbonyl compounds, in [bmim][PF$_6$], [emim][OTf] and [bmim][BF$_4$] at room temperature.[25] While fluorine was introduced efficiently, by employing 2 equiv of DFI in the case of benzyl alcohol and 1-phenylethanol, (*E*)-1-cinnamyl alcohol was converted into (*E*)-1-phenyl-3-fluoro-1-propene in only 11% yield. In the case of phenyl ketones, the target difluoromethylene compound was obtained in [bmim][PF$_6$]. Although methyl ketone derivatives produced a tarry material, the chiral α,β-epoxy carbinol compounds were converted into the corresponding chiral monofluoro-methylated α,β-epoxy compounds. Dehydroxy-fluorination of alcohols with aliphatic chains, unsaturated side chains or aromatic moieties (**14**→**15**) and *gem*-difluorination of carbonyl compounds (**16**→**17**) were studied in [C$_8$mim][PF$_6$] as solvent, employing diethylaminosulfur trifluoride (DAST) as the fluorinating agent (Scheme 7).[26] DAST-mediated fluorination reactions of alcohols were performed at room temperature, yielding the corresponding fluorinated products in 50–96% yield, which were isolated either directly by distillation (in the case of volatile fluorinated small molecules) or via extraction. The [C$_8$mim][PF$_6$] IL could be recycled for the same or other DAST-mediated reactions. *gem*-Difluorination of carbonyl compounds was carried out at 50 °C, employing 2 molar equivalents of DAST, and gave the corresponding products in good yields (>90%).



Scheme 7. DAST-mediated fluorination of alcohols and carbonyl compounds in [C$_8$mim][PF$_6$].

A classical method for the synthesis of fluoroaromatics is the fluorodediazoniation reaction, known also as the Balz–Schiemann reaction, which involves the thermal decomposition of an aryldiazonium tetrafluoroborate or hexafluorophosphate salt. Laali and Gettwert[27a] employed imidazolium-based ILs with $\mathrm{BF_4^-}$ and $\mathrm{PF_6^-}$ counteranions as solvents for fluorodediazoniation (Table 5) and for in situ diazotization/fluorodediazoniation, in order to produce fluoroaromatics in quantitative yields. In the case of the alkyl-substituted diazonium salts, the BF$_3$ or PF$_5$ Lewis acid byproducts and HF impurities initiated some alkyl disproportionation, but these side reactions could be prevented by addition of the Hünig base $\mathrm{NEt}^i\mathrm{Pr}$ prior to product extraction.

Table 5
Fluorodediazoniation in ILs



IL	R	Base	*T* (°C)	Yield[a] (%)
[emim][BF$_4$]	*p*-MeO	—	120	100
	2,4,6-(Me)$_3$	$\mathrm{NEt}^i\mathrm{Pr}_2$	70	100
	p-tBu	NaHCO$_3$	70	100
	p-Br	—	90	100
	p-Cl	$\mathrm{NEt}^i\mathrm{Pr}_2$	110	100
	o-Me	$\mathrm{NEt}^i\mathrm{Pr}_2$	30	100
	H	—	70	100
	p-NO$_2$	NaHCO$_3$	80	100
	m-NO$_2$	—	80	100
	p-CN	$\mathrm{NEt}^i\mathrm{Pr}_2$	50	100
[bmim][PF$_6$]	2,4,6-(Me)$_3$	$\mathrm{NEt}^i\mathrm{Pr}_2$	80	100
	H	$\mathrm{NEt}^i\mathrm{Pr}_2$	100	100
	p-NO$_2$	$\mathrm{NEt}^i\mathrm{Pr}_2$	100	100

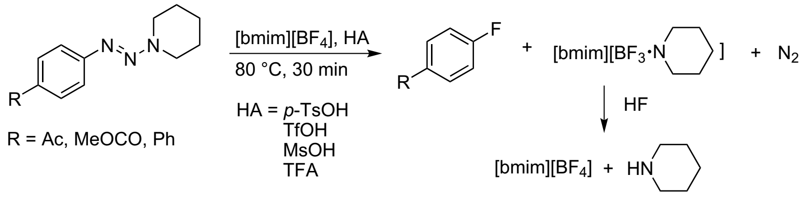
[a] Determined by ^{1}H NMR.

In a different study by Laali et al.,[27b] minimal amounts of the Schiemann products ArF were formed during thermal or photolytic dediazoniation of arenediazonium tetrafluoroborate salts ($\mathrm{ArN_2^+BF_4^-}$) immobilized in [bmim][NTf$_2$]. Arenediazonium salts undergo methathesis, and upon dediazoniation, yield the corresponding oxy-anion quenching products (ArO–SO(CF$_3$=NTf)) as the major and ArNTf$_2$ as the minor products. A similar competing fluorodediazoniation was observed by Laali et al.[27c] in their halodediazoniation studies of $\mathrm{ArN_2^+BF_4^-}$ salts with TMSX (X=Br, I) in [bmim][PF$_6$] as the solvent.

Fluorine can be introduced into aromatics bearing electron-withdrawing substituents via the Wallach reaction, which involves the acid-catalyzed decomposition of triazenes (Scheme 8). The reaction has been performed in [bmim][BF$_4$], where the IL acts both as the solvent and as the fluoride anion source.[28]

Ionic liquids were also investigated as reaction media for nucleophilic trifluoromethylation reactions of aryl, allyl, benzyl and alkyl halides with trifluoromethyl(trimethyl)silane in Cu(I)-mediated C–C bond-forming reactions.[29] Morpholinium-based ILs proved to be comparable to organic solvents and superior to oxazolidinium-, imidazolium- and triazolium-based ILs. Trifluoromethylation reactions of ketones and aldehydes, conducted as part of the same investigation, were solvent and catalyst dependent, but proceeded smoothly in a morpholinium-based IL, catalyzed by Ph$_3$P or CsF.

The IL 1-ethyl-3-methylimidazolium oligo hydrogen fluoride (emimF(HF)$_{2,3}$) is made up of the 1-ethyl-3-methylimidazolium



Scheme 8. Fluorination by decomposition of triazenes.

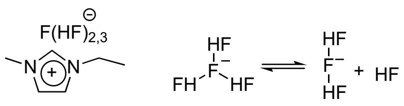
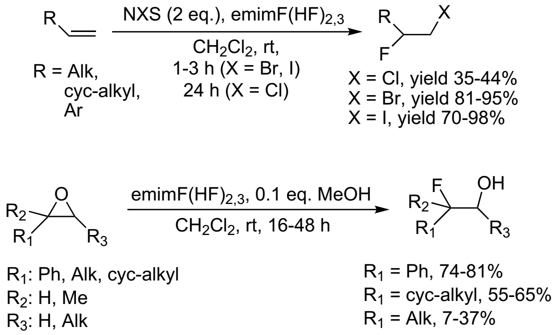


Figure 3. emimF$(HF)_{2,3}$.

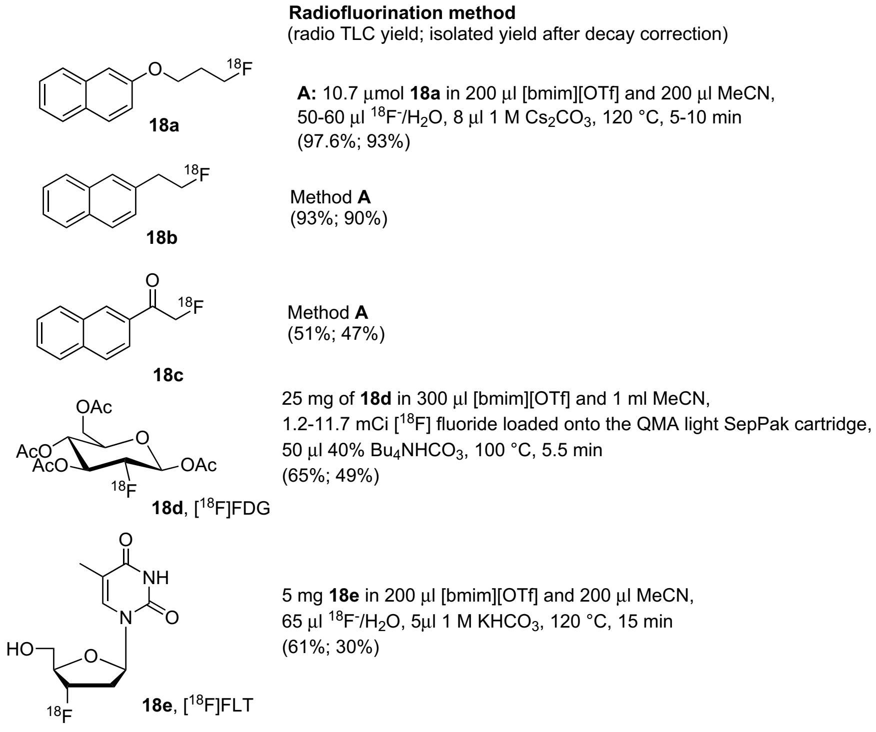


Scheme 9. Haloflourination of alkenes and ring-opening fluorination of epoxides in emimF$(HF)_{2,3}$.

(emim) cation and the $F(HF)_{2,3}$ anion, in which a rapid exhange of HF occurs between H_2F_3 and H_3F_4 (Fig. 3). This air- and moisture-stable IL was prepared and used as a fluoride ion source in the halofluorination reactions of alkenes,[30,31] and for ring-opening fluorination of various epoxides[32] without aqueous work-up. Aliphatic, cyclic and aryl alkenes were converted into the corresponding β-halo-organofluorides in emimF$(HF)_{2.3}$ in the presence of NXS (X=Cl, Br or I), with *anti* stereochemistry and in good yields. Methanol-catalyzed ring-opening fluorination of epoxides in emimF$(HF)_{2,3}$ provided moderate yields of the fluorohydrins in the case of aryl and cyclic epoxides, while, with mono-alkyl-substituted epoxides, the starting materials were recovered. This underscores the importance of the stability of the carbocation intermediate formed upon epoxide ring opening (Scheme 9).

2.1.1. Nucleophilic fluorine-18 labelling in ILs

Due to its favourable physical properties (half-life of 110 min and a low emission energy allowing for high-resolution imaging), fluorine-18 has been found to be a suitable positron emitter for positron emission tomography (PET). The conventional labelling methods for the introduction of ^{18}F into complex organic molecules are often characterized by multistep synthetic pathways, synthesizing small ^{18}F-labelled molecules (prosthetic groups) by rather complex procedures, before final conjugation to the biomarker of interest. More recent novel approaches in this field include enzymatic fluorination and the use of ionic liquids.[33] The most common labelling procedure involves nucleophilic ^{18}F-fluorination, which is conventionally carried out in dipolar aprotic solvents (MeCN, DMF or DMSO). 'Naked' highly nucleophilic unsolvated ^{18}F is of crucial importance in these solvents, which requires that traces of water be fully removed by



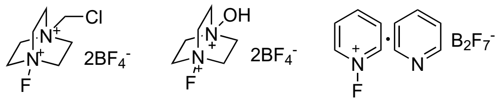
Scheme 10. [^{18}F]Fluorine-labelled radiopharmaceuticals.

azeotropic drying of the aqueous (H_2 [^{18}O]O)/$^{18}F^-$ solution, employing the phase-transfer catalyst Kryptofax2.2.2® (K222) or an appropriate base. Alternatively, based on their findings of enhanced nucleophilicity of the fluoride ion in ILs, Kim et al. utilized ILs as reaction media for the nucleophilic ^{18}F-labelling of an aliphatic mesylate (Scheme 10, **18a**, **18b**) and α-bromoacetophenone (Scheme 10, **18c**).[34] Among the various ILs investigated, reaction in [bmim]-[OTf] using [^{18}F]fluoride ion in the presence of Cs_2CO_3 gave the highest radiochemical yield. Addition of a base and reaction temperatures of 110–140 °C were necessary. In addition to its efficiency and speed (5–10 min at 120 °C), another benefit of this labelling procedure is that it tolerates the presence of water, enabling the direct addition of [^{18}F]fluoride in H_2O to the reaction media, without prior dehydration, thus obviating the usual time-consuming drying procedure. The method was further applied for the synthesis of 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG, **18d**, Scheme 10), which is the most commonly utilized PET-radiopharmaceutical.[35] The ^{18}F-fluorination proceeded with a labelling efficiency of 64.6±7.4% under optimized conditions in 13 min. Following alkaline hydrolysis and purification, requiring 19 min reaction time in total, it provided a 48.8±6.0% (n=3) yield of 96±4% radiochemical purity. In this example, Kim et al. developed a rapid and straightforward synthesis of [^{18}F]FDG, by eliminating all of the evaporation steps, which is achievable in the IL media. Using the same approach, the synthesis of another promising F-18 labelled radiopharmaceutical was reported recently in an IL. Thus, 3′-deoxy-3′- [^{18}F]fluorothymidine ([^{18}F]FLT, **18e**, Scheme 10), used for the imaging of proliferating tumour cells, was synthesised in 61.5±4.3% yield (n=10) in [bmim][OTf].[36] The optimized labelling reaction conditions were 5 mg of the nosylate precursor **18e**, 200 µl of MeCN, 200 µl of [bmim][OTf], 65 µl of [^{18}F]fluoride in H_2O and 5 µl of 1 M $KHCO_3$ for 15 min at 120 °C. The optimized labelling procedure required 70 min, including deprotection steps and HPLC purification, and was achieved without an evaporation step, with an overall radiochemical yield of 30±5% and >95% radiochemical purity.

Pascali et al. evaluated a radiofluorination method based on the properties of the complex between 1,8-(dimethylamino)-naphthalene (proton sponge) and [^{18}F]HF in MeCN with various cosolvents, including 1-pentyl-3-methylimidazolium bromide ([pmim][Br]) and [emim][OTf], with thermal and MW heating for various substrates, and compared it to the conventional procedure involving K_{222}/K_2CO_3 in MeCN.[37] In the case of a 2:1 solution of [pmim][Br] and MeCN as the solvent, in an MW-assisted procedure, and by employing 0.2 mmol of the reagent, HF/proton sponge, fluorinated products were detected only for a few compounds activated towards the S_NAr mechanism, while no fluorination was observed in the case of aromatic chlorides not activated to S_NAr. In the case of a 1:1 solution of [emim][OTf] and MeCN, both under thermal and MW heating, the yields were lower, as compared to the yields obtained in 10% H_2O in MeCN as the solvent. Based on these results, the authors concluded that the proton sponge/HF method is of rather limited scope as a radiofluorinating technique, but it could serve as an alternative to the more established methods in certain cases.

2.2. Electrophilic fluorination in ILs

The first utilization of ILs for the introduction of fluorine into aromatic compounds in an electrophilic manner was reported by Laali and Borodkin[38a] utilizing several N–F fluorinating reagents (Fig. 4), in various imidazolium-based ILs. The dication salt F–TEDA–BF_4 (Selectfluor™) was found to be a superior fluorinating reagent relative to NFTh–BF_4 (Accufluor®) and NFPy–B_2F_7 in [emim][OTf] IL, in the reaction with anisole as a model substrate (Table 6, entires 1–5). Fluorination using F–TEDA–BF_4 was performed in [emim][OTf], [emim][BF_4], [bmim][PF_6] and [bmim][BF_4] ILs at 80 °C. With reactive aromatics, optimal fluorination yields using 1 equiv of the N–F reagent were typically around 50%, while with less reactive substrates no fluorotransformation occurred (Table 7, entires 7 and 8). The 50% conversion in the cases of activated substrates was rationalized by proposing complexation of the free base produced upon fluorine transfer with the unreacted dication salt, generating a bulky dimer complex, which may be ineffective as a transfer-fluorination agent. Nevertheless, the yields were comparable, and in some cases, higher than those in MeCN and in trifluoroacetic acid, but lower than those reported in TfOH.[38b] This IL fluorination process offers several advantages over conventional methods, as it does not employ strong acids and does not require an aqueous work-up. Furthermore, the used ILs can be recycled and reused.



F-TEDA-BF_4 NFTh-BF_4 NFPy·B_2F_7

Figure 4. N–F fluorinating reagents.

Table 6
Electrophilic fluorination of anisole with N–F reagents in ILs

Entry	IL	Anisole/NF (molar ratio)	Yield[a] (%)	Isomer distribution (*ortho*/*para*)
	F-TEDA-BF_4			
1	[emim][OTf]	9:1	53	47:53
2	[emim][BF_4]	10:1	37	43:57
3	[emim][PF_6]	12:1	43	48:52
	NFTh-BF_4			
4	[emim][OTf]	10:1	28	56:44
	NFPy-B_2F_7			
5	[emim][OTf]	10:1	11	54:46[b]

[a] Yields of fluorinated products determined from ^1H NMR using mesitylene as internal standard.

[b] Determined from ^{19}F NMR spectra.

Cahard et al. reported a greatly increased yield and chemoselectivity by employing ILs as solvents for the fluorination of 3-methylindole (**19**) with F–TEDA–BF_4 to give **20**.[39] They also observed that the reaction in an IL minimizes the production of the protonated oxoindole (**21**), when using methanol or ethanol as a co-solvent (Scheme 11). Similar observations on increased chemoselectivity and yield of the fluorinated products were recently reported in the fluorination of β-naphthol and some acetamido aromatics in [bmim][PF_6] and [bmim][BF_4] ILs at room temperature, with MeOH or EtOH as the co-solvent and F-TEDA-BF_4 as the fluorinating reagent.[40]

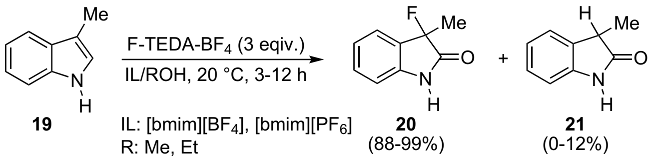
2.2.1. Enantioselective electrophilic fluorination in IL media

Asymmetric synthesis of stereogenic fluorinated centres is a highly challenging task. Reagent-controlled enantioselective electrophilic fluorination in ILs was reported in 2002 by Cahard et al.,[41] utilizing a class of chiral $[N–F]^+$ reagents derived from naturally occurring cinchona alkaloids. *N*-Fluoroammonium salts of cinchona alkaloid derivatives bearing a capped hydroxyl function were reacted with silyl enol ethers **22** in the ILs [hmim][PF_6], [bmim][PF_6] and [emim][BF_4] (Scheme 12). The enantioselectivity of **23** was found to be superior or identical to that measured in MeCN. Moreover, while the reactions in ILs were run at 0 °C, a temperature below −40 °C was essential to obtain a similar enantioselectivity in MeCN. The co-solvent had no significant effect on the enantioselectivity, and using wet ILs or anhydrous ILs did not change the enantiomeric excess or the yield of the reactions. The authors also reported that the IL and the cinchona alkaloid can be reused without a significant change in enantioselectivity.

Table 7
Fluorination of aromatics with F–TEDA–BF_4

Entry	Substrate	IL	ArH/NF (molar ratio)	Yield[a] (%)	Product distribution (%)
1	*p*-Methylanisole	[emim][OTf]	4:1	56	2-*F*-4-Me-anisole (93), 3-*F*-4-Me-anisole (6), 2,6-diF-4-Me-anisole (1)
2	*p*-Chloroanisole	[emim][OTf]	5:1	50	2-*F*-4-*Cl*-anisole (95), 2,6-diF-4-*Cl*-anisole (5)
3	*p*-Fluoroanisole	[emim][OTf]	4:1	24	2,4-diF-anisole (∼100)
4	*p*-Xylene	[emim][BF_4]	10:1	24	2-*F*-1,4-diMe-benzene (∼100)
5	*p*-Xylene	[bmim][OTf]	10:1	51[b]	2-*F*-1,4-diMe-benzene (∼100)
6	Mesitylene	[bmim][PF_6]	4:1	52[c]	2-*F*-mesitylene (∼100)
7	*p*-Nitrotoluene	[bmim][BF_4]	4:1	<1	
8	*p*-Nitrotoluene	[emim][OTf]	4:1	<1	
9	Naphthalene	[emim][OTf]	4:1	88	1-*F*-Naphthalene (91), 2-*F*-naphthalene (7), 1,8-diF-naphthalene (2)[d]
10	1-Methylnaphthalene	[bmim][PF_6]	2:1	23	1-*F*-4-Me-naphthalene (53), 2-*F*-1-Me-naphthalene (21), 5-*F*-1-Me-naphthalene (11), 1-*F*-8-Me-naphthalene (15)[d]
11	Dibenzofuran	[emim][OTf]	4:1	49[e]	1-*F*-Dibenzofuran (20), 2-*F*-dibenzofuran (41), 3-*F*-dibenzofuran (39)[d]

[a] Yields of fluorinated products determined from ^1H NMR using mesitylene as internal standard.
[b] Yield of 2-*F*-1,4-diMe-benzene after repeating fluorination reaction in same vessel by adding second equiv of F-TEDA-BF_4.
[c] Yield determined from ^1H NMR using anisole as internal standard.
[d] Determined from ^{19}F NMR spectra.
[e] Determined from ^1H NMR using 4-fluoroanisole as internal standard.



Scheme 11. Electrophilic fluorination of 3-methylindole (**19**) in ILs.

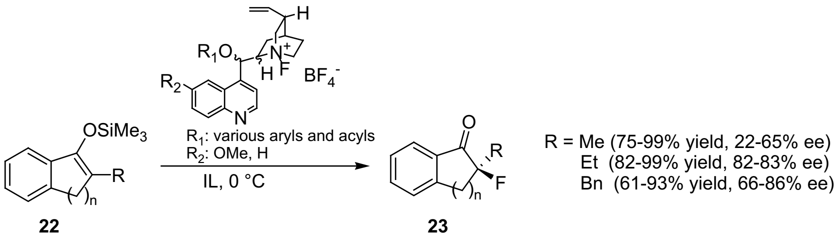
Cahard's group subsequently prepared and evaluated various *N*-fluoroammonium salts of cinchona alkaloids for transfer fluorination of **24** with the aid of achiral N–F fluorine-transfer reagents **25a–j** (Scheme 13), of which Selectfluor™ (**25a**, **25b**), Accufluor™ (**25c**), NFSi (**25e**) and *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate (**25i**) proved to be effective for fluorine transfer, giving good yields of **26** and a high degree of enantioselectivity. The reactions were carried out either in MeCN or in [hmim][PF_6] IL.[42] Reagents possessing a lower fluorinating power failed to transfluorinate the cinchona alkaloids.

Another approach to enantioselective fluorination includes the use of a suitable chiral catalyst. Hamashima et al. reported a successful application of immobilized chiral palladium complexes in ILs for catalytic asymmetric fluorination, which enabled the reuse of the catalyst ninefold.[43] They examined three ILs, namely [bmim][BF_4], [bmim][OTf] and [hmim][BF_4], for the reaction of β-keto esters with *N*-fluorobenzenesulfonimide (NFSi, **25e**) (Scheme 14) at room temperature, catalyzed by the chiral Pd complex **28**, which had been developed in earlier investigations of enantioselective reactions.[44] While in the case of **27a** a prolonged reaction time was required to achieve a similar chemical yield and enantioselectivity to those obtained in EtOH, for **27b** and **27c** a substantial acceleration of the reaction rate was noted. After extraction of the products **29a–c**, upon completion of the fluorination reaction, the Pd catalyst **28** was retained in the IL and could be repeatedly reused (ninefold) for other enantioselective fluorination reactions, maintaining a high and reproducible ee (91%). The authors remarked that although the use of solvents like ethanol and water for the enantioselective fluorination reaction is advantageous for environmental reasons, recovery of the Pd complexes from the reaction mixture presents great difficulty, thus indicating the beneficial value of ILs for immobilization and recycling of the catalyst.[44]

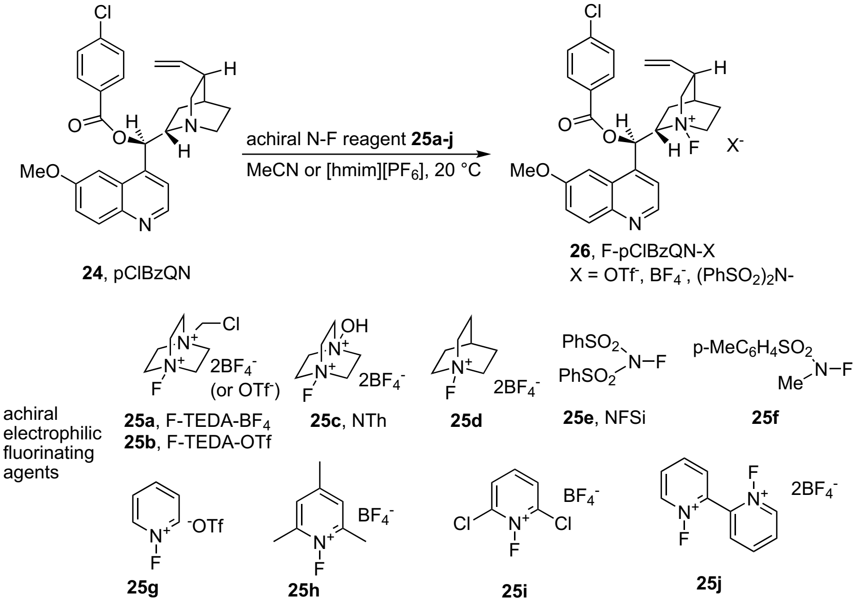
In a similar manner, Kim et al. carried out catalytic enantioselective electrophilic fluorination with NFSi of β-keto phosphonates (**30**) using the chiral palladium complex (**31**) in IL media (Scheme 15).[45] In [bmim][BF_4] and [bmim][OTf], the yields and enantioselectivities of the corresponding α-fluoro-β-keto phosphonates (**32**) were as high as those obtained in MeOH (88–93% yield, 90–97% ee), although a longer reaction time was necessary for completion of the reaction in the IL media, while fluorination in [bmim][PF_6], [bmim][SbF_6] and [emim][BF_4] led to either lower yields and enantioselectivities or to no reaction. The recycling/reuse of the catalyst in [bmim][BF_4] was also demonstrated.

2.3. Electrochemical methods

Electrochemical fluorination has been conventionally carried out in organic solvents containing IL fluoride salts like $Et_3N \cdot mHF$ (m=2–5) and $Et_4NF \cdot nHF$ (n=3–5). While such methods have been utilized for the selective fluorination of various heterocycles,[46–48] successful examples of the anodic fluorination of oxygen-containing heterocyclic compounds have been limited. Electrosynthesis, which has been commonly carried out in MeCN, often caused severe passivation of the anode, thus suppressing the anodic current, and causing acetoamidation as a side reaction, consequently lowering the yield of the fluorinated products. As electrochemical reactions are heterogeneous processes, mass transport of substrates

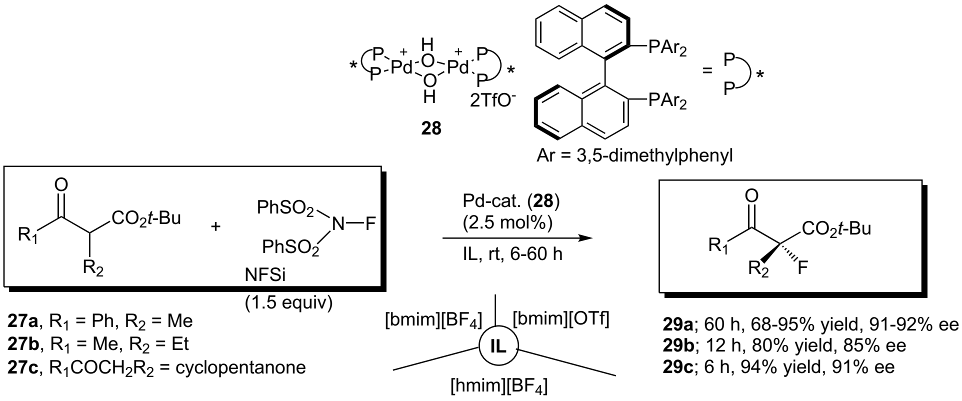


Scheme 12. Enantioselective electrophilic fluorination of silyl enol ethers in ILs.

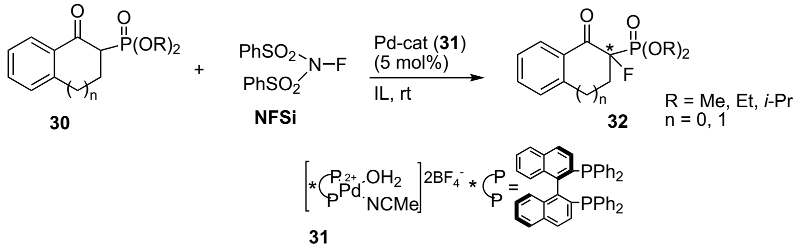


Scheme 13. Transfer fluorination of *p*-chlorobenzoylquinine (*p*-ClBzQn).

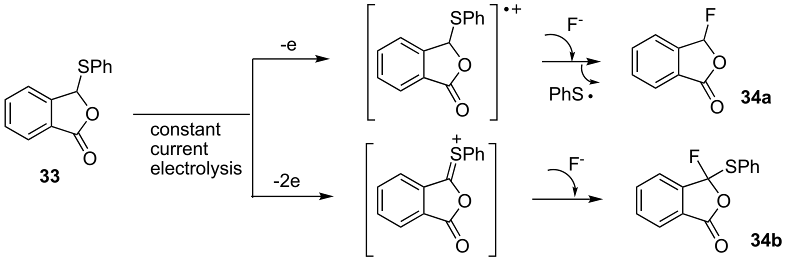
to the electrode surface is very often the rate-determining step, but it can be markedly assisted by sonication. Conventional electrolysis usually requires large quantities of supporting electrolytes and organic solvents to provide a medium with sufficient electrical conductivity and solubilizing ability. This is very inconvenient from an environmental perspective, and thus its avoidance (or minimization) and recycling are highly desirable. Since the proper combination of a cation and an anion constituting the IL can provide a large electrochemical window, ILs are considered very promising as electrolytic media for applications in electro-organic synthesis without the need for any organic solvent. Indeed, electrochemical partial fluorinations in the absence of organic solvents have been performed, with varied degrees of success, on different organic substrates containing IL fluoride salts such as $Et_3N \cdot m HF$ (m=2–5) and $Et_4NF \cdot n HF$ (n=3–5). While $Et_3N \cdot 3HF$ as a supporting electrolyte proved to be of rather limited utility and thus unsuitable for the fluorination of substrates having high oxidation potentials, $Et_3NF \cdot 5HF$, $Et_4NF \cdot 4HF$ and $Et_4NF \cdot 5HF$ were successfully employed



Scheme 14. Catalytic asymmetric fluorination in ILs.



Scheme 15. Catalytic enantioselective fluorination of β-keto phosphonates in ILs.



Scheme 16. Electrochemical fluorination of 3-phenylthiophthalide (**33**).

at high current densities for the anodic partial fluorination of arenes without employing solvents, in good-to-high current efficiencies (66–90%). Nevertheless, a drawback associated with these methods is the use of a large excess of the liquid salts.[49] On the other hand, a small amount of $Et_4NF\cdot4HF$ or $Et_4NF\cdot5HF$ (1.5–2.4 equiv of F^- to substrate) under a high current density (150 mA/cm^2) was reported to be effective for fluorination, without an organic solvent, for ether substrates.[50–52] Cyclic and open-chain ethers, lactones, carbonates and esters were selectively converted into the corresponding monofluoroinated products in moderate-to-high yields, while some fluorinated ethers could be isolated simply by distillation of the electrolytic solution.[50,51] Fuchigami and Hasegawa studied the anodic fluorodesulfurization of phthalide, ethylene carbonate and glucopyranosides possessing arylthio groups in IL electrolytic media such as $Et_3N\cdot mHF$ (m=3–5) and $Et_4NF\cdot nF$ (n=4,5) without using any other solvents. They found that the product selectivity was greatly affected by the choice of the liquid fluoride salt.[52] While in $Et_3N\cdot mHF$ (m=4,5) and $Et_4NF\cdot nF$ (n=4,5) electrolytic media monofluorinated products were formed (Table 8, entries 2–5), α-fluorination without desulfurization was either the exclusive or predominant process in $Et_3N\cdot3HF$ (Table 8, entry 1). The authors linked the media effect of these electrolytes ($Et_3N\cdot mHF$ (m=4,5) and $Et_4NF\cdot nF$ (n=4,5)) to that of CH_2Cl_2 as solvent, accounting for the destabilization of the electrogenerated radical cation intermediate from 3-phenylthiophthalide (**33**), leading to desulfurization (Scheme 16). Additionally, they also demonstrated the reuse of the reaction media, without a significant decrease in the product yield, in the case of the anodic fluorodesulfurization reaction of **33** in $Et_4NF\cdot4HF$.

When the anodic fluorination of 3-phenylthiophthalide (**33**) was performed in various solvents using $Et_3N\cdot3HF$ or $Et_3N\cdot5HF$ as the supporting electrolyte (Table 8, entries 6–10), a dramatic effect of [emim][OTf] IL was noticed (Table 8, entry 10).[53] Anodic fluorination utilizing a combination of [emim][OTf] and $Et_3N\cdot5HF$ selectively converted 3-phenylthiophthalide (**33**) into the fluorodesulfurized product **34a** in high yield, and a similar outcome was found for the electrochemical reaction performed in CH_2Cl_2 as the solvent (Table 8, entry 7). On the other hand, by using DME or THF as the solvent, α-fluorination without desulfurization with the formation of product **34b** became the predominant process (Table 8, entries 8 and 9). Fuchigami et al. also studied the anodic fluorination of hard-to-oxidize phthalides such as **35**, using $Et_4N\cdot4HF$ and $Et_3N\cdot5HF$, in combination with various imidazolium-based ILs.[53] They found that the combination of $Et_3N\cdot5HF$ and [emim][OTf] was highly effective for the synthesis of the corresponding monofluorinated product, e.g., **36** while either no fluorination occurred or low yields of fluorinated products were obtained when the electrolysis was carried out in organic solvents or other tested ILs, namely [emim][BF_4], [bmim][BF_4], [bmim][NTf_2], [bmim][OTf] and [EMIF][2.3HF] (Table 9, entries 1–13).

Table 8

Effect of media on anodic fluorination of 3-phenylthiophthalide (**33**)

Entry	Reaction medium	Charge passed (F/mol)	Yield[a] (%)	
			34a	**34b**
1	$Et_3N\cdot3HF$	4.2	4	21
2	$Et_3N\cdot4HF$	4.2	77	—
3	$Et_3N\cdot5HF$	3.2	96	—
4	$Et_4N\cdot4HF$	3.3	99	—
5	$Et_4N\cdot5HF$	4	93	—
6	MeCN/$Et_3N\cdot3HF$	4	44	—
7	CH_2Cl_2/$Et_3N\cdot3HF$	4	86	—
8	THF/$Et_3N\cdot3HF$	4	6	22
9	DME/$Et_3N\cdot3HF$	3	9	72
10	[emim][OTf]/$Et_3N\cdot5HF$	4	83	Trace

[a] Determined by ^{19}F NMR.

An overview of the efforts of Fuchigami's group on selective anodic fluorinations of organic compounds utilizing ILs is presented in several review papers.[49,54–56]

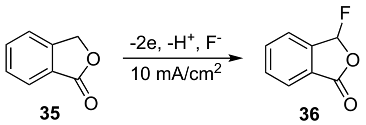
3. Chlorofunctionalization of organic compounds in ILs

3.1. Electrophilic chlorination procedures in ILs

Common methods for electrophilic chlorination typically involve one of the following approaches: use of molecular chlorine or oxidation of a chloride salt or reagents bearing a partially positively charged chlorine atom (such as *N*-chlorosuccinimide (NCS) and trichloroisocyanuric acid). Although using Cl_2 is generally efficient for activated substrates, only half of the reagent is utilized, with the other half forming corrosive HCl as waste, while for deactivated substrates the need for the presence of stoichiometric amounts of the Lewis acid further increases the waste. Since Cl_2 exists in the

Table 9

Anodic fluorination of phthalide (**35**) under various conditions



Entry	Reaction medium	Supporting electrolyte	Charge passed (F/mol)	Yield[a] (%)
1	MeCN	$Et_3N\cdot5HF$	6	16
2	CH_2Cl_2	$Et_3N\cdot5HF$	8	23[b]
3	DME	$Et_4NF\cdot4HF$	8	0
4	—	$Et_3N\cdot3HF$	4	17
5	—	$Et_3N\cdot5HF$	8	16[b]
6	[emim][OTf]	$Et_3N\cdot3HF$	6	78
7	[emim][OTf]	$Et_4NF\cdot4HF$	4.7	70
8	[emim][OTf]	$Et_3N\cdot5HF$	6	90
9	[emim][BF_4]	$Et_3N\cdot5HF$	4	16
10	[bmim][BF_4]	$Et_3N\cdot5HF$	6	23
11	[bmim][NTf_4]	$Et_3N\cdot5HF$	5	29
12	[bmim][OTf]	$Et_3N\cdot5HF$	4	39
13	[EMIF][2.3HF]	$Et_3N\cdot5HF$	6	31

[a] Determined by ^{19}F NMR.

[b] Reaction was complicated.

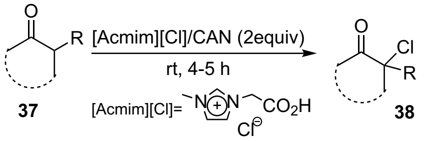
gaseous state at room temperature, its transportation, storage, and handling present further complications. Therefore, methods involving HCl or a chloride salt in the presence of an oxidant, and chlorination using reagents such as NCS, are more appealing from the experimental chemist's point of view, but usually require the presence of an appropriate catalyst and/or large quantities of acids, contributing to byproduct waste. A further advantage of the oxidative methods is that a higher atom economy can be achieved.

Chlorination reactions in IL media have not been extensively studied. Interestingly, in some cases, a different transformation was initially attempted, but, unexpectedly, chlorination occurred. The latter was the case when Earl et al., in an attempt to effect the nitration of arenes (benzene, toluene and anisole) by using 67% nitric acid in combination with a chloride anion in an IL [C_{10}mim][Cl], found that chlorinated products were formed instead.[57] They reported the chlorination of these substrates using HCl in [bmim][NO_3] IL acting as the catalyst.

Chiappe et al. investigated the chlorination of non-activated and sterically hindered arenes via the oxidative approach employing a Brønsted acidic [Hmim]$^+$ IL-containing NO_3^- or Cl^- as the counteranion.[58] In comparing three potential chlorinating systems, namely [Hmim][NO_3]–HCl (37%), [Hmim]Cl–HNO_3 (67%) and [Hmim][NO_3]–[Hmim][Cl], the first system was found to provide the highest conversion and selectivity for monochlorination with mesitylene as the substrate, in a reaction performed at 80 °C for 24 h, while in [Hmim][NO_3]–[Hmim][Cl] only the unreacted substrate remained in the reaction mixture. Following extraction of the products, the ESI-MS analysis of the recovered IL confirmed the exclusive presence of the starting IL [Hmim][NO_3]. The authors suggested the involvement of another oxidant in the halogenation process, attributing this role to oxygen, while [Hmim][NO_3] was considered to be a solvent promoter (or catalyst) for the synthesis of aryl halides. The high atom economy (99%) of the process and the reusability of the halogenating system [Hmim][NO_3]–HCl were also pointed out.

While investigating the iodination of arenes in ILs with I_2 in the presence of F–TEDA–BF_4 (Selectfluor™), Chiappe and Pieraccini tested the generality of the method for the formation of other halogen electrophiles in ILs, utilizing the oxidative properties of the Selectfluor™ reagent.[59a] When the reaction was performed with NaCl as a source of the electrophile in [bmim][PF_6] at 70–80 °C for 24 h, anisole was converted into a mixture of *ortho*- and *para*-chloroanisole in 45% yield, with the *o*:*p*-selectivity corresponding to 55:45. Chiappe et al. also examined the effect of ILs on the activity of the haeme enzyme, chloroperoxidase (CPO), in the CPO-catalyzed chlorination of monochlorodimedone.[59b] A kinetic investigation carried out in phosphate buffer in the presence of increasing concentrations of the IL, and of the substrate, chloride ion and H_2O_2 (standard assay conditions), showed that the enzyme activity varied significantly with the nature and concentration of the IL. While no chlorination was observed in the presence of [mmim][$MeSO_4$], [emim][$EtSO_4$], [Mor_{11}][$MeSO_4$] and [N_{1112OH}][OAc], CPO activity was observed in the presence of [mmim][Me_2SO_4], [N_{1112OH}][H_2PO_4] and [N_{1112OH}][$HOC(CH_2COOH)_2COO$]. Although the catalytic activity decreased progressively with increasing IL concentration, a higher tolerance towards ILs in comparison to molecular solvents was observed.

An ionic liquid, an acetylmethylimidazolium halide [Acmim][X], reported to act as a reaction medium, in combination with ceric ammonium nitrate (CAN) as a reagent was used for the halogenation of a wide variety of ketones and 1,3-keto esters **37** at the α-position (Scheme 17).[60] The 2- and 3-substituted cyclohexanones produced mixtures of the 2- and 6-chloro-substituted products, but the 2-chloro-substituted isomer **38** was predominantly formed. Acyclic ketones with both α-positions available for electrophilic attack formed a mixture of regioisomeric products. The α,β-unsaturated cyclic ketones generally furnished 2-chloroenones, and chlorination of β-keto esters furnished the corresponding α-chloro products. In the absence of either [Acmim][X] or CAN, the reaction did not take place at all and 2 equiv of CAN were required for the efficient transformation, highlighting CAN as a necessary one-electron oxidant during the halogenation proccess. The addition of a radical quencher (TEMPO) prevented the chlorination proccess, thus indicating a somewhat surprising radical pathway for this proccess in the IL media.

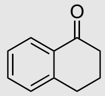
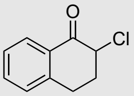
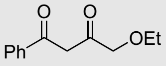
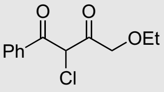
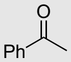
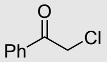


Scheme 17. Use of [Acmim][Cl] and CAN for α-chlorination of carbonyl compounds.

Lee and Park reported the smooth conversion of aryl methyl ketones and aryl methylene ketones into the corresponding α-chloro ketones, utilizing aluminium chloride (1.1 equiv) and urea/H_2O_2 (UHP, 2.0 equiv) in [bmim][BF_4] at 60 °C for 4–20 h (Table 10, entries 1 and 8).[61] The same authors later utilized UHP as an activator of NXS (X=Cl, Br) to achieve the chlorination and bromination of similar carbonyl compounds in [bmim][BF_4].[62] Treatment of an aryl ketone with 2.0 equiv of NCS and 1.2 equiv of UHP in 1 ml [bmim][BF_4] at 60 °C for 1–20 h readily afforded the corresponding α-chloroaryl ketones in high yield (68–98%, Table 10, entries 2, 5 and 9). On the other hand, Yadav et al. reported on the utility of NXS (X=Cl, Br, I) in the α-monohalogenation of cyclic ketones, 1,3-diketones and β-keto esters in a hydrophobic IL [bmim][PF_6] at

Table 10

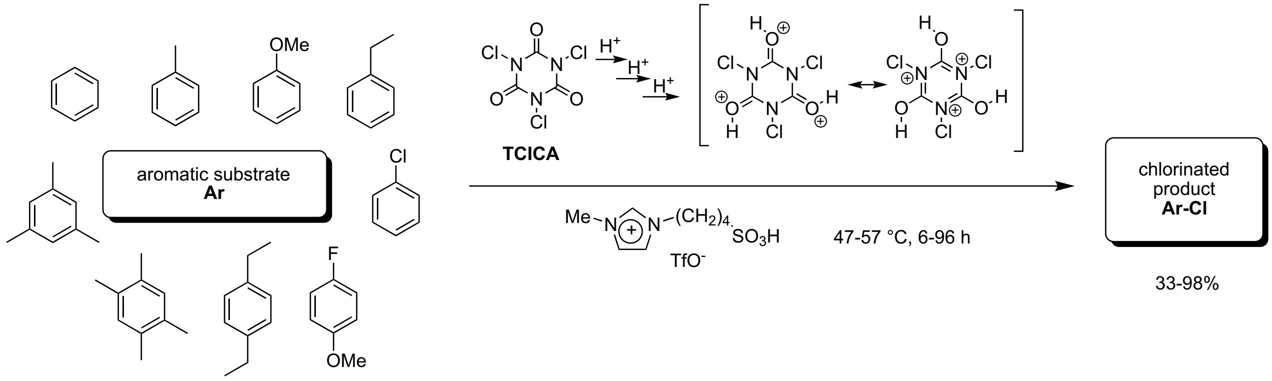
Comparison of various reagent systems in selected examples of chlorination of carbonyl compounds in ILs

Entry	Substrate	Product	Reagent	IL	*T* (°C)	Reaction time (h)	Yield[a] (%)	Ref.
1			$AlCl_3 \cdot 6H_2O$/UHP	[bmim][BF_4]	60	6	89	61
2			NCS/UHP	[bmim][BF_4]	60	ns[b]	98	62
3			NCS	[bmim][PF_6]	rt	0.5	84	63
4			NCS	[bmim][BF_4]			[c]	63
5			NCS/UHP	[bmim][BF_4]	60	ns[b]	95	62
6			NCS	[bmim][PF_6]	rt	0.3	94	63
7			NCS	[bmim][BF_4]			[c]	63
8			$AlCl_3 \cdot 6H_2O$/UHP	[bmim][BF_4]	60	6	77	61
9			NCS/UHP	[bmim][BF_4]	60	ns[b]	78	62

[a] Isolated yield.

[b] 1–20 h, not specified.

[c] Similar to that in [bmim][PF_6].



Scheme 18. Chlorination of arenes with TCICA in Brønsted acidic IL.

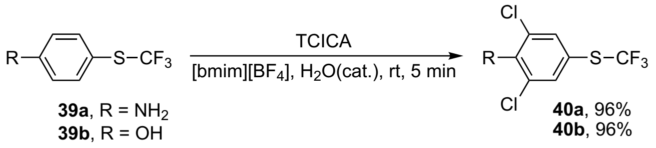
ambient temperature, without any other activator or catalyst, to give high yields of the corresponding α-halo-substituted carbonyl products.[63] They attributed the enhanced reactivity of NXS reagents in IL to increased polarization of the N–X bond in the polar ionic medium and to stabilization of the charged ionic intermediates. It was mentioned that similar results could be obtained in a hydrophilic IL [bmim][BF_4] (Table 10, entries 3, 4, 6 and 7), but the authors preferred the hydrophobic medium [bmim][PF_6], from which the succinimide byproduct could be removed easily, thus enabling IL recycling and reuse. The dual role of ILs [bmim][PF_6] and [bmim][BF_4], as solvent and promoter in halogenation reactions with NXS reagents (X=Cl, Br, I), was also demonstrated for various other aromatics activated towards electrophilic functionalization.[64]

Electrophilic chlorination of aromatics with trichloroisocyanuric acid (TCICA) in the Brønsted acidic IL [bmim(SO_3H)][OTf] was studied by Laali et al. (Scheme 18).[65] This work demonstrated the moderately electrophilic nature of the TCICA–[bmim(SO_3H)][OTf] system and the dual solvent/catalyst role of the Brønsted acidic IL. As 3 mol of ArCl was formed for each mole of TCICA employed, the high atom economy of the method was pointed out. Whereas by raising the TCICA/substrate molar ratio (2:1 or 1:1) in the case of more reactive arenes (mesitylene, durene and anisole) it was possible to switch the chemoselectivity in favour of dichlorination, attempted chlorinations of *p*-nitroanisole and nitrobenzene were unsuccessful under these conditions. Based on substrate selectivity measurements and a model DFT study, a protosolvated trication was suggested as key intermediate undergoing sequential transfer-chlorination/N-protonation.

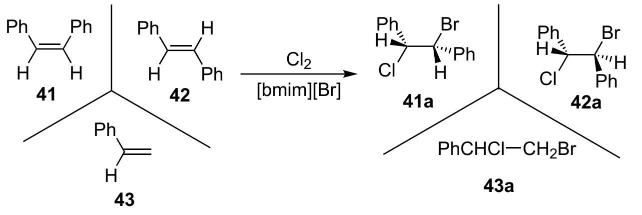
The TCICA was also found to be an efficient ring-chlorinating agent for aryl trifluoromethyl sulfides in [bmim][BF_4] at room temperature.[66] Interestingly, the authors' original intention was chemoselective oxidation of aryl trifluoromethyl sulfides (**39a**,**b**) to the corresponding sulfoxides, but, instead, the chlorinated products (**40a**,**b**) were formed in high yield, even in excess TCICA (Scheme 19). A synthesis of 2,3-dichloropropionitrile was reported by the chlorination of acrylonitrile with molecular chlorine catalyzed by various ILs, namely imidazolium and pyridinium cations with Cl^-, Br^-, BF_4^-, and PF_6^- counterions.[67] While the ILs containing Cl^- and Br^- anions showed good catalytic properties, the chlorination of acrylonitrile was limited in the ILs containing BF_4^- and PF_6^-, which was assumed to be due to the steric effects of the anions.

3.2. Addition reactions to unsaturated systems

The utility of ILs as solvents and reagents for the halogenation of alkenes and alkynes was studied by Chiappe et al.[68] Reaction of *cis*-stilbene (**41**), *trans*-stilbene (**42**) and styrene (**43**) with Cl_2 in [bmim][Br] at room temperature gave the corresponding 1,2-bromochlorides (**41a**–**43a**) in an *anti*-stereospecific manner (Scheme 20). Based on the regiochemistry of the addition product to styrene, the authors proposed that $BrCl_2^-$ was the reactive species, accounting for the ability of the anion formed to react with the double bond, yielding electrophilic bromine and nucleophilic chloride. Chiappe's group also prepared trihalide-based ILs and investigated their utility as reagents/solvents for the iodochlorination and iodobromination of alkenes and alkynes.[69] Moreover, a careful kinetic investigation of the addition of trihalides to unsaturated compounds in ILs revealed a pronounced solvent effect in the reaction of ICl_2^-.[70] The water-immiscible trihalide-based IL [hmim][ICl_2] was synthesized by reacting [hmim][Cl] with an equivalent of ICl or by the addition of an equivalent of Cl_2 to [hmim][I] at 0 °C. This resulting IL was found to be stable and could be stored in the dark at 4 °C for several months without signs of degradation. Reactions carried out using 1–5 equiv of [hmim][ICl_2] in [hmim][Cl] with alkyl- and aryl-substituted alkenes and alkynes at 0 °C, even after 24 h, hardly produced any, if at all, of the corresponding iodochloro adducts, thus proving unsuitable for the preparation of dihalo derivatives. On the other hand, the reaction of ICl with alkenes in [bmim][PF_6] at 0 °C was completed in a few minutes, while longer times were necessary for the reactions utilizing [hmim][ICl_2] as the reagent/solvent and with [hmim][ICl_2] in [bmim][PF_6]. The study of alkene reactions with ICl_2^- in ILs revealed that it was *anti*-stereospecific, forming the Markovnikoff adducts exclusively, unlike the IBr_2^- anion, the reactivity of which was more affected by steric factors.[69] The regiospecificity of the addition reaction with aryl-substituted alkenes and alkynes using ICl in [bmim][PF_6] depends upon the substrate structure, providing the Markovnikoff

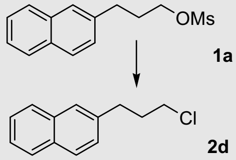
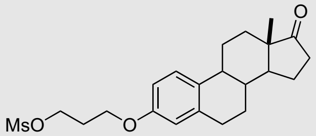


Scheme 19. Chlorination of aryl trifluormethyl sulfides with TCICA (1 equiv) in [bmim][BF_4].



Scheme 20. Bromochlorination of alkenes.

Table 11
Methods for the formation of alkyl chlorides utilizing ILs

Transformation	Reagent	T, t	Substrate	Ref.
R–OH → R–Cl	1 equiv [bmim][Cl], 1 equiv HA ($MeSO_3H$, H_2SO_4, HCl)	rt, 19–24 h	R=*n*-Bu, *n*-octyl, *sec*-Bu, *tert*-Bu	71
	1 equiv [bmim][Cl], 1 equiv HA ($MeSO_3H$, H_2SO_4)	MW, 10 min	1-heptanol, 1-decanol, 10-undecen-1-ol, 1,8-octanediol, 2-propyn-1-ol, geraniol, benzyl alcohol	72
	[Hmim][Cl]	120 °C, 12 h	*n*-octanol, *sec*-octanol, cyclohexanol, benzyl alcohol, hexandiol	73
R–OM → R–Cl M=TMS, TBDMS, Ac, Ts, THP	*t*Bu-Cl, [pmim][Br]	60 °C, 3–10 h	R=$PhCH_2$, (p-Cl)$C_6H_4CH_2$, (p-OMe)$C_6H_4CH_2$, n-C_5H_{11}, PhCH=CHEt, c-C_5H_9, c-C_6H_{11}	74
	*t*Bu-Cl, [pmim][Br]	60 °C, 3–12 h	R=$PhCH_2$, c-C_6H_{11}	74
R–OMs → R–Cl	5 equiv KCl, 3 ml [bmim][BF_4], 3 ml MeCN (5% H_2O)	100 °C, 30 min	 **1a** **2d**	15
	3 equiv KCl, 0.5 equiv PS[bmim][BF_4] in 3 ml MeCN	100 °C, 6 h		17
	3 equiv KCl, 0.5 equiv PS[him-^{t}OH][OMs] in 3 ml MeCN	100 °C, 5 h		21

adducts exclusively, while a mixture of Markovnikoff and anti-Markovnikoff products was obtained in the case of simple alkyl-substituted alkenes. A kinetic investigation of the addition reactions of ICl_2^- to alkenes and alkynes was carried out in the following ILs: [bmim][PF_6], [emim][NTf_2], [bmim][NTf_2], [hmim][NTf_2], [bm_2im][NTf_2] and [bPy][NTf_2]. The kinetic constants and activation parameters were evaluated in comparison to the kinetic data obtained in 1,2-dichloroethane (DCE), as a typical molecular solvent for this transformation. The rates increased in going from DCE to ILs, and this was attributed to the hydrogen-bonding ability of the imidazolium core. The chlorofluorination reaction of alkenes was reported by using NCS in EMIMF$(HF)_{2.3}$ ILs. The reported yields of the addition products were moderate (35–44%), requiring longer reaction times as compared to the corresponding bromofluorination and iodofluorination reactions.[32]

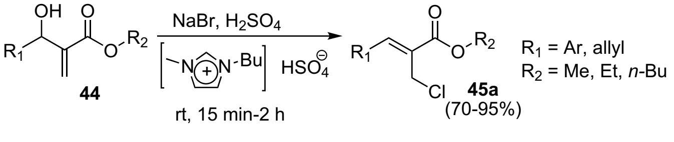
3.3. Nucleophilic substitutions and the formation of alkyl chlorides

An imidazolium-based IL with a chloride counteranion was utilized as a solvent and halogenating reagent for the conversion of alcohols into alkyl halides. The transformation of *n*-butyl-, *n*-octyl-, *sec*-butyl- and *tert*-butyl alcohol into their corresponding alkyl chlorides was performed at room temperature using [bmim][Cl] and an equivalent of a Brønsted acid.[71] The conversions employing $MeSO_3H$ were significantly higher as compared to the reactions utilizing HCl or H_2SO_4 as the Brønsted acids. Leadbeater et al. later reported the same transformation, but with a significantly shorter reaction time (from 19–48 h, formerly, to 10 min), which was made possible by employing microwave heating.[72] Again, *p*-toluenesulfonic acid was superior to H_2SO_4. While the MW-assisted reaction utilizing [bmim][Cl] efficiently converted simple primary alkyl, allylic and benzylic alcohols into their corresponding alkyl chlorides, secondary and tertiary alcohols decomposed rapidly. An added improvement included the use of an immobilized acid in the IL. It is notable that, in these reactions, the IL is acting as a halogenating agent, recyclable catalyst and solvent. Such an IL was prepared by the reaction of HX with methylimidazole, forming the Brønsted acidic IL [Hmim][Cl], which was successfully utilized for the conversion of *n*-octanol, *sec*-octanol, cyclohexanol and benzyl alcohol into their corresponding alkyl chlorides. While hexanediol was converted into the corresponding dichloride, in the case of tertiary alcohols the major product was the alkene.[73]

Ranu and Jana reported the direct conversion of primary and secondary alcohols and their derivatives (such as OTMS, OTBDMS, OAc, OTs, OTHP) into the corresponding halides by using a combination of *tert*-butyl chloride and the IL [pmim][Br].[74] Yields of 55–87% were achieved after 3–12 h by heating at 60 °C.

While investigating the reactivities of various metal fluorides in the nucleophilic fluorination of 2-(3-methanesulfonyloxy-propyl)naphthalene (**1a**) in ILs, Kim et al. tested various other nucleophilic substitutions, including chlorination with KCl.[15] They found an enhanced nucleophilicity of the reagent in [bmim][BF_4], providing 2-(3-chloropropyl)naphthalene (**2d**) in 30 min at 100 °C, almost quantitatively. Following the synthesis of the polymer-supported IL PS[hmim][X] (X=BF_4, OTf) and the demonstration of its utility in enhancing the nucleophilicity of fluoride, the PSIL was also tested as a catalyst for other nucleophilic substitution reactions.[17] After 6 h at 100 °C, the mesylate (**1a**, 1 mmol) was 97% converted into the corresponding chloride (**2d**), using 3 equiv of KCl as the source of nucleophile and 0.5 equiv of PS[hmim][BF_4] as a catalyst in 3 ml of MeCN, again confirming the enhanced nucleophilicity of the halogenide ion in the presence of this particular IL. Another publication reporting on the reactivity of KCl in ILs suggested that PS[hmim–^{t}OH][OMs], namely a polymer-supported imidazolium-based IL functionalized with a *tert*-alcohol moiety, is responsible for the enhanced nucleophilicity of chloride (Table 11).[21]

Sodium chloride in the Brønsted acidic IL [bmim][HSO_4] was reported to be efficient for the conversion of 3-hydroxy-2-methylenealkanoates (**44**) into (2*Z*)-2-(chloromethyl)alk-2-enoates (**45a**) with high stereoselectivity (Scheme 21).[75] Despite the acidity of the IL employed, a molar ratio of H_2SO_4 was additionally required

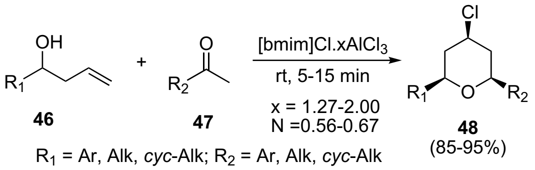


Scheme 21. Synthesis of (2*Z*)-2-(chloromethyl)alk-2-enoates.

in order to bring about this transformation. The chlorotransformation was completed within 2 h at room temperature. The authors claimed that this method represents a significant improvement over the existing procedures with regard to reactivity, yield and stereoselectivity.

3.4. Other transformations to chlorofunctionalized compounds and dechlorination in IL media

The Prins cyclization reaction was reported to proceed efficiently in chloroaluminate ILs, providing various chlorofunctionalized tetrahydropyran derivatives.[76] The coupling reaction between a benzaldehyde (**46**) and a homoallylic alcohol (**47**) was investigated in [bmim]Cl·xAlCl$_3$ (x=1.27–2.00; N=0.56–0.67) at ambient temperature (Scheme 22). Near-quantitative conversions into 2,6-disubstituted 4-chlorotetrahydropyrans (**48**) were achieved, with the molar ratio of the aldehyde/homoallyl alcohol/IL corresponding to 1.0:1.2:0.5, where the Lewis acidic species is $Al_2Cl_7^-$ and its concentration in the IL is a function of the molar fraction (N) of AlCl$_3$, with the optimum N determined to be 0.67 ([bmim]Cl·AlCl$_3$). On the other hand, no reaction was observed in the basic ($N<0.5$) and neutral ($N=0.5$) ILs. The scope and generality of the process were demonstrated by efficient coupling reactions between aromatic aldehydes and the corresponding homoallylic alcohols, which in the presence of [bmim]Cl·AlCl$_3$ yielded 2,6-disubstituted 4-chlorotetrahydropyrans, while the reactions of an aromatic homoallylic alcohol with aliphatic aldehydes and coupling of an aliphatic homoallylic alcohol with aromatic aldehydes gave the corresponding unsymmetrical chloropyrans. The authors highlighted the dual role of [bmim]Cl·AlCl$_3$, as a solvent and catalyst. Its efficacy was compared to [bmim][PF$_6$], [bmim][BF$_4$] and [bmim][Cl] for the same transformation in the absence of the Lewis acid; but these reactions proved unsuccessful.



Scheme 22. Prins cyclization reaction.

Regioselective ring opening of epoxides (**49** and **51**) with LiCl was reported to proceed efficiently under mild conditions in [bmim][PF$_6$] and [bmim][BF$_4$] ILs, providing the corresponding *vic*-halohydrins (**50a**, **50b** and **52**, Scheme 23) in high yields.[77] The reactions in the absence of an IL were sluggish, with most of the unreacted starting material being recovered. The induction of the ring opening of epoxides by LiCl in the imidazolium-based ILs was rationalized by epoxide activation by the acidic hydrogen of the imidazolium core, eliminating the need for an additional acid catalyst. Facile conversion of epoxides (**53**) into the corresponding *vic*-chlorohydrins (**54**, Scheme 23) was also reported to take place in [Acmim][Cl], with the IL acting as a solvent, reagent and catalyst.[78] The epoxide ring opening proceeded regio- and stereoselectively, with chlorination at the less substituted end in the case of open-chain terminal epoxides, while cyclic epoxides gave *trans* chlorohydrins.

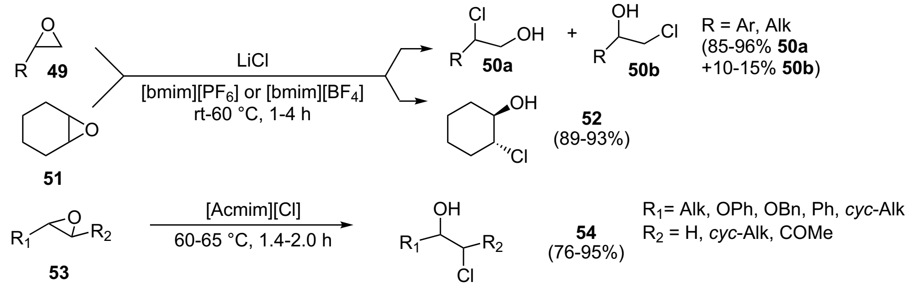
Calò et al. reported the stabilization of Pd nanoparticles in tetrabutylammonium bromide (TBAB), which, in the presence of tetrabutylammonium acetate (TBAA) as base and under hydrogen at atmospheric pressure, catalyzed the hydrodechlorination of various aryl chlorides.[79] In addition, recycling of both the solvent and the IL could be achieved.

4. Bromofunctionalization of organic compounds in ILs

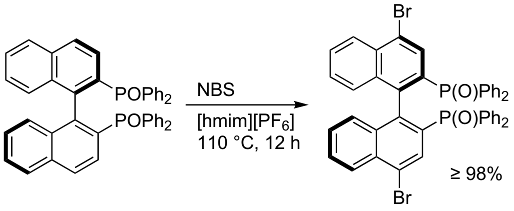
Brominated organic compounds are of paramount importance as building blocks in organic synthesis. In addition to being key intermediates in the preparation of organometallic reagents, and their important roles in transition-metal-mediated coupling reactions, brominated organic compounds often exert enhanced bioactive properties, such as antitumour, antibacterial, antifungal, antiviral and antioxidant activities. Consequently, bromination reactions utilizing a variety of reagents have been extensively studied not only in conventional organic solvents, but also in ILs. In fact, bromination reactions in ILs have received more attention as compared to other halotransformations. Similar to chlorination methods, bromine can be introduced into organic compounds by using one of the following approaches: use of molecular bromine, by oxidative bromination methods, or by utilizing other bromine-containing reagents such as N-bromosuccinimide (NBS). Although molecular bromine is widely used for the functionalization of organic and inorganic substrates, due to its toxicity and high vapour pressure it is a hazardous chemical and cumbersome to handle. Ionic liquids, especially those acting both as media and as brominating reagents, seem to provide new opportunities for bromotransformations in terms of efficiency, enhanced reaction rates, ease of manipulation and 'greener' reaction protocols.

4.1. Bromination with NBS

N-Bromosuccinimide (NBS) is one of the most popular brominating reagents, due to its ease of handling, low price, and to the fact that the byproduct, succinimide, can be easily recovered, and reconverted back into NBS and, as such, reused in subsequent reactions. Generally, the radical bromination of allylic and benzylic substrates takes place in CCl$_4$, while the nuclear brominations of activated aromatic systems are favoured in polar aprotic solvents, such as propylene carbonate, DMF and MeCN. The regioselectivity of bromination reactions utilizing NBS in ILs with substrates possessing both an aromatic ring and alkyl group(s) strongly indicated an electrophilic aromatic substitution process to be favoured over

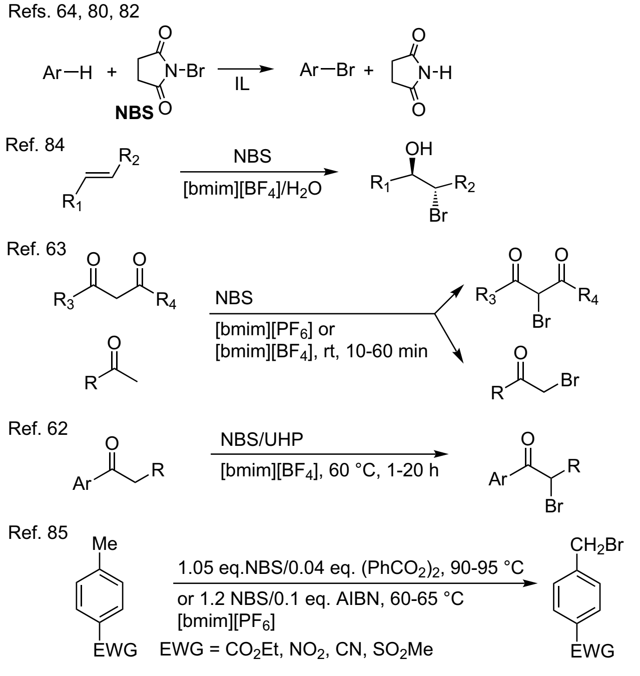


Scheme 23. Conversion of epoxides to *vic*-chlorohydrins in IL media.



Scheme 24. Bromination of BINAPO with NBS in [hmim][PF$_6$].

a radical process, similar to the behaviour in dipolar aprotic organic solvents, but with a significant enhancement of the reactions rates in ILs. A variety of substrates such as phenols, anisoles, xylenes, aniline, acetanilide and 2-naphthol were reported to be ring brominated with NBS in [bbim][BF$_4$] at room temperature in just 5 min to the corresponding monobromo derivatives regioselectively and in high yields.[80] The large rate enhancements were rationalized by an increased polarization of the N–Br bond in the IL medium, enhancing the reactivity of the reagent. Similarly, a rate enhancement was observed in the bromination of activated aromatics at room temperature using NBS in [bmim][PF$_6$] and [bmim][BF$_4$], while in [bmim][Cl] and in [n-Bu$_4$N][Cl] a higher temperature (60 °C) and longer reaction times (5–8 h) were required to obtain comparable yields.[64] Taking advantage of the ease of aromatic ring bromination with NBS in [bmim][BF$_4$], Handy[81] devised a one-pot bromination–Heck coupling procedure in [bmim][BF$_4$], without isolation of the brominated product prior to Heck coupling, using anisole, naphthalene and m-xylene as the starting substrates.[81] Highly regioselective aromatic ring bromination of aromatics and heteroaromatics with NBS was reported in tetrabutylammonium bromide (TBAB) with both conventional heating and MW irradiation.[82] Reactions performed in TBAB at 100 °C gave the corresponding monobrominated products in the *para*-position. With activated aromatics (phenols and anilines), the reactions took place much faster in IL as compared to DMF without any additives. On the other hand, for moderately activated substrates (like acetanilide), the addition of BF$_3$ etherate or solid acidic montmorillonite K-10 clay to the reaction mixture substantially accelerated the bromination, which could be further expedited with MW heating. This method also proved to be efficient for bromination of the nucleoside bases, uracil and cytosine, while the purine bases, adenine and guanine, were reported to be resistant to this protocol.[82] A method for bromination at the 4,4′-position of BINAPO utilized NBS in [hmim][PF$_6$].[83] The bromination reaction was performed at 110 °C for 12 h, forming 4,4′-dibromoBINAPO in 98% yield (Scheme 24), while at lower temperatures (90 °C) and in [bmim][Cl] or in [bmim][BF$_4$] the transformation did not occur.



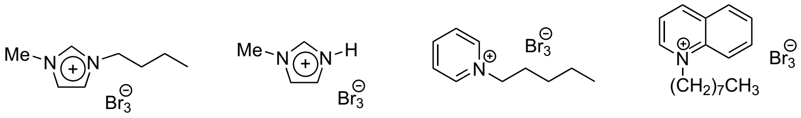
Scheme 25. Bromination with NBS in ILs.

Yadav et al. reported that alkenes are smoothly converted into the corresponding bromohydroxylated products with NBS in the [bmim][BF$_4$]/water system in high-to-quantitative yields at room temperature, while in [bmim][Cl] and in [n-Bu$_4$N][Cl] a temperature of 60 °C and longer reaction times were needed to achieve comparable yields.[84] NBS was also utilized for the α-bromination of 1,3-diketones, β-keto esters and cyclic ketones in a hydrophobic IL [bmim][PF$_6$] and in a hydrophilic IL [bmim][BF$_4$].[63] Reactions performed for 10–60 min at room temperature and without any catalyst afforded the corresponding α-brominated products in high yields (88–95%). α-Bromination of aryl ketones and 1,3-dicarbonyl compounds was also reported in [bmim][BF$_4$] with NBS in the presence of UHP, which was used to activate the brominating reagent.[62] The reactions were performed at 60 °C for 1–20 h and yielded 76–97% of the corresponding α-bromocarbonyl products.

The Wohl–Ziegler bromination of benzylic methyl groups to the corresponding benzylic bromides was reported in [bmim][PF$_6$] for electron-deficient aromatics by the use of NBS and a catalytic amount of benzoyl peroxide or 2,2′-azobis(isobutyronitrile) (AIBN) as initiator of the radical reaction, while in the case of electron-rich aromatics, mainly ring bromination occurred[85] (Scheme 25).

4.2. Tribromide-based ILs as brominating reagents and solvents

An IL such as [bmim][Br$_3$] (**55**) (Fig. 5) with a tribromide anion can play the dual role of reagent and solvent. It is readily prepared by the reaction of equimolar amounts of [bmim][Br] and bromine and is a stable liquid that can be stored for several months without loss of activity. This tribromide-based IL was utilized for the nuclear bromination of activated aromatics[86–88] and α-monobromination of carbonyl compounds.[89,90] Reactions with primary, secondary and tertiary anilines or amides were carried out in the temperature range of −10 to 25 °C for 2–120 min and provided the corresponding monobrominated products, preferentially in the *para*-position, in high yields (85–98%).[86] Phenols and methoxy-substituted aromatics were reacted with/in [bmim][Br$_3$] (**55**) for 10–60 min at −10 to 25 °C and gave the monobrominated product regioselectively



55 [bmim][Br$_3$]
56 [Hmim][Br$_3$]
57 [C$_5$Py][Br$_3$]
58 [C$_8$Qui][Br$_3$]

Figure 5. Tribromide-based ILs utilized as reagents and solvents for bromination of organic compounds.

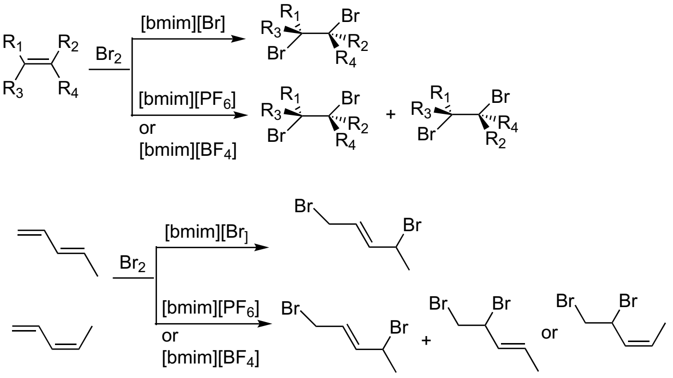
and in high yield.[87,88] A variety of alkanones dissolved in [bmim][Br_3] (**55**) were transformed into the corresponding α-monobrominated carbonyl products after 10 min at 15 °C or at room temperature.[89,90]

Chiappe et al. reported that an acidic IL having a tribromide anion ([Hmim][Br_3] (**56**)) displays improved reactivity as compared to the non-acidic trihalide-based IL ([bmim][Br_3], **55**).[91] Bromination utilizing [Hmim][Br_3] (**56**) was not only effective for activated aromatic compounds, but also with aldehydes and with sterically hindered aromatic compounds, while bromobenzene, iodobenzene and benzonitrile did not react. The acidic IL [Hmim][Br_3] (**56**) also proved to be efficient for the synthesis of vicinal dibromides from *trans*-β-styrene. After the reaction, the halogenating agent can be recovered by addition of the required amount of Br_2 to 3-methylimidazolium bromohydrogenate ([Hmim][HBr_2]), which is the sole byproduct, or, alternatively, the latter can be isolated and used as a reagent/solvent in other reactions.[92]

Another IL, which can function as solvent and reagent is pentylpyridinium tribromide (**57**), which is a hydrophobic and proton-free room temperature IL/bromine reagent.[93] This compound proved to be efficient for the bromination of activated aromatics, carbonyl compounds and unsaturated systems. Utilizing **57** at room temperature, phenol, anisole and *N*,*N*-dimethylaniline were regioselectively monobrominated at the *para*-position (20 min, 93%; 1.5 h, 90%; 81%, respectively). Ketones were cleanly and selectively α-monobrominated without the formation of side products, while alkenes and alkynes were selectively dibrominated in high yields. Similarly, *N*-octylquinolinium tribromide (**58**) was reported to be an efficient bromine analogue for the bromination of phenol, aromatic amines, alkenes and alkynes at room temperature to the corresponding brominated products in good-to-excellent yields.[94] Reagent **58** was regenerated by treatment with bromine and was effectively reused for up to six cycles.

4.3. Bromination of unsaturated systems in ILs

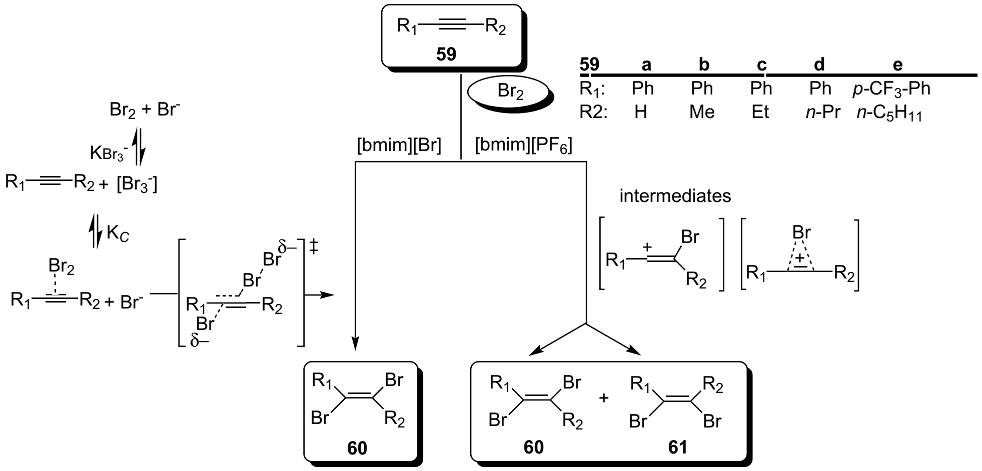
Since the addition of bromine to double and triple bonds has been considered a fundamental reaction in organic chemistry, its synthetic and mechanistic aspects have been thoroughly studied over the years in molecular solvents. Typically, CCl_4 has been employed as a solvent for halogen addition reactions, despite the fact that electrophilic additions often proceed slowly in this solvent, and radical reactions could ensue, leading to different product distribution. Because health hazards and environmental concerns are associated with the use of CCl_4, bromination in water would be a much more attractive proposition, but unfortunately nucleophilic attack of solvent competes with Br^- quenching, leading to substantial amounts of bromohydrins. Ionic liquids possessing low nucleophilicity counterions provide suitable media for bromination with the added advantages of high stereoselectivity and enhanced rates. The ILs [bmim][PF_6], [bmim][BF_4], [bmim][Br] and [bmim][Cl] have been studied as 'green' recyclable alternatives to chlorinated solvents for the stereoselective addition of Br_2 to several alkyl- and aryl-substituted alkenes, alkynes and dienes at room temperature.[68] Alkene and diene bromination reactions were complete within 1 min, while a longer reaction time was needed for the bromination of alkynes, especially in [bmim][Br]. Bromination of alkenes and alkynes with Br_2 in [bmim][Br] was *anti*-stereospecific, while in [bmim][BF_4] and in [bmim][PF_6] the stereoselectivity was more dependent upon the structure of the substrate, although a higher antistereoselectivity as compared to molecular solvents was observed. Dienes selectively gave the 1,4-addition product in [bmim][Br], but in [bmim][BF_4] and in [bmim][PF_6] a mixture of isomers was obtained (Scheme 26). Based on these results, the authors anticipated the involvement of Br_3^- in the reactions performed in [bmim][Br] and free Br_2 as an electrophile in reactions carried out in [bmim][BF_4] and in [bmim][PF_6]. The same group studied the kinetic behaviour and the product (**60**/**61**) distributions of bromination with Br_2 for several arylalkynes (**59a**–**e**) in [bmim][Br] and [bmim][PF_6] (Table 12).[95] They reported that, in [bmim][Br], the reactions followed a second-order rate law with alkynes stereospecifically yielding *anti* addition products, while in [bmim][PF_6] mixtures of *syn* and *anti* addition products were obtained in the reactions following a second- or a third-order kinetics, depending upon the structure of the alkyne and the concentration of Br_2. The experimental data in [bmim][Br] were explained by the presence of Br_3^- as electrophile, via a mechanism involving product- and rate-determining nucleophilic attack of bromide on the alkyne–Br_2 π-complex. On the other hand, formation of both diastereoisomers in [bmim][PF_6], according to authors, suggests the initial formation of a 1:1 alkyne–Br_2 π-complex, followed by ionisation to a bromirenium (or bromovinyl cation) bromide or tribromide intermediate (Scheme 27). Furthermore, comparison of the kinetic data obtained in ILs with the data determined in molecular solvents implied that, in addition to polarity, hydrogen-bonding capability and viscosity of the ILs could also affect the reaction pathway and substrate reactivity.



Scheme 26. Regioselectivity of bromination with Br_2 in ILs.

The kinetic constants and activation parameters were investigated for the reactions of the Br_3^- anion with alkenes and alkynes in [bmim][PF_6], [emim][NTf_2], [bmim][NTf_2], [hmim][NTf_2], [bm_2im][NTf_2] and [bPy][NTf_2] and were evaluated in comparison to the data obtained in 1,2-dichloroethane (DCE).[70] The addition of tribromide anion to alkenes and alkynes proceeds with complete antistereoselectivity. Although the kinetic and product distribution data suggest a very similar mechanism for the reactions in ILs and in molecular solvents, the reactions in ILs are 5- to 30-fold faster in comparison to DCE, showing that ILs are able to influence the stability of reactants and/or transition state.

The ILs bearing tribromide anions (**56**, **57**, **58** in Fig. 5) were demonstrated to be efficient vapour pressure-free bromine analogues, acting as brominating reagents and as solvents for the synthesis of dibromides from alkenes and alkynes. The reaction of *trans*-β-methylstyrene with an acidic IL [Hmim][Br_3] (**56**) was completed in 20 min, yielding 90% of the *anti* vicinal dibromide adduct along with 10% of the *syn* adduct.[91] Utilizing [C_5Py][Br_3] (**57**) with cyclohexene, *cis*-1,2-diphenylethene, phenylacetylene and ethyl propiolate afforded the corresponding dibrominated products with complete or high *anti* stereoselectivity.[94] In addition, [C_8Qui][Br_3] (**58**) also proved to be an efficient brominating agent and solvent with various substrates with ethylenic (cyclodecene, cyclooctene, 1-hexadecene-cyclooctene or 4-vinylpyridine) or acetylenic (1-nonyne, 1-octadecyne, 1-hexadecyne, 1-tetradecyne, 1-undecyne, 1-pentadecyne or 1-tridecyne) moieties, forming the



Scheme 27. Regioselectivity and mechanism for bromination with Br_2 of arylalkynes in [bmim][Br] and [bmim][PF_6].

Table 12
Product distribution in bromination of **59a-e** with Br_2 in [bmim][PF_6] and DCE

Alkyne	Solvent	Products **60/61**
59a	[bmim][PF_6]	88:12
	DCE	57:43
59b	[bmim][PF_6]	77:23
	DCE	78:22
59c	[bmim][PF_6]	75:25
	DCE	70:30
59d	[bmim][PF_6]	75:25
	DCE	66:34
59e	[bmim][PF_6]	99:1
	DCE	99:1

corresponding dibrominated product in high yields and with high *anti* stereoselectivity.[94]

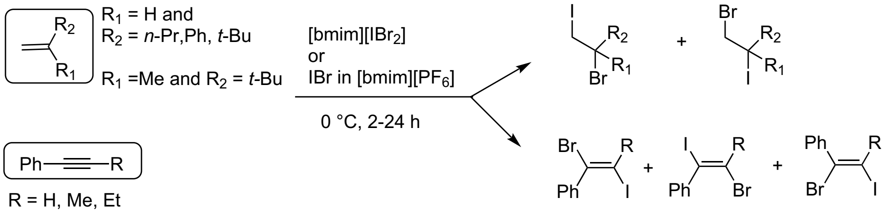
The trihalide-based IL [bmim][IBr_2] was prepared by a reaction of [bmim][Br] with 1 equiv of IBr at 0 °C and investigated for the iodobromination of alkenes and alkynes.[69] The regioselectivity of the addition reaction was reported to depend upon the structure of the alkene or alkyne, providing a mixture of Markovnikoff (M) and *anti*-Markovnikoff (AM) adducts, the ratio of which seems to be heavily influenced by steric and electronic factors. The chemo-, regio- and stereoselectivities of analogous reactions are similar to those performed with TBAI/Br_2 in CH_2Cl_2, but reactions in the latter system are slower, compared to those in trihalide-based ILs. Another route to *vic*-iodobromo adducts involves the addition of IBr to alkenes and alkynes in [bmim][PF_6] (Scheme 28). As is the case in chlorinated solvents, the regiospecificity of the process in [bmim][PF_6] proved to be dependent upon the structure of the substrate. Aryl-substituted alkenes and alkynes were transformed solely into the M-adducts, while a mixture of M- and AM-adducts was obtained with simple alkyl-substituted alkenes. Replacing the propyl group on the alkene by a *tert*-butyl group resulted in the exclusive formation of the AM-adducts.

Fluorobromination of alkenes was reported, utilizing a combination of NBS and an IL possessing a fluoride anion source, namely EMIM$(HF)_{2,3}$.[30,32] The authors reported that various aliphatic, cyclic and aryl alkenes were transformed into *vic*-bromofluoroalkanes in good yields and with high stereoselectivity at room temperature (Scheme 9).[30]

Yadav et al. reported the bromohydroxylation reactions of alkenes utilizing NBS in the [bmim][BF_4]/H_2O system at room temperature.[84] Various olefinic systems were selectively transformed into the corresponding *vic*-bromohydrins in high-to-quantitive yields.

Oxidative bromination of a carbon–carbon double bond was carried out in a [bmim][CCl_3COO] IL, employing NaBr in the presence of 30% H_2O_2 and 60% H_2SO_4 at room temperature.[96] Hydrogen peroxide, generally accepted as a 'green' oxidant, was used to generate molecular bromine, while H_2SO_4 was employed in order to activate the oxidizing power of H_2O_2. The procedure provided the dibrominated addition products in high yield (70–95%) with almost complete trans-stereoselectivity, except in the case of phenylacetylene, where the trans/cis ratio of 1,2-dibromo-1-phenylethylene corresponded to 80:20. The authors also utilized [bmim][CF_3COO] and [emim][BF_4] as media for the same transformation. The IL-recycling and atom-economy aspects of this study were underscored by the authors.

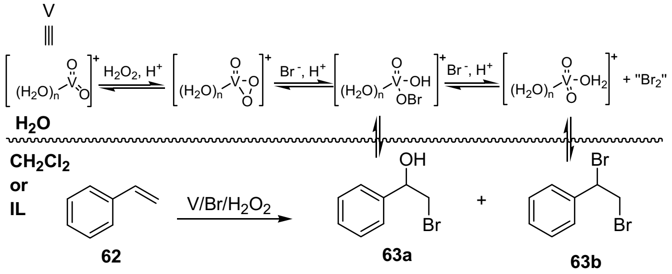
Conte et al. investigated the vanadium(V)-catalyzed oxybromination of styrene (**62**) in a water/IL system for comparison with a water/CH_2Cl_2 biphasic system, utilizing KBr as the bromine source and H_2O_2 as the oxidant.[97] Previous studies in the water/CH_2Cl_2 system confirmed two parallel processes involving two different intermediates, i.e., the vanadium-bound hypobromite ion, responsible for the formation of the bromohydrin product (**63a**),



Scheme 28. Iodobromination of alkenes and alkynes in ILs.

and ‘bromine’ leading to the formation of the dibrominated compound (**63b**). The ionic liquids investigated as replacements for the organic phase included the hydrophilic [bmim][BF_4] and [bmim][OTf] and the hydrophobic [bmim][PF_6], [bm_2im][PF_6] and [bmim][NTf_2]. The hydrophilic ILs did not provide any improvement in terms of yield and selectivity, compared to the oxybromination reaction performed in the water/CH_2Cl_2 system (Table 13, entries 1–3). In contrast, the hydrophobic ILs investigated in a two-phase system with water as the reaction medium provided much higher yields with significantly better selectivities towards the formation of the bromohydrin (**63a**) over a shorter reaction time (Table 13, entries 4–6).

Table 13
Vanadium(V)-catalyzed oxybromination of styrene (**62**) with KBr and H_2O_2



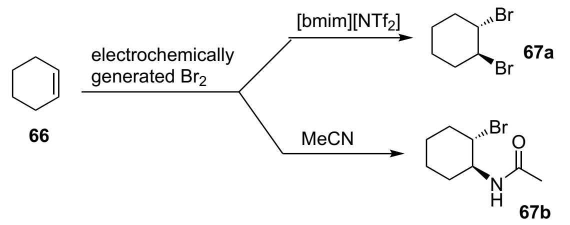
Entry	Solvent(s)	Time (h)	Yield (%)	**63a**/**63b**
1	H_2O/CH_2Cl_2[a]	24	65	78:22
2	H_2O/[bmim][BF_4][b]	2	27	58:42
3	H_2O/[bmim][OTf][b]	2	68	79:21
4	H_2O/[bmim][PF_6][b]	4	96	98:2
5	H_2O/[bmim][NTf_2][b]	6	92	97:3
6	H_2O/[bm_2im][PF_6][b]	5	>99	94:6

[a] NH_4VO_3=0.01 mol/l, H_2O_2=0.01 mol/l, KBr=0.05 mol/l, styrene=0.01 mol/l, pH ca. 1 ($HClO_4$), rt.

[b] NH_4VO_3=0.01 mol/l, H_2O_2=0.02 mol/l, KBr=0.1 mol/l, styrene=0.02 mol/l, pH ca. 1 ($HClO_4$), rt.

In the same vein, Conte’s group studied the oxybromination of acetylene (**64**) with KBr/H_2O_2 in two two-phase water/IL and water/CH_2Cl_2 systems at room temperature, using the more reactive Mo(VI) species as the catalyst.[98] The oxybromination reaction of acetylene provided four products (**65a**–**d**) in different ratios, depending upon the concentration of the reacting species and the solvent used. In a water/CH_2Cl_2 system, the overall yield did not exceed 50% and favoured the formation of the dibrominated products (**65a** and **65b**), but the selectivity could be shifted in favour of α,α-dibromoacetophenone (**65d**) by increasing the alkyne/Br^- ratio (Table 14, entries 1 and 2). With the hydrophobic [bmim][PF_6] and [bmim][NTf_2] as potential replacements for CH_2Cl_2, the authors found that the reactions performed in water/IL systems were faster and the yields were comparable, but were significantly shifted towards the formation of the α,α-dibromoketone (**65d**) (Table 14, entries 3 and 4), which is an important compound with antibacterial, fungicidal and algicidal properties. The yields were improved further (88%) by portion-wise addition of H_2O_2, minimizing its decomposition (Table 14, entry 5). Based on a mechanistic study, these authors suggested that the formation of the dibromoketone derivative occurs after bromine addition to the triple bond and prior to transformation of the bromoenol into α-bromoketone. The proposed reactive species are analogous to those in the vanadium(V)-catalyzed oxybromination of the alkene, for which the reactive species were experimentally detected.

In addition to chemical oxidants, the oxidation of bromide can also be carried out electrochemically. Electrochemical bromination of an alkene was comparatively evaluated in [bmim][NTf_2] and in MeCN using cyclohexene (**66**) as the substrate.[99] Although the direct oxidation of bromide resulted in similar voltammetry in both media, the reaction of electrogenerated bromine with cyclohexene yielded different products. Bromination in the IL resulted in the formation of *trans*-1,2-dibromocyclohexane (**67a**), while *trans*-1-(*N*-acetylamino)-2-bromocyclohexane (**67b**) was formed in MeCN. Solvent incorporation in the case of MeCN was explained by the greater nucleophilicity of MeCN compared to [NTf_2]$^-$ (Scheme 29).

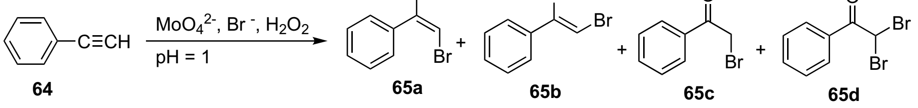


Scheme 29. Reactivity of electrogenerated bromine with cyclohexene (**66**) in [bmim][NTf_2] and MeCN.

4.4. Formation of alkyl bromides

Conversion of alcohols into alkyl bromides was investigated at room temperature in [bmim][Br] in the presence of methanesulfonic acid or H_2SO_4. The latter Brønsted acid proved to be superior, which is in contrast to chlorination in [bmim][Cl], where

Table 14
Mo(VI)-catalyzed oxybromination of acetylene (**64**) with KBr and H_2O_2



Entry	Solvent(s)	Time[a] (h)	Conversion (%)	Absolute yield[b] (%)	Selectivity **65a**/**65b**/**65c**/**65d**
1	H_2O/CH_2Cl_2[c]	18	50	42	20:56:20:4
2	H_2O/CH_2Cl_2[d]	18	50	47	11:31:7:51
3	H_2O/[bmim][Tf_2N][e]	2	50	32	3: 8:43:46
4	H_2O/[bmim][PF_6][e]	2	55	53	0: 7:19:74
5	H_2O/[bmim][PF_6][f]		100	88	6: 9:10:75

[a] Time necessary for oxidant to be consumed.

[b] Relative to initial concentration of alkyne.

[c] [MoO_4^-]=0.005 mol/l, [H_2O_2]=0.01 mol/l, [KBr]=0.05 mol/l, [**64**]=0.01 mol/l, rt.

[d] [MoO_4^-]=0.01 mol/l, [H_2O_2]=0.02 mol/l, [KBr]=0.025 mol/l, [**64**]=0.02 mol/l, rt.

[e] [MoO_4^-]=0.01 mol/l, [H_2O_2]=0.02 mol/l, [KBr]=0.10 mol/l, [**64**]=0.02 mol/l, rt.

[f] [MoO_4^-]=0.01 mol/l, [KBr]=0.10 mol/l, [**64**]=0.02 mol/l, rt, [H_2O_2]=0.04 mol/l added in two portions, time not specified.

Table 15
Conversion of alcohols into alkyl halides using ILs

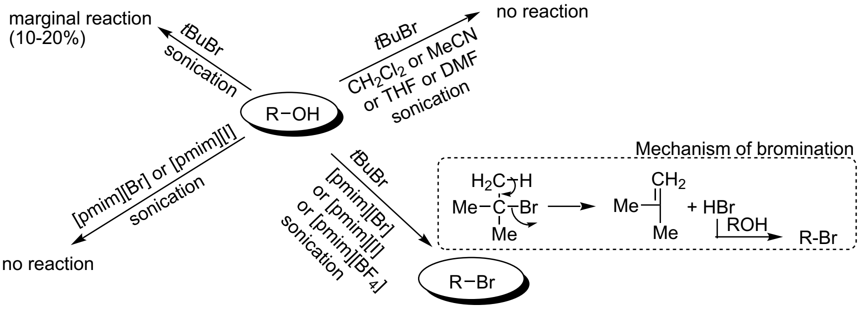
Entry	IL	Reagent	*T*, *t*	ROH (*t*, yield)	Ref.
1	[bmim][Br]	IL/H_2SO_4	rt	*n*-BuOH (20 h, 95%), 1-octanol (5.5 h, 98%), *sec*-BuOH (12 h, 95%), *t*-BuOH (1 h, 95%)	71
2	[Pr^{i}mim][Br]	IL/PTSA	MW (100 W), 3 min	1-Octanol (95%), 1-heptanol (95%), 1-decanol (98%), 10-undecen-1-ol (89%), 1,8-octanediol (86%),[a,b] geraniol (47%),[a] benzyl alcohol (68%)[a]	72
3	[Hmim][Br]	IL	120 °C, 12 h	1-Octanol (99%), *sec*-octanol (85%), cyclohexanol (99%), benzyl alcohol (99%), hexanediol (98%)[b]	73
4	[omim][Br]	IL/PTSA	90–120 °C, 30–75 min	C_8–C_{18} fatty alcohols (97–100%)	100
5			MW (75 W), 3-4 min	C_8–C_{18} fatty alcohols (78–95%)	100
6			110 °C, 2 h	1,ω-Dialcohols (C_6-C_{16}) (90–95%)	101
7			MW (75 W), 45–90 s	1,ω-Dialcohols (C_6–C_{16}) (95–100%)	101
8	[pmim][Br] or [pmim][I] or [pmim][BF_4]	^{t}BuBr or *t*-amyl-Br	rt, sonication	Primary, secondary, benzylic, allylic alcohols, isoborneol, primary allylic diols (1–2 h, 82–95%)	74
9	[$^{2\text{-OH}}C_3$mim][PF_6]	IL–$OPPh_2(Br)_2$	80 °C, 0.1–24 h	Primary, secondary, tertiary, benzyl alcohols (86–95%), TMS and THP ethers (73–89%)	102

[a] With co-solvent toluene (2 ml).
[b] Dibromide.

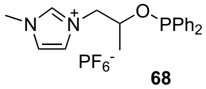
the use of $MeSO_3H$ provided higher conversions.[71] The method employing [bmim][Br]/H_2SO_4 at room temperature for 1–22 h with *n*-butyl-, *n*-octyl-, *sec*-butyl- and *tert*-butyl alcohol worked well for the formation of the corresponding bromides (Table 15, entry 1). The reaction time could be significantly reduced by MW heating in the case of primary alcohols, while in the case of secondary and tertiary alcohols decomposition occurred.[72] 1-Octanol reacted in [Pr^{i}mim][Br] in the presence of *p*-toluenesulfonic acid (PTSA) using MW irradiation (100 W power for 3 min), and 1-octyl bromide was obtained in 95% yield. Similarly, alkyl bromides (and dibromides) were efficiently prepared from 1-heptanol, 1-decanol and 10-undecen-1-ol, and 1,8-octanediol, but propargyl alcohol was decomposed. Moreover, benzylic and allylic substrates of primary alcohols could be converted into the corresponding bromides employing this MW procedure (Table 15, entry 2). The authors remarked, however, that the method using toluene as a co-solvent is preferred, because it prevented the decomposition of the bromide at the high temperatures reached during MW exposure.[72]

By immobilizing HX in an IL (via the reaction of HX with methylimidazole), the Brønsted acidic IL [Hmim][X] is formed, which can be used as a recyclable catalyst/solvent/halogenating agent. Thus, [Hmim][Br] was used at 120 °C for 12 h for the formation of alkyl bromides from *n*-octanol, *sec*-octanol, cyclohexanol and benzyl alcohol, while the corresponding dibromide was obtained from hexanediol (Table 15, entry 3). In the case of tertiary alcohols, [Hmim][Br] was not beneficial for bromination, as the substrate was converted into the corresponding alkene. Due to the low solubility of fatty alcohols in [bmim][Br] and [Pr^{i}mim][Br], the formation of alkyl bromides possessing longer alkyl chains (C_8–C_{18}) requires the use of a more lipophilic IL. For such instances, 1-octyl-3-methylimidazolium bromide ([omim][Br]) in the presence of PTSA was shown to be efficient for the transformation of fatty alcohols (C_8–C_{18}) into the corresponding alkyl bromides, either under conventional heating at around 100 °C for 1 h (Table 15, entry 4), or under MW irradiation (75 W) for a few seconds to a few minutes (Table 15, entry 5).[100] Furthermore, the reagent system [omim][Br]/PTSA was efficiently utilized for the conversion of 1,ω-dialcohols (C_6-C_{16}) into the corresponding dibromides.[101] This transformation could be carried out for 2 h at 110 °C (Table 15, entry 6), whereas the reaction occurs more rapidly when exposed to MW irradiation for 45–90 s (using 25-s cycles: irradiation for 5 s at 75 W followed by 20-s stirring, which maintained the reaction temperature under 100 °C) (Table 15, entry 7).

Direct bromination of alcohols was reported with BuBr/[pmim][Br] under sonication at room temperature.[74] Primary, secondary, benzylic and allylic alcohols were smoothly converted into the corresponding bromides, sterically hindered alcohols were transformed into the *exo* bromides, primary allylic diols formed the dibromides, whereas tertiary alcohols remained inactive (Table 15, entry 8). Moreover, hydroxyl-protected derivatives (OTMS, OTBDMS, OAc, OTs and OTHP) were efficiently converted into the corresponding bromides by this procedure. In addition to ^{t}BuBr, *tert*-amyl bromide was also effective, while primary and secondary bromides like *n*-butyl bromide and *sec*-butyl bromide were ineffective. The combination of *tert*-butyl bromide and an IL was shown to be essential for an efficient transformation, as no reaction occurred in the absence of either of them. The reaction utilizing ^{t}BuBr in conventional organic solvents (CH_2Cl_2, MeCN, THF, DMF) under sonication or heating did not take place. As regards the choice of IL, besides [pmim][Br], [pmim][BF_4] and [pmim][I] also proved to be equally effective. The effectiveness of the reagent system ^{t}BuBr/IL was explained by the IL-initiated formation of 2-methylpropene and HBr from ^{t}BuBr and the subsequent bromination of alcohols with the HBr produced (Scheme 30).



Scheme 30. Bromination utilizing ^{t}BuBr and [pmim][Br] under different conditions and suggested mechanism of bromination employing reagent system ^{t}BuBr/IL.



68

Figure 6. IL-OPPh$_2$.

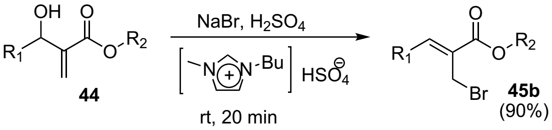
Iranpoor et al. introduced diphenylphosphinite IL (IL–OPPh$_2$) as a solvent and reagent for the conversions of alcohols and TMS as well as tetrahydropyranyl (THP) ethers into their corresponding alkyl bromides.[102] The reagent was prepared from 1-(2-hydroxypropyl)-2-methylimidazolium hexafluorophosphate, PPh$_2$Cl and Et$_3$N in CH$_2$Cl$_2$, furnishing IL–OPPh$_2$ (**68**, Fig. 6). A mixture of the newly formed IL and Br$_2$ provided IL–OPPh$_2$(Br)$_2$, which was applied in reactions with primary, secondary, tertiary and benzylic alcohols, to give the corresponding alkyl bromides at 80 °C in high yields (Table 15, entry 9). Moreover, the TMS and THP ethers were converted into their corresponding alkyl bromides efficiently under the same reaction conditions as those used for alcohols. The authors noted that the bromination reactions were highly selective for primary alcohols in the presence of secondary alcohols, and that primary and secondary alcohols were more reactive in the presence of tertiary alcohols or TMS and THP ethers.

In the course of an investigation on the enhanced nucleophilicity of metal fluorides in ILs, Kim et al. tested the nucleophilic bromination of mesylate **1a**. Employing 5 equiv of KBr in 3 ml of [bmim][BF$_4$] and 3 ml of MeCN (5% H$_2$O) for 30 min at 100 °C yielded 96% of 2-(3-bromopropyl)naphthalene (**2e**) (Scheme 31), thus demonstrating the increased nucleophilicity of bromide in the presence of IL.[15] Furthermore, these workers synthesised the polymer-supported IL PS[bmim][BF$_4$] and showed its catalytic role in the nucleophilic bromination of mesylate **1a** to the corresponding bromide **2e**.[17] Reaction of **1a** with 3 equiv of KBr, in 0.5 equiv of PS[bmim][BF$_4$] and 3 ml of MeCN (performed at 100 °C for 50 min), gave the bromoalkane **2e** in 99% yield. In continuation, they investigated structurally modified PSILs for nucleophilic reactions, including bromination (Scheme 31), by varying the length of the alkyl chain linker, the IL counterion and the loading level on the PS.[18] For the bromination of **1a**, they employed 3 equiv of KBr at 100 °C in MeCN in the presence of 0.5 equiv of various PSIL systems (PS[mim][BF$_4$], PS[pmim][BF$_4$], PS[hmim][BF$_4$] and PS[domim][BF$_4$]). The reactions utilizing the PSIL system with the longest linker procceded most efficiently, affording the bromoalkane **2e** almost quantitatively (99%). The superior activity of the PSIL with a longer alkyl linker was rationalized by the ease of approach of the reagent to the IL moiety of the PSIL. As regards the loading level on the polystyrene backbone, a PSIL system with a lower ionic portion showed a better catalytic activity in the bromination reactions, which was ascribed to matrix and site isolation effects.

A polymer-supported functionalized IL possessing a tertiary alcohol moiety was shown to increase the solubility and reactivity of halide anions. When 0.5 equiv of PS[him–^{t}OH][OMs] was used as a catalyst for the bromination of the mesylate derivative **69** with 3 equiv of bromide (NaBr, KBr, CsBr) in MeCN (3 ml, at 100 °C for 1–6 h), the corresponding alkyl bromide **70a** was obtained in high yield (Scheme 31). This result represents a significant improvement over the case when an analogous PSIL, lacking tertiary a alcohol functionalization (PS[hmim][OMs]) was used, for which the bromination yield was a modest 18–32%.[21]

Bao et al. reported a continuous-flow process for the synthesis of alkyl bromides by a nucleophilic substitution reaction of tosylate and LiBr in [emim][OTs].[103] The reaction was conducted on a large scale with 4-methylbenzenesulfonate as the substrate and LiBr as the brominating reagent at 80 °C in such a way that the substrate continuously passed into the reactor and the product continuously distilled out at the same time, which was possible due to the relatively fast completion of the reaction. The reuse of IL was achieved by filtering off the LiOTs. Comparison of the batch and continous-flow processes showed that a higher yield of the product and a shorter reaction time were achieved by utilizing the continous-flow procedure.

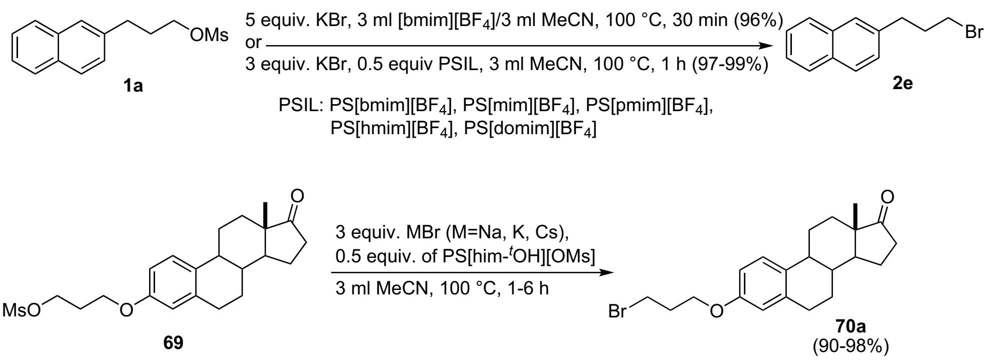
NaBr immobilized on a [bmim][HSO$_4$] IL, in the presence of H$_2$SO$_4$ (60%), was found to be an efficient bromination system for converting 3-hydroxy-2-methylenealkanoates (**44**) into (2*Z*)-2-(bromomethyl)alk-2-enoates (**45b**) with high stereoselectivity at room temperature (Scheme 32).[75]



Scheme 32. Synthesis of (2*Z*)-2-(bromomethyl)alk-2-enoates.

4.5. Other bromination approaches

Oxidative bromination of anisole using NaBr as the electrophile and F–TEDA–BF$_4$ (Selectfluor™) as the oxidant, performed for 24 h at 70–80 °C in [bmim][PF$_6$], transformed anisole into *para*-bromoanisole (>90%).[59a] Reaction of mesitylene, utilizing the Brønsted acidic IL [Hmim][NO$_3$] and HBr (48%) for 24 h at 80 °C, selectively provided the monobromo derivative in relatively low yield (30%).[58] On the other hand, Earle et al. reported the oxidative bromination of toluene and anisole with HBr (49%) in [bmim][NO$_3$], where the oxidant was considered to be air.[57] The bromination of toluene was performed at 100 °C for 96 h and yielded 49% of 2-bromotoluene



Scheme 31. Bromination of mesylate enhanced in the presence of ILs.

Table 16
Overview of selected bromination methods

Entry	Substrate	IL	Reagent	T, t	Product	Yield (%)	Ref.
1	Anisole	[bmim][PF_6]	NaBr/F-TEDA-BF_4	70–80 °C, 24 h	4-Br-anisole	> 90	59
2	Mesitylene	[Hmim][NO_3]	48% HBr/IL	80 °C, 24 h	mono-Br-mesitylene	30	58
3	Anisole	[bmim][NO_3]	49% HBr	80 °C, 18 h	4-Br-anisole	99	57
4	Toluene			100 °C, 96 h	2-Br-toluene, 4-Br-toluene	49, 50	57
5	Anisole	[C_{12}mim][Br]	67% HNO_3/IL	50 °C, 1 h	4-Br-anisole	99	57
6	Toluene			110 °C, 72 h	2-Br-toluene, 4-Br-toluene	39, 60	57
7	Naphthalene			50 °C, 2 h	1-Br-naphthalene	98	57
8	$ArN_2^+BF_4^-$	[bmim][PF_6]	TMSBr	rt or 55 °C	ArBr	70–90	27c
9	Carbonyl compounds	[Acmim][Br]	IL/CAN	rt, 3–5.5 h	α-bromo-carbonyl product	80–90	60

and 50% of 4-bromotoluene, while in the case of anisole the reaction was carried out for 18 h at 80 °C and provided 99% of 4-bromoanisole. The same authors reported a high conversion into the brominated products for toluene, anisole and naphthalene, employing 67% nitric acid in combination with [C_{12}mim][Br]. Toluene, after 72 h reaction at 110 °C, was 99% converted into the *ortho*- and *para*-bromo derivatives with an *o*/*p* isomer ratio of 39:60, anisole required a 1 h reaction at 50 °C to yield 99% of 4-bromoanisole, whereas naphthalene after 2 h at 50 °C gave 98% 1-bromonaphthalene.[57]

Laali et al.[27c] studied the reactions of arenediazonium tetrafluoroborates ($ArN_2^+BF_4^-$) with TMSBr in [bmim][PF_6]. The bromodediazoniations performed at room temperature typically gave better yields as compared to those carried out at 55 °C. Various substituted arenes were converted into the bromoarenes in 70–90% yields. Competing fluorodediazoniation (ArF formation) and hydrodediazoniation (ArH formation) were also observed.

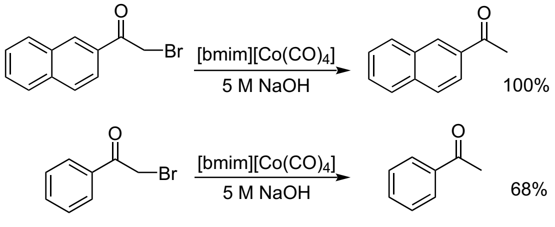
Acetylmethylimidazolium bromide, [Acmim][Br], in combination with ceric ammonium nitrate (CAN), was shown to act as a reagent and solvent for the α-bromination of various carbonyl compounds, including cyclic and acyclic α,β-unsaturated ketones and β-keto esters.[60] Bromination of 2- and 3-substituted cyclohexanones produced mixtures of 2- and 6-brominated products, with the formation of the 2-bromo isomer being favoured. Acyclic ketones with both α-hydrogens available also produced a mixture of regioisomers, while α,β-unsaturated cyclic ketones generally furnished the 2-bromo enones. As regards the rate of halotransformation, with a combination of [Acmim][X] and CAN, bromination was faster in comparison to chlorination. The experimental findings further showed that CAN acted as a one-electron oxidant and that the radical quencher TEMPO arrested the halogenation, thus pointing to a radical process for halotransformation (Table 16).

Xu et al. reported that the addition of either 1 equivalent of CF_3COOH or CF_3SO_3H to *N*-pentylpyridinium bromide [C_5Py][Br] forms an IL reagent that behaves as an acidic, hydrobrominating agent, but is safer than fuming aqueous HBr.[104] They efficiently utilized the so-formed HBr-surrogate reagent in ring-opening reactions of cyclopropyl ketones to the corresponding 3-bromopropyl ketones (Scheme 33). The use of [C_5Py][Br]/CF_3COOH proved to be efficient with 2,2-difluorocyclopropyl aryl ketones, while for nonfluorinated cyclopropyl ketones this combination resulted also in the formation of the trifluoroacetate derivative as a side product in addition to the brominated main product. Competition in the nucleophilic ring-opening process in the case of nonfluorinated ketones could, however, be readily eliminated by using triflic acid instead of trifluoroacetic acid. The rapid ring opening of epoxides was reported to take place in the presence of LiBr in [bmim][PF_6] or in [bmim][BF_4] under mild conditions, forming the corresponding *vic*-bromohydrins stereoselectively and in high yields.[77] The reactivity enhancement in the imidazolium-based IL, as compared to conventional molecular solvents, was attributed to the activating power of the acidic hydrogen of imidazole. Another imidazolium-based IL, [Acmim][Br], was found to act as a solvent, reagent and catalyst for the formation of *vic*-bromohydrins from the corresponding epoxides.[78]

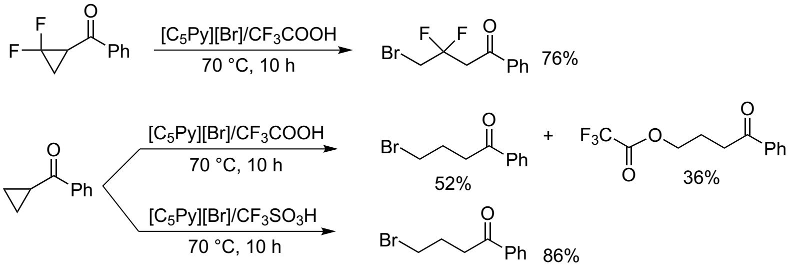
4.6. Debromination reactions

There have been a few reports of ILs catalyzing the elimination of bromine or HBr from brominated organic compounds. An IL with a transition-metal carbonyl anion, namely [bmim][Co(CO_4)], in the presence of NaOH, was reported to catalyze the debromination of 2-bromo-2′-acetonaphthone and 2-bromoacetophenone to their corresponding ketones (Scheme 34).[105]

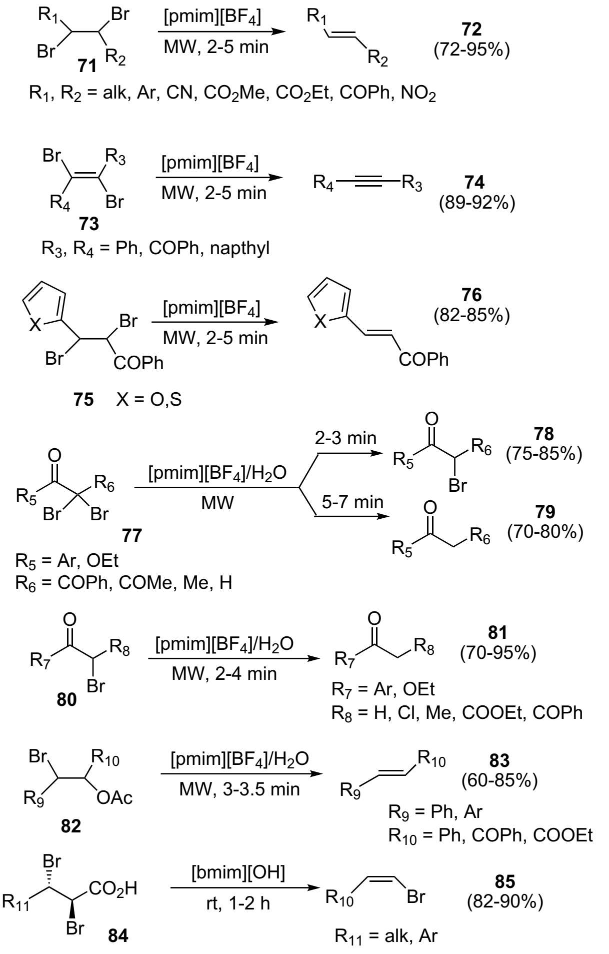
Various structurally diverse *vic*-dibromides (**71** and **73**) were reported to be stereoselectively converted into the corresponding (*E*)-alkenes (**72**) and alkynes (**74**) in [pmim][BF_4] after exposure to MW irradiation for 2–5 min (Scheme 35).[106] While no reaction



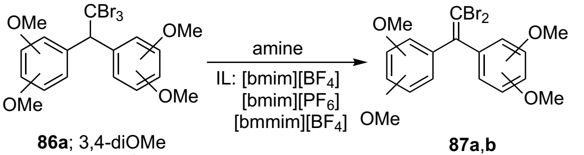
Scheme 34. Debromination using [bmim][Co(CO_4)].



Scheme 33. Synthesis of γ-bromo ketones from cyclopropyl ketones using IL brominating agent.



Scheme 35. Stereoselective debromination of *vic*-dibromides, and α-bromocarbonyl- and *vic*-acetoxybromo compounds by [pmim][BF_4] under MW.

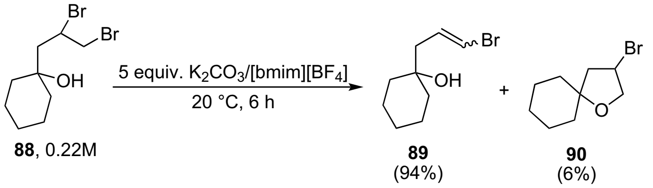


Scheme 36. Base-induced elimination of **86**.

occurred at room temperature or under conventional heating at 90 °C for 12 h, debromination was effective under MW irradiation and in the presence of [pmim][BF_4] in particular. In the absence of IL and under MW irradiation no transformation occurred. The use of [pmim][Br] IL with MW irradiation also led to no reaction. Elimination of bromine was highly efficient in [pmim][BF_4] under MW for aryl, alkyl and cyclic dibromides, as well as sensitive molecules like furan and thiophene derivatives (**75**), while *vic*-dibromoalkenes (**73**) were transformed into the corresponding alkynes (**74**). Furthermore, [pmim][BF_4] was demonstrated to play a vital role in the debromination of α-bromoketones (**77**, **80**) under MW irradiation.[107] The authors did not observe any reaction in the absence of IL, and no transformation took place at room temperature or under conventional heating. In addition to [pmim][BF_4], [pmim][Br] also showed a catalytic effect in the debromination reaction of α-bromoketones under MW irradiation, but the former IL was superior, due to the increased rate, higher efficiency and cleanliness of the transformation. The selectivity of the debromination of *gem*-α-dibromoketones (**77**) can be tuned by proper control of the reaction time, affording either debrominated monobromo- (**78**) or debromoketones (**79**). Following an MW-assisted procedure in [pmim][BF_4], α-monobromoketones (**80**) were converted into the parent ketones (**81**), while *vic*-acetoxybromo compounds (**82**) underwent debromination–elimination, yielding the corresponding (*E*)-alkenes (**83**). The same authors reported that [bmim][OH] acted as an efficient promoter and reaction medium for the debrominative decarboxylation of dibromo α,β-unsaturated carboxylic acids (**84**), yielding the (*Z*)-vinyl bromides (**85**) with high stereoselectivity and yields.[108]

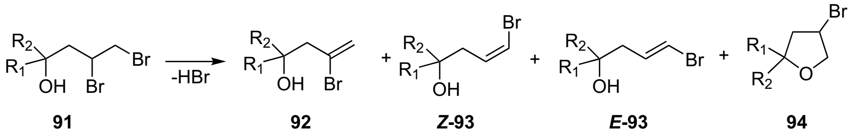
Noto et al. studied the base-induced elimination of 1,1,1-tribromo-2,2-bis(phenyl-substituted)ethanes (**86a**,**b**) to the corresponding 1,1-dibromo-2,2-bis(phenyl-substituted)ethenes (**87a**,**b**) in [bmim][BF_4], [bmim][PF_6] and [bm_2im][BF_4] ILs (Scheme 36).[109] The kinetic data showed that the reaction occurred faster in the IL media than in conventional organic solvents. After analyzing various amines for the base-induced elimination reaction in ILs, it was concluded that the amine structure (i.e., flexibility and steric hindrance) plays an important role, while the base strength seems to have only a minor influence. It was suggested that the ILs have the ability to cause a mechanism shift from $E1_{cb}$ (in MeOH) to E2 (in IL).

While developing a synthesis of substituted 3-bromotetrahydrofurans from homoallylic alcohols, Chirskaya et al. found that the reaction of 1-(2,3-dibromopropyl)cyclohexanol (**88**) with K_2CO_3 in [bmim][BF_4] after 6 h at 20 °C proceeded regio- and stereoselectively to give the dehydrobrominated product, (*E*)-1-(3-bromoprop-2-en-1-yl)cyclohexanol (**89**). In addition to the main vinylic bromide product **89** (94%), a minor cyclized product (**90**) was also formed (6%) (Scheme 37).[110] In continuation, some other 1,2-dibromoalkanes (**91**) bearing a hydroxyl group at the 4-position were investigated, by applying 4 equiv of K_2CO_3 in [bmim][BF_4] at 20 °C for 1–4 h.[111] The reaction gave a mixture of isomers **92**, *Z*-**93** and *E*-**93**, together with the cyclized 3-bromotetrahydrofuran derivative **94** with high selectivity for either the *E*-**93** isomer or the cyclized product (**94**) (Table 17, entries 1–3). Furthermore, these workers investigated the dehydrobromination of *vic*-dibromoalkanes in the absence of a hydroxyl functionality (**95a**–**c**) to the corresponding bromoalkene isomers (**96a**–**c**, *Z*-**97a**–**c**, *E*-**97a**–**c**) in the presence of different bases in various ILs (Scheme 38).[111] Chemoselectivity towards the formation of the product **96** was observed for these substrates. The effect of the following bases was studied: K_2CO_3, K_3PO_4 and KOH. As regards the range of media, DMSO, DMF and DMA were among the organic solvents tested, and the ILs included [bmim][BF_4] and mixtures of 1,2-dimethoxyethane (DME)/[bmim][BF_4], DME/[bmim][Cl], and DME/Bu_4NBr. In polar aprotic solvents (DMSO, DMF, DMA), a high temperature (100 °C) was required for effective dehydrobromination. The use of K_2CO_3 in [bmim][BF_4] resulted in a much higher conversion and a better selectivity at a much lower temperature (20 °C). Combinations of DME and ∼30 mol % of the imidazolium salts, [bmim][BF_4], [bmim][Cl] or Bu_4NBr, enabled a further increase in yield and chemoselectivity, with KOH proving to be the most efficient base.



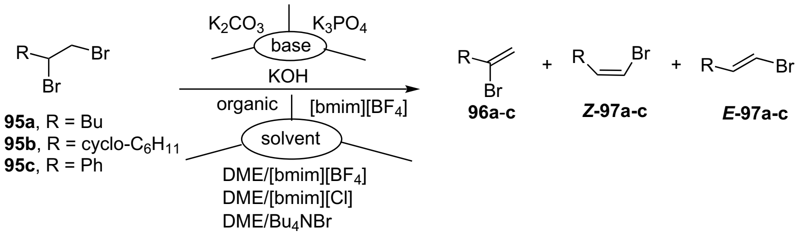
Scheme 37. Dehydrobromination of **88** using reagent system K_2CO_3/[bmim][BF_4].

Table 17
Dehydrobromination of hydroxyl-containing dibromo derivatives



Entry	Substrate	R_1, R_2	*t* (h)	Product distribution (%)			
				92	***Z*-93**	***E*-93**	**94**
1	**91a**	H, C_6H_{13}	4	7	7	16	70
2	**91b**	$(CH_2)_5$	4	5	11	56	28
3	**91c**	$(CH_2)_4$	1	7	9	59	25

Reaction conditions: 4 equiv K_2CO_3, [bmim][BF_4], 20 °C; 100% conversion.



Scheme 38. Effect of base and medium on efficiency and selectivity of dehydrobromination of vicinal dibromides.

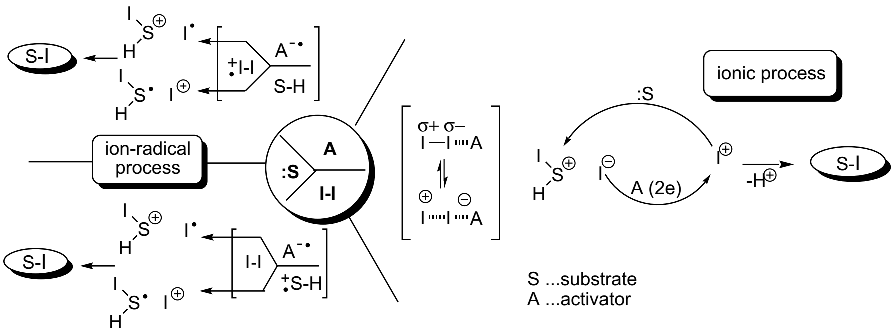
5. Iodofunctionalization of organic compounds in ILs

As pointed out in the introductory section, iodine is the bulkiest, the least electronegative and the most polarizable of the halogens (see also Table 1). Iodides are more reactive than the respective bromides and chlorides because the C–I bond is comparatively weak. Because of these characteristics, the related chemistry and reactivity towards iodine incorporation differ as compared to other halogenation approaches. Unlike fluorine, elemental iodine is scarcely reactive, requiring an appropriate activator for efficient introduction into organic compounds. Alternatively, iodinating reagents that are more reactive than I_2 should be employed. Due to the importance of iodo-substituted organic compounds as synthons or precursors in organic synthesis, mainly for C–C and C–N bond formation,[112] and because iodinated compounds can be used as radioactively labelled markers or contrast agents in medical diagnosis,[113] numerous iodination methods have been developed in molecular solvents, while more attention has been given to 'greener' protocols in recent years.[12h] Iodination in IL media, however, has so far gained less attention relative to fluorination or bromination.

5.1. Iodination of aromatics and carbonyl compounds in IL media

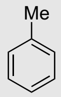
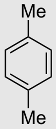
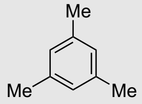
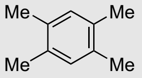
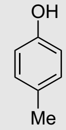
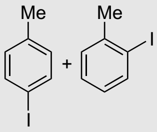
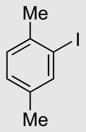
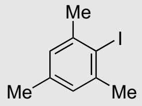
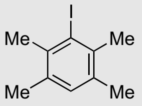
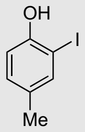
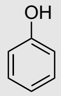
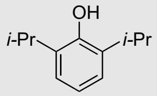
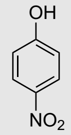
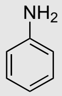
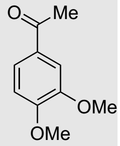
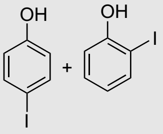
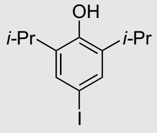
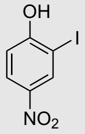
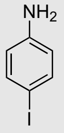
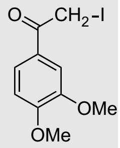
The presence of an appropriate oxidizer can significantly enhance the electrophilicity of elemental iodine, thus enabling its efficient incorporation into organic compounds. In the case of ionic processes, a high atom economy with regard to iodine can be achieved as both iodine atoms of the I_2 molecule are consumed, requiring 0.5 molar equivalent of the reagent relative to the substrate. On the other hand, the involvement of either ion–radical intermediates or radicals requires 1 molar equivalent of the reagent system I_2/oxidant (Scheme 39).

Chiappe et al. reported the iodination of various aromatics employing the reagent system, I_2/F–TEDA–BF_4 (Selectfluor™) in [bmim][PF_6] and [bPy][BF_4] ILs.[59a] Although Selectfluor™ is recognized as a mild and efficient fluorinating reagent, it also possesses oxidizing properties, thus promoting the reactivity enhancement needed for efficient electrophilic iodination. Iodination reactions in the studied ILs were carried out at 70–80 °C for 24 h, forming the ring-iodinated aromatic products with *para*-selectivity where possible, whereas 3,4-dimethoxyacetophenone was



Scheme 39. Reaction pathways for functionalization of organic molecules with molecular iodine.

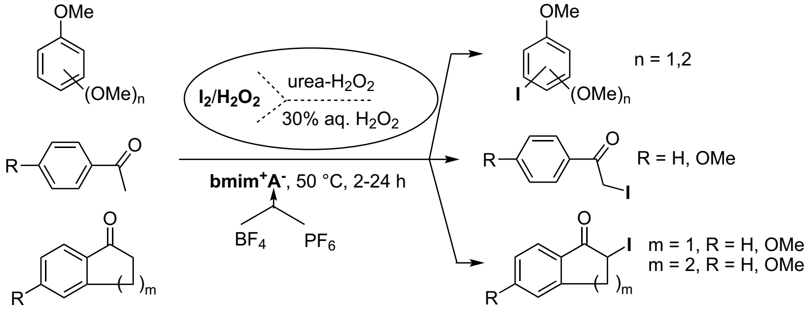
Table 18
Conversions into iodinated products in ILs employing I_2/F–TEDA–BF_4 reagent system

Substrate[a]					
Product					
[bmim][PF_6]	50% (*p*-I/*o*-I=65:35)	100%	100%	45%	70%
[bPy][BF_4]	nr[b]	100%	100%	nr	50%
Substrate					
Product					
[bmim][PF_6]	80% (*p*-I/*o*-I=90:10)	55%	nr	50%	30%
[bPy][BF_4]	nr	45%	15%	70%	90%

[a] Reaction conditions: 1.8 mmol arene, 0.9 mmol I_2, 0.9 mmol F–TEDA–BF_4, 3 ml IL, 80 °C, 24 h.
[b] Not reported.

converted into the α-iodocarbonyl derivative (Table 18). Interestingly, no fluorination occurred in these reactions as a competing process. The substrate selectivity was measured in competitive reactions using mesitylene/durene (1:1). The k_{mes}/k_{dur} ratio in [bmim][PF_6] was 54. A polar mechanism was suggested, which was further supported by using 0.5 molar equivalent of the iodinating reagent for efficient transformation.

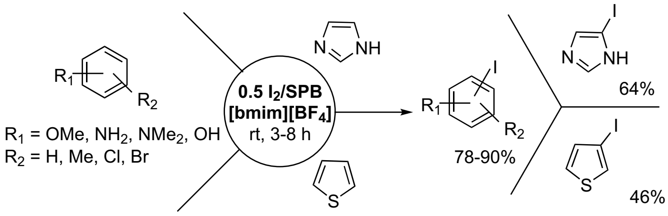
Hydrogen peroxide is consided to be an environmentally friendly oxidant, due to the formation of water as the only oxidation byproduct. In a joint recent study, Stavberet al.[114] used H_2O_2 as a mediator of iodination in hydrophilic [bmim][BF_4] and hydrophobic [bmim][PF_6]. Two different forms of H_2O_2, namely a 30% aqueous solution and a solid form, urea/H_2O_2 (UHP), were studied in combination with elemental I_2 as the iodinating reagent, and the results were evaluated in comparison to the reactions carried out in conventional organic solvents, in water, and under solvent-free conditions (SFRCs). The reagent systems I_2/30% H_2O_2 and I_2/UHP proved to be efficient for ring iodination in various methoxy-substituted benzene derivatives, and at the α-alkyl position of the carbonyl in aryl alkyl ketones in the studied ILs (Scheme 40). The high atom economy with regard to iodine was highlighted in the case of 1,3-dimethoxybenzene, 1,3,5-trimethoxybenzene and 1,2,4-trimethoxybenzene, for which a molar ratio of substrate/I_2/oxidant corresponding to 1:0.5:0.6 was employed to achieve complete or nearly complete conversion. For these cases, the iodotransformation was rationalized by an ionic mechanism and a dual role was ascribed to H_2O_2, namely as an activator of the iodinating system and as a regenerator of iodine. For substrates requiring a 1:1:1 molar ratio of substrate/I_2/oxidant in order to achieve optimal conversions, the atom economy principle was not followed, implying that, in these cases, the H_2O_2 acted solely as an activator of the iodinating system. In terms of efficiency, 30% aq H_2O_2 was reported to be more efficient for ring iodofunctionalization of arenes in both ILs, UHP worked better for α-alkyl iodofunctionalization of carbonyl compounds in hydrophilic [bmim][BF_4], while in [bmim][PF_6] the reaction course greatly depended upon the substrate structure, the reagent employed and the reaction conditions. Although iodofunctionalization utilizing I_2/H_2O_2 in ILs was efficient in most cases, the use of water was preferable as the medium or SFRC, as these provided either higher conversions or reduced the reaction times to achieve similar conversions for the studied substrates. The fact that recycled [bmim][PF_6] could be reused for iodination of either the same



Scheme 40. Iodination with I_2 in the presence of hydrogen peroxide in [bmim][BF_4] and [bmim][PF_6].

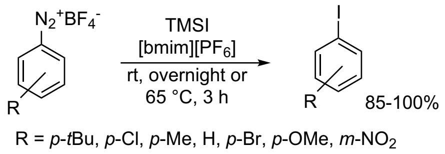
substrate or a structurally different substrate that required 0.5 molar equivalent of iodinating reagent, however, underscored the advantages of ILs as media for these reactions.

Salunkhe et al.[115] reported the use of sodium perborate (SPB, $NaBO_3 \cdot 4H_2O$) as an efficient mediator for iodination in IL media (Scheme 41). Iodination of anisole as a model substrate was studied in various ILs ([bmim][BF_4], [bmim][PF_6], [bmim][Cl], [hmim][BF_4]) and in organic solvents (DMSO, THF, $CHCl_3$) at room temperature. The ILs showed a significant improvement in conversions into the iodinated product, with the highest yield of *p*-iodoanisole achieved in [bmim][BF_4] (90% after 4 h reaction). Therefore, subsequent reactions with other substrates were carried out in [bmim][BF_4]. The authors showed that the reagent I_2/SPB can be used in a mild and efficient method for the iodination of arenes and heterocycles in [bmim][BF_4].



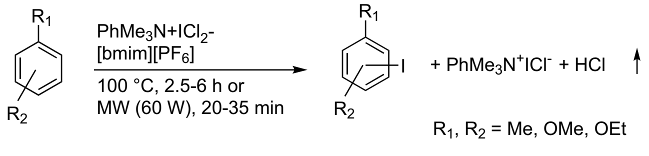
Scheme 41. Iodination of aromatics with $I_2/NaBO_3 \cdot 4H_2O$ (SPB) in [bmim][BF_4].

The preparation of iodo-substituted aromatics can be achieved via the dediazoniation reaction (Scheme 42).[27c] Variously substituted arenediazonium tetrafluoroborates ($ArN_2^+BF_4^-$) were reported to react with TMSI in [bmim][PF_6] at room temperature to give the corresponding iodo-substituted compounds (Ar–I) in high yields (85–90%). Depending upon the structure of the diazonium salt, hydrodediazoniation products (ArH) were detected in minor amounts (1–13%). Significant amounts of the 'Schiemann product' (ArF) and the hydrodediazoniation product (ArH) were formed in the case of mesityldiazonium tetrafluoroborate.



Scheme 42. Formation of iodoaromatics via dediazoniation.

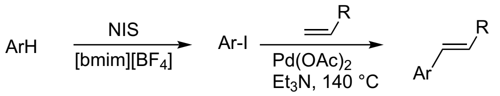
Phenyltrimethylammonium dichloroiodate (PTMAICl_2) was investigated as an iodinating reagent for aromatics in ILs under conventional heating and with MW irradiation (Scheme 43).[116] A temperature of 100 °C was required to achieve the highest conversion into *p*-iodoanisole in [bmim][PF_6]. This water-immiscible IL was also superior with regard to yield and reaction rate compared to hydrophilic [bmim][BF_4]. In the molten salts, Bu_4NCl and [bmim][Cl], iodination did not occur, while in MeCN and in toluene under reflux, longer reaction times and lower yields were obtained. By utilizing PTMA ICl_2 in [bmim][PF_6], iodine was efficiently incorporated into various methoxy-, ethoxy- and methyl-substituted aromatics, with the reactions carried out under conventional heating at 100 °C, requiring 3–5 h, while the respective iodo transformations could be achieved in 20–35 min with similar efficiency under MW irradiation.



Scheme 43. Iodination of activated arenes with PTMA ICl_2 in [bmim][PF_6].

When investigating the influence of ILs on the outcome of chemical reactions, Earle et al. found that anisole was efficiently converted into *p*-iodoanisole (minor amounts of the *ortho* isomer were also detected) with [Bu_4N][I] in 100% nitric acid (after 24 h at 100 °C).[57]

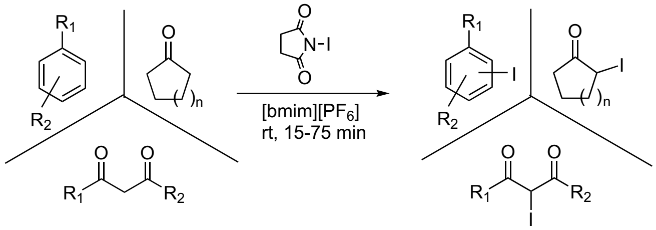
A convenient route to iodinated compounds is possible with the reagent iodosuccinimide (NIS). Yadav et al. reported its efficient utilization for aromatic ring iodination of various arenes activated towards electrophilic functionalization[64] and for α-iodination of cyclic ketones and β-dicarbonyl compounds (Table 19).[63] Reactions carried out at room temperature either in [bmim][PF_6] or in [bmim][BF_4] gave high yields of the corresponding mono-iodinated products within 15–75 min (faster than could be achieved in molecular solvents). The enhanced reactivity of NIS was suggested to be

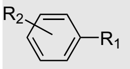
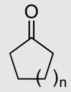
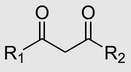


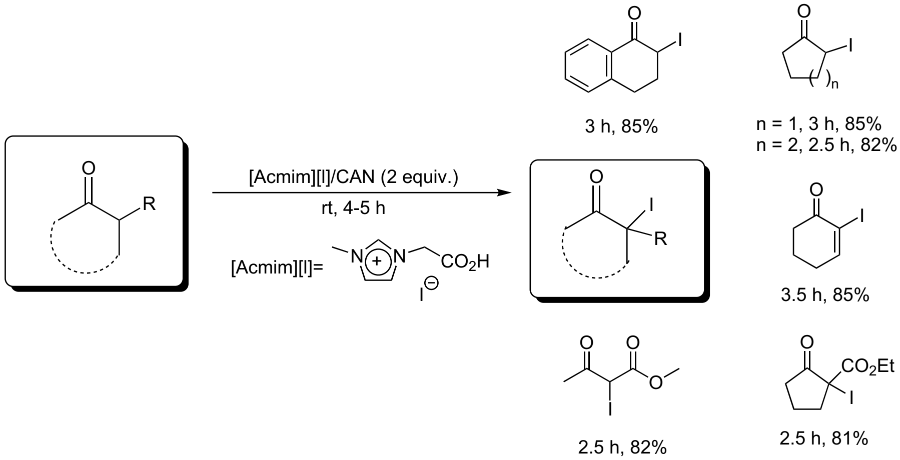
Scheme 44. One-pot iodination/Heck-coupling reactions in [bmim][BF_4].

Table 19

Iodination of aromatics and carbonyl compounds with NIS in [bmim][PF_6] at room temperature



								
R_1, R_2	*t* (min)	Yield (%)	Substrate	*t* (min)	Yield (%)	R_1, R_2	*t* (min)	Yield (%)
OMe, H	20	95	*n*=1	40	82	Ph, OEt	25	89
1,2-diOMe	25	91	*n*=2	40	87	Me, OEt	50	86
1-OH, 2-OMe	10	93	1-Indanone	40	86	Ph, Ph	20	87
1-OH, 2-CHO	40	90	1-Tetralone	30	86	^{i}Pr, OEt	60	90
1-OH, 4-*i*Pr	10	93				^{t}Bu, OCH_2Ph	75	97



Scheme 45. Iodination utilizing IL [Acmim][I] as solvent and reagent in combination with CAN.

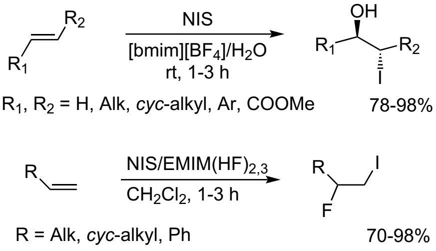
due to increased polarization of the N–I bond in polar ionic media, and stabilization of the charged ionic intermediates in the IL media.

The approach developed by Yadav et al.[63] was employed by Handy in a one-pot iodination/Heck-coupling protocol in [bmim][BF_4] as solvent (Scheme 44).[81] The iodination step with NIS was performed at room temperature for electron-rich substrates, namely anisole, dimethylaniline, thiophene and mesitylene. Less reactive substrates such as *m*-xylene required either heating at 80 °C for 6–12 h or an acid catalyst in conjunction with NIS in the IL to afford the corresponding Heck-coupling product. The reaction failed with naphthalene, even with activation.

The α-iodination of ketones and β-keto esters was reported in acetylmethylimidazolium iodide ([Acmim][I]) in the presence of CAN at room temperature (Scheme 45).[60] In the absence of either [Acmim][I] or CAN, the reaction did not occur. Furthermore, it was established that CAN functions as a one-electron oxidant and thus 2 molar equivalents of CAN were required in this process. Additional experiments with TEMPO pointed to the involvement of a radical pathway in this system.

5.2. Iodofunctionalizations through addition reactions to unsaturated systems

In the reaction of an alkene and NIS in the [bmim][BF_4]/H_2O system at room temperature, the iodohydroxylated product was selectively formed in high or quantitative yield, while in the case of [bmim][Cl]/H_2O or Bu_4NCl/H_2O as the reaction medium, a higher temperature (60 °C) and a longer reaction time were required to reach comparable efficiency (Scheme 46).[84] EMIMF$(HF)_{2,3}$ ionic liquid (Fig. 3), earlier shown to act as a fluoride-ion source (Section 2.1), was applied in combination with NIS for the iodofluorination of olefinic systems. Various aliphatic, cyclic and aryl alkenes were converted into the corresponding iodofluorinated products with high stereoselectivity with *anti* stereochemistry by using NIS/EMIMF$(HF)_{2,3}$ in CH_2Cl_2 at room temperature (Scheme 46).[30,32]

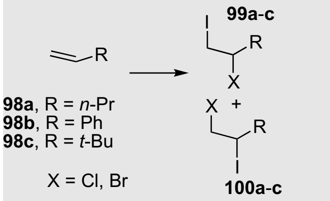
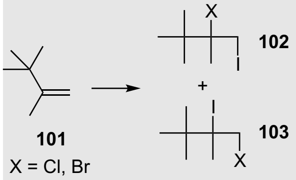
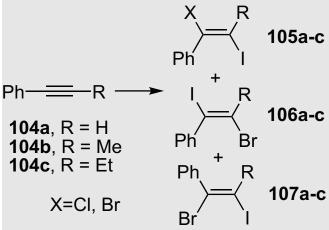


Scheme 46. Iodohydroxylation and iodofluorination of olefinic systems.

Chiappe et al. studied trihalide-based ILs, namely [hmim][ICl_2] and [bmim][IBr_2], as reagents/solvents for the stereoselective iodochlorination and iodobromination of alkenes (**98a**–**c**, **101**) and alkynes (**104a**–**c**) at 0 °C.[69] A brief comparative evaluation of these transformations (which have already been discussed in Sections 3.2 and 4.3) is provided in this section. The authors observed that the regioselectivity of the addition reactions was dependent upon the trihalide halogenating agent and on the structure of the alkene or alkyne (Table 20). While the reactions of ICl_2^- in the ILs always occurred in an *anti*-stereospecific manner, those of IBr_2^- also gave *syn* adducts. With ICl_2^-, arylalkynes (**104a**–**c**) provided the Markovnikoff (M, **105a**–**c**) adducts exclusively, while with IBr_2^- both M and AM (**106a**–**c**) adducts were formed, depending upon the alkyne structure. Experiments revealed that the addition reactions of ICl_2^- and IBr_2^- to alkenes and alkynes are affected differently by steric and electronic effects. In addition to [hmim][ICl_2] and [bmim][IBr_2] employed as reagents/solvents, *vic*-iodochloro and iodobromo compounds (**99a**–**c**, **100a**–**c**, **102**, **103**, **105a**–**c**, **106a**–**c**, **107a**–**c**) may be obtained by the addition of ICl or IBr in [bmim][PF_6] as the solvent to olefinic and alkynic substrates.[69] The adducts were generally formed by *anti* addition to double and triple bonds, irrespective of the halogenating reagent employed, with the exception being the addition of IBr to 1-phenyl-propyne (**104b**), which gave the *syn* adduct (**107b**). When utilizing ICl or IBr as the reagents, the regiospecificity of the process was dependent upon the structure of the substrate. With aryl-substituted alkenes (**98b**) and alkynes (**104a**–**c**) M-adducts (**99b**, **105a**–**c**, respectively) were formed exclusively, mixtures of M- and AM-adducts were obtained in the case of simple alkyl-substituted alkenes (**98a**), while introducing a bulkier group on the alkene (**98c**) resulted in the exclusive formation of AM-adducts (**100c**).

In continuation, Chiappe and Pieraccini carried out a kinetic study on the addition reactions of ICl_2^- ([Bu_4N][ICl_2] used as an iodochlorinating agent) to unsaturated compounds in 1,2-dichloroethane (DCE) and in the following ILs: [bmim][PF_6], [emim][Tf_2N], [bmim][Tf_2N], [hmim][Tf_2N] and [bPy][Tf_2N].[70] The rate enhancement observed for iodochlorination in the IL media relative to molecular solvents was explained by the hydrogen-bonding ability of the imidazolium cation. The activation parameters obtained from kinetic studies indicated that the reaction rate was more dependent upon the IL structure than its viscosity, although the activation energy values, $\Delta G^{\ddagger}_{298}$, were very similar in all of the ILs examined.

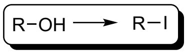
Table 20
Regio- and stereoselectivity of iodochlorination and iodobromination of unsaturated systems utilizing ILs at 0 °C

Reagent	[hmim][ICl$_2$]		[bmim][IBr$_2$]		ICl[a] or IBr[b] in [bmim][PF$_6$]	
Transformation	Conversion	Product distribution	Conversion	Product distribution	Conversion	Product distribution
	>95%	**99a**/**100a**=50:50	>95%	**99a**/**100a**=45:55	>95%	**99a**/**100a**=55:45[a] or 50:50[b]
	>95%	dichloro-derivative	>95%	100% **99b**	>95%	100% **99b**
	>95%	100% **100c**	>95%	80% **100c**[c]	>95%	100% **100c**
	>95%	100% **102**	>95%	100% **103**	>95%	80% **102**[a,d], complex mixture[b]
	>95%	>95% **105a**	>95%	**105a**/**106a**=90:10	65%[a], 45%[b]	100% **105a**[a,b]
	>95%	>95% **105b**	>95%	**105b**/**107b**=66:34	50%[a],40%[b]	100% **105b**[a], 100%**107b**[b]
	>95%	>95% **105c**	83%	>95% **105c**	45%[a]	100% **105c**

[a] Percentage corresponds to result obtained using ICl as reagent.
[b] Percentage corresponds to result obtained using IBr as reagent.
[c] Other product identified as corresponding dibromo adduct.
[d] Adduct **102** was formed besides a complex mixture of products.

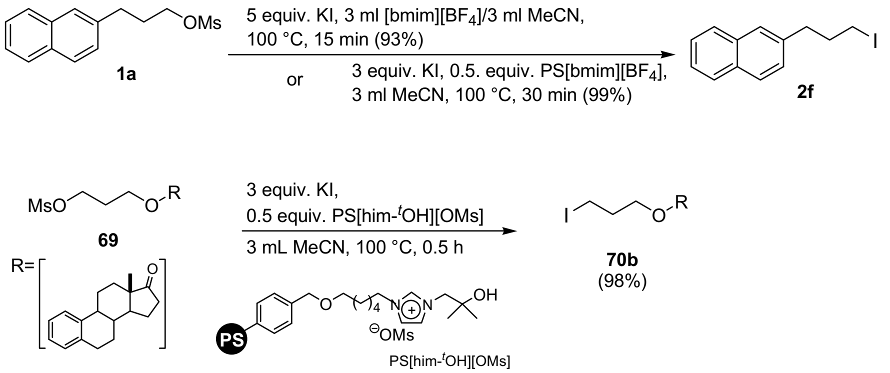
5.3. Formation of alkyl iodides by nucleophilic substitution reactions in ILs

The most common procedure for the formation of alkyl iodides in ILs employs either the corresponding alcohol (Scheme 47) or the mesylate as the substrate. The first publication utilizing an IL for this transformation appeared in 2001.[71] Thus, *n*-butyl, *n*-octyl, *sec*-butyl and *tert*-butyl alcohols were converted into the corresponding alkyl iodides by using the [bmim][I]/HA system (HA=H$_2$SO$_4$ or MeSO$_3$H). The [bmim][I] ionic liquid was used



Reaction conditions	Applicable substrates	Ref.
1 equiv. [bmim][I], 1 equiv. HA (HA = CF$_3$SO$_3$H, H$_2$SO$_4$), rt, 5-30 h	primary, secondary, tertiary alcohols (C$_4$-C$_8$)	71
1 equiv. [Pr^{n}mim][I], 1 equiv. PTSA MW (100 W), 30 s	primary alcohols (C$_7$, C$_8$)	72
[Hmim][I] 60 °C, 12-20 h	primary, secondary and cyclic alcohols, diols (C$_6$-C$_8$)	73
1 equiv. [omim][I], 1 equiv. PTSA 90 °C, 1 h or MW (75 W): 30 s MW, 10 s stirring (3-4 cycles)	fatty alcohols (C$_8$-C$_{18}$)	100
1 equiv. [omim][I], 1 equiv. PTSA 110 °C, 2 h or MW (75 W): 5 s MW, 20 s stirring (10-15 cycles)	1,ω-dialcohols (C$_6$-C$_{16}$)	101
1.2 eq. *t*BuI, [pmim][Br] (2 g) sonication, 0.5-2 h	primary and secondary alcohols, primary allylic diols; OTMS, OTBDMS, OAc, OTs, OTHP protected derivatives of cyclohexanol and benzyl alcohol	74

Scheme 47. Procedures utilizing ILs for conversion of alcohols or derivatives into the corresponding alkyl iodides.



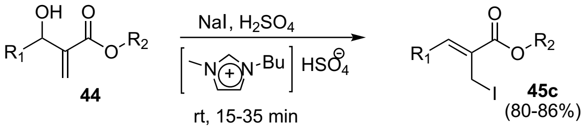
Scheme 48. Nucleophilic iodination of mesylate.

both as a reagent and as the solvent, while methanesulfonic acid seemed to be superior to H_2SO_4. The reactions were performed at room temperature and required rather a long time (up to 30 h). Using MW irradiation caused a significant decrease in the reaction time, but worked well only with primary alcohols, while secondary and tertiary alcohols readily decomposed.[72] By using microwaves, 1-heptanol and 1-decanol were converted into their corresponding alkyl iodides (77 and 73% yield, respectively) within 30 s in [^{n}Prmim][I] in the presence of PTSA. Another study reported on the immobilization of HI in an IL, thus forming the Brønsted acidic IL [Hmim][I] that acts as an iodinating agent/recyclable catalyst/solvent for the near-quantitative conversion of primary, secondary, cyclic alkyl alcohols, benzyl alcohols and alkyldiols into their corresponding alkyl iodides, while in the case of a tertiary alcohol, the major product was the corresponding alkene (60 °C, 12–20 h).[73] For the conversion of fatty alcohols with longer alkyl chains (C_8–C_{18}) into iodides, the more lipophilic IL [omim][I] was used in the presence of PTSA (1 h reaction with conventional heating at 100 °C, or within a few minutes under MW irradiation). In [bmim][I] and [Pr^{i}mim][I], fatty diols gave moderate yields of the iodides under MW irradiation.[100] The combination of [omim][I] and PTSA also worked well for the conversion of 1,ω-dialcohols (C_6–C_{16}) into their diiodides.[101] Diiodination was successful either by 2 h conventional heating at 110 °C (82–95% conversion) or by using MW irradiation for 50–75 s (97–98% conversion).

A combination of ^{t}BuI and [pmim][Br] under sonication was reported to be effective for the conversion of a variety of primary and secondary alcohols into their corresponding iodides, but tertiary alcohols did not react. Moreover, the procedure was successfully applied to hydroxy-protected derivatives of cyclohexanol and benzyl alcohol, including OTMS, OTBDMS, OAc, OTs and OTHP derivatives, which were directly converted into their corresponding iodides.[74]

In the context of their study on nucleophilic fluorination utilizing metal fluorides in [bmim][BF$_4$], Kim et al. found increased nucleophilicity in other metal halides.[15] Mesylate **1a** reacted at 100 °C with KI in a mixture of [bmim][BF$_4$]/MeCN (1:1) forming 2-(3-iodopropyl)naphthalene (**2f**, 93%) in 15 min. The polymer-supported IL, PS[bmim][BF$_4$], proved to be an efficient catalyst for the synthesis of **2f** (99%) from **1a** in a reaction carried out for 30 min at 100 °C with 3 equiv of KI, 0.5 equiv of PS[bmim][BF$_4$] and 3 ml of MeCN (Scheme 48).[17] When the IL moiety of the PSIL was functionalized with a *tert*-alcohol group, the resulting PS protic functionalized IL, PS[him–^{t}OH][OMs], showed superior catalytic activity for nucleophilic halogenation in comparison to other ionic resins, including PS[hNEt$_3$][OMs] and PS[hmim][OMs].[21] Mesylate **69** (Scheme 48) in a 0.5 h reaction, carried out at 100 °C, was 98% converted into the corresponding iodide with 3 equiv of KI and 0.5 equiv of PS[him–^{t}OH][OMs] in 3 ml of MeCN.

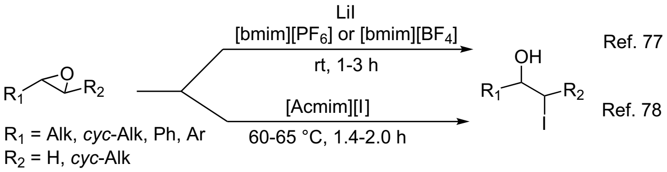
NaI in [bmim][HSO$_4$] and in the presence of H_2SO_4 (60%) was reported to be an efficient iodinating system for the stereoselective conversion of Baylis–Hillman adducts such as 3-hydroxy-2-methylenealkanoates (**44**) into their corresponding allyl iodides (**45c**) at room temperature (Scheme 49).[75]



Scheme 49. Synthesis of (2*Z*)-2-bromomethyl)alk-2-enoates.

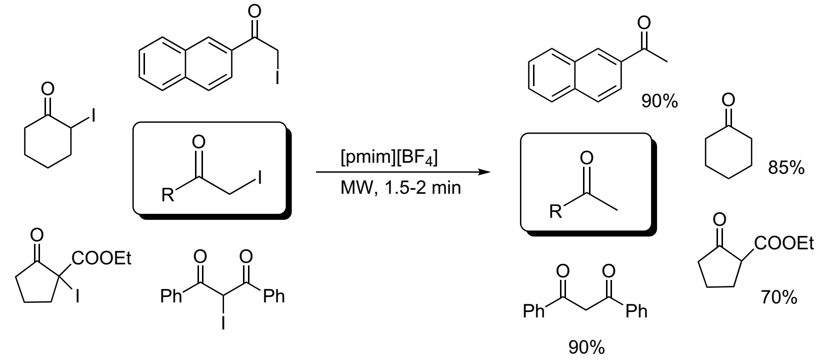
5.4. Other iodination approaches and deiodination reactions in ILs

Yadav et al. reported the synthesis of *vic*-iodohydrins from oxiranes employing LiI in [bmim][PF$_6$] or [bmim][BF$_4$] (Scheme 50).[77] They noted an increased reactivity of epoxides, undergoing smooth ring opening in imidazolium-based IL media. The corresponding *vic*-iodohydrins were obtained in high yields and with high stereoselectivity, without the need for an acidic catalyst. It was proposed that the acidic hydrogen of imidazole facilitates the process. Ring-opening transformation of epoxides to the corresponding *vic*-iodohydrins was also reported to take place in [Acmim][I], without the need for any additional reagent or catalyst (Scheme 50).[78] The [Acmim][I] ionic liquid acts as a reagent, catalyst and solvent for this transformation, which is applicable to a wide variety of cyclic oxiranes under mild conditions.

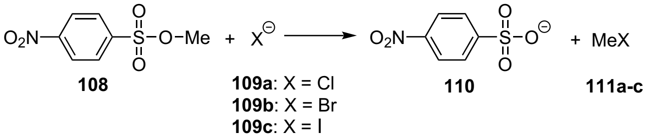


Scheme 50. IL-facilitated ring opening of epoxides to corresponding *vic*-iodohydrins.

Ranu et al. reported the rapid removal of iodine from α-iodocarbonyl compounds in [pmim][BF$_4$] under a short MW irradiation.[107] The carbonyl functionality remained intact and the corresponding ketone products were obtained in high yields (Scheme 51).



Scheme 51. Deiodination of α-iodocarbonyl compounds.



Scheme 52. Substititution of halides for *p*-nitrobenzenesulfonate anion in methyl *p*-nitrobenzenesulfonate.

6. Miscellaneous

6.1. Nucleophilicity of halides in ILs

An account of the nucleophilicity of halides was already mentioned in Sections 2.1, 3.3, 4.4 and 5.3, dealing separately with each halogen. The goal of the present section is to make a comparative evaluation of the nucleophilicity of halides.

The reports of Chi et al. on the enhanced nucleophilicity of halides, especially fluoride, in ionic liquids as compared to molecular solvents[14,15,20] were challenged by the kinetic studies of Lancaster,[117] who investigated halide substitution (**109a**–**c**) for the *p*-nitrobenzenesulfonate anion in methyl *p*-nitrobenzenesulfonate (**108**), a substrate chosen as a probe of anion nucleophilicity (Scheme 52). Based on an earlier kinetic investigation, Welton et al. had reported that the nucleophilicities of chloride, bromide and iodide ions are actually lower in the investigated ILs than in non-hydrogen-bond-donor molecular solvents. Furthermore, they remarked that not all ILs are the same, but rather that the nucleophilicity of halides is IL-specific, (as determined by a combination of cation and anion properties). The relative reactivity order determined in [bmim][BF$_4$] was chloride (1.06)/bromide (1)/iodide (1.41),[118] while a different trend was previously observed by Ford et al. in a tetraalkylammonium trialkylboride-based IL, namely triethylhexylammonium triethylhexylboride ($N_{2226}B_{2226}$). The relative reactivities of halide salts towards methyl tosylate in trimethylhexylammonium trimethylhexylboride IL ($N_{1116}B_{1116}$) were reported as 2.2:1.2:1.0 for Cl$^-$, Br$^-$ and I$^-$, respectively.[119] Welton et al. further evaluated the cation/anion effects of ILs on halide nucleophilicity (Table 21). In order to investigate the cation effect, the reaction of **108** with halides (**109a**–**c**), yielding **110** and **111a**–**c**, was studied in a series of [NTf$_2$]$^-$ ILs with [bmim]$^+$, [bm$_2$im]$^+$ and [bmpy]$^+$ as cations.[120] In [bmim][NTf$_2$] iodide was most nucleophilic, followed by bromide and chloride. The nucleophilicity order changed in [bm$_2$im][NTf$_2$], with chloride becoming most nucleophilic and iodide being slightly more nucleophilic than bromide. The effect of the cation upon reactivity was additionally confirmed by the data obtained in [bmpy][NTf$_2$], where the chloride ion was by far the most nucleophilic of the halides, while the iodide anion was less nucleophilic than the bromide anion. Nevertheless, the reaction rates for Br$^-$ and I$^-$ were very similar in each of the three ILs, but the variation was significant for Cl$^-$. Comparing the kinetic data for the chloride reaction in ILs with the data obtained in CH_2Cl_2 and $(CF_3)_2CHOH$ (HFIP), the rate was much faster in dichloromethane than in the ILs, but significantly lower in the highly ionizing, hydrogen-bond-donating and weakly nucleophilic HFIP (Table 21). Evaluation of the solvent properties, in the light of the kinetic data obtained, suggested that the reaction rate does not depend upon the viscosity of the IL alone, but is better explained by

Table 21
Effect of cation and anion of ILs on relative nucleophilicity of halides

Solvent	k_2 (M^{-1} s^{-1})[a]			Relative k_2 values	Kamlet–Taft parameters		
	Cl$^-$	Br$^-$	I$^-$	Cl$^-$/Br$^-$/I$^-$	α	β	π*
Effect of cationic part of IL							
[**bmim**][NTf$_2$]	0.0124	0.0195	0.0232	0.64:1:1.19	0.617	0.243	0.984
[**bm$_2$im**][NTf$_2$]	0.0296	0.0221	0.0238	1.34:1:1.08	0.381	0.239	1.010
[**bmpy**][NTf$_2$]	0.0391	0.02226	0.0188	1.73:1:0.83	0.427	0.252	0.954
CH_2Cl_2, ion pair[b]	0.51	0.42		1.21:1:—	0.042	−0.014	0.791
CH_2Cl_2, free ion[c]	1.04	0.46		2.26:1:—			
$(CF_3)_2CHOH$	0.00011	0.00045	0.00039	0.24:1:8.67			
Effect of anionic part of IL							
[bmim][**BF$_4$**]	0.0403	0.0381	0.0538	1.06:1:1.41	0.627	0.376	1.047
[bmim][**PF$_6$**]	0.0144	0.0086	0.0278	1.67:1:3.23	0.634	0.207	1.032
[bmim][**SbF$_6$**]	0.0115	0.0123	0.0180	0.93:1:1.46	0.639	0.146	1.039
[bmim][**OTf**]	0.0197	0.0314	0.0619	0.63:1:1.97	0.625	0.464	1.006
[bmim][**NTf$_2$**]	0.0124	0.0195	0.0232	0.64:1:1.19	0.617	0.243	0.984

[a] Second-order rate constants for reaction of halides with **108** in IL at 25 °C.
[b] Values obtained at 22 °C using bis(triphenylphosphoranylidene)ammonium chloride or bromide.
[c] Values obtained at 50 °C using tetramethylammonium halide.

the hydrogen-bond-donor ability of the cation. The greatest effect was observed with chloride, which is a good hydrogen-bond acceptor. With [bmim][NTf_2], which is the best hydrogen-bond donor in the group of ILs investigated, there is a strong interaction with chloride, consequently stabilizing it, the outcome being a slower reaction in this IL and an order of halide nucleophilicity corresponding to $Cl^- < Br^- < I^-$. In contrast, [bmpy][NTf_2] is the poorest hydrogen-bond donor, which interacts weakly with chloride, and thus chloride reacts more rapidly. In addition, the order of nucleophilicity in [bmpy][NTf_2] is changed to $I^- < Br^- < Cl^-$. The differences in rates among the ILs and the molecular solvents were rationalized by the Hughes–Ingold rules, with the prediction that an increased solvent polarity would lead to a decrease in the rate due to charge dispersal, leading to a less stabilized activated complex. The IL anion effect on halide nucleophilicity was studied in $[bmim]^+$ with the following anions: $[BF_4]^-$, $[PF_6]^-$, $[SbF_6]^-$, $[OTf]^-$ and $[NTf_2]^-$.[121] The kinetic data showed that the relative halide nucleophilicity does depend upon the anion. For example, in [bmim][OTf] and in [bmim][NTf_2], chloride was less nucleophilic than bromide, while, in [bmim][PF_6], chloride was more nucleophilic. Additionally, the nucleophilicity of each halide was found to be different in each IL, with chloride being almost fourfold as nucleophilic in [bmim][BF_4] as in [bmim][SbF_6]. Similarly, bromide was more than fourfold more nucleophilic in [bmim][BF_4] than in [bmim][PF_6]. The activation parameters $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, determined for the reaction of chloride in each of the investigated ILs, indicated a high activation barrier. This was rationalized by solvent–solute interactions within the IL. The comparative reaction rates were difficult to rationalize solely based on hydrogen-bonding-related effects, but correlations with other polarity effects, namely H-bond acidity (Kamlet–Taft parameter α), H-bond basicity (β) and polarity/polarizability ($\pi*$) were sought. A minor effect was noticed on changing the IL anion with the value of α, which was ascribed to a better H-bond acceptor ability of the probe solute than the IL anion. The predicted trend that the halide would be most nucleophilic in the least strongly coordinated ILs (those with the lowest α) was observed, although imperfectly. A high value of β is associated with good H-bond acceptor ability and, consequently, in these ILs the anion competes with the nucleophile for H bonding to the cation, and thus halides become relatively poorly coordinated and hence more nucleophilic. This assumption, although not perfect, proved to be true for the reactions of halides in those ILs with the highest β, namely [bmim][BF_4] and [bmim][OTf].

Welton et al. also studied the reactivity of other anionic nucleophiles in ILs.[122] An investigation of the nucleophilicity of polyatomic anions, namely acetate, trifluoroacetate, cyanide and thiocyanide, was made in comparison to halides in [bmpy][NTf_2], [bmpy][OTf], [bmim][NTf_2] and in the conventional organic solvents CH_2Cl_2, DMSO and MeOH. The authors observed that the relative nucleophilicity of each anion differs, depending upon the solvent used (Table 22). Applying the Kamlet–Taft linear solvation energy relationship approach (which explains the variation of any solute property in terms of three microscopic properties (α, β, $\pi*$)) to kinetic data from the anionic nucleophilic substitution of methyl *p*-nitrobenzenesulfonate (**108**) in both molecular solvents and ILs gave consistent results. The correlation was explained primarily in terms of the solvent donating a hydrogen bond to the nucleophilic anion, consequently reducing its nucleophilicity. More basic anions showed a higher degree of solvent dependency. Additionally, their hard/soft nature was also considered to have a significant role. The ILs possessing a $[bmim]^+$ cation were considered to act as hard solvents, reacting better with hard solutes like Cl^- than soft nucleophiles like CN^-.

Table 22
Relative anion nucleophilicity in various ILs and molecular solvents

Solvent	Relative order of nucleophilicity
[bmim][NTf_2]	$[CN]^- > I^- > Br^- > Cl^- > [Ac]^- > [SCN]^- > [TFA]^-$
[bmpy][NTf_2]	$[CN]^- > [Ac] > Cl^- > Br^- >{}^- I^- > [SCN]^- > [TFA]^-$
[bmpy][OTf]	$[CN]^- > Cl^- > [Ac]^- > Br^- > I^- > [TFA]^- > [SCN]^-$
CH_2Cl_2	$[CN]^- > Cl^- > Br^- > [Ac]^- > I^- > [SCN]^- > [TFA]^-$
DMSO	$[CN]^- > [Ac]^- > Cl^- > Br^- > I^- > [TFA]^- > [SCN]^-$
MeOH	$[CN]^- > I^- > [SCN]^- > Br^- > [Ac]^- > Cl^- > [TFA]^-$

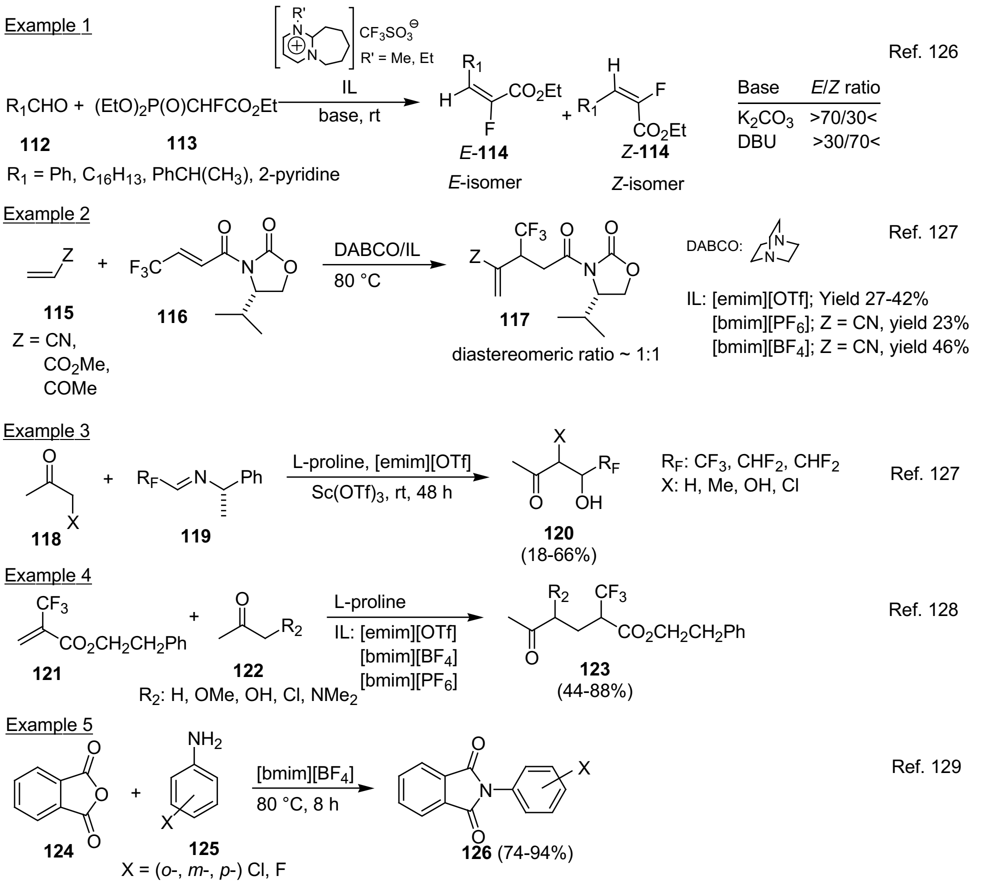
Landini and Maia studied the reactivity of various anions, including halides, in the nucleophilic substitution reactions of the methanesulfonate group in two non-nucleophilic ILs, namely [hmim][ClO_4] and [hmim][PF_6], and compared the results with the data obtained in molecular solvents of different polarity (chlorobenzene, DMSO and MeOH).[123] They found that the rate constants measured in the ILs were approximately similar order to those obtained for the same reaction in methanol and were lower in the ILs than in chlorobenzene or DMSO (polar aprotic solvents). The authors observed that the reactivity of different anions in the ILs spans a narrow range, but the presence of water can have a dramatic influence on the reaction rate. The nucleophilicity sequence of halides in [hmim][ClO_4] corresponded to $I^- > Cl^- > Br^-$, while in [hmim][PF_6] the nucleophilic reactivity of iodide, bromide and chloride was nearly the same.

That the nucleophilic character of halides and the nucleophilicity scale of common ions could change significantly in ionic liquids also became apparent from the work of Chiappe et al.,[124] who focused on heterolytic dediazoniation in [bmim][Tf_2N] with Br^- or Cl^- as nucleophiles. Despite the general belief that Tf_2N is an innocent nucleophile, it could compete effectively with halides for the phenyl cation. This study indicated that the nucleophilicity of Br^- is drastically reduced by interaction with the $[bmim]^+$ cation. Among the halides studied, only iodide was able to compete significantly with $[Tf_2N]^-$. This observation seems contradictory to the findings of Chi et al., namely that the increased nucleophilicity of bromide ion in imidazolium-based ILs enabled nucleophilic displacement of an alkyl group from the corresponding aryl alkyl ethers to form phenols.[125] Chi et al. reported that bromide ion either in the form of IL [bmim][Br] or by using stoichiometric amounts of HBr (47%) in other ILs, namely [bmim][BF_4], [bmim][PF_6], [bmim][NTf_2] or [bmim][OTf], afforded phenols from aryl alkyl ethers.[125]

6.2. Building-block approach to halogenated organic compounds in ILs

Although the primary aim of this review is to highlight the direct methods for halogen introduction into organic molecules in the IL media, a brief discussion of the building-block approach, dealing with C–C or C–N bond formation, starting from a relatively small readily available and easily handled halo-substituted molecule, seems warranted in the framework of this review. This approach is usually adopted by synthetic chemists as a way to avoid hazardous, toxic reagents or special equipment required when dealing with such reagents. As a synthetic/preparative procedure for halogenated compounds, its utility/value for the synthesis of fluorinated molecules is clearly paramount.

Kitazume et al. utilized this approach in ILs as a way to prepare fluorinated alkenes[126] and fluoromethylated materials.[127,128] They reported the synthesis of α-fluoro-α,β-unsaturated esters (**114**) via Horner–Wadsworth–Emmons reactions of triethyl 2-fluoro-2-phosphonoacetate (**113**) with aldehydes (**112**) in the presence of K_2CO_3 or 1,8-diazabicyclo-[5,4,0]-7-undecene (DBU) as base, at room temperature, utilizing 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecene trifluoromethanesulfonate and 8-methyl-1,8-diazabicyclo[5,4,0]-7-undecene trifluoromethanesulfonate as recyclable IL solvents (Scheme 53, example 1).[126] The same group reported the synthesis of fluoromethylated materials (**117**) via Michael additions with a Baylis–Hillman type reaction using olefins (**115**), activated towards α,β-



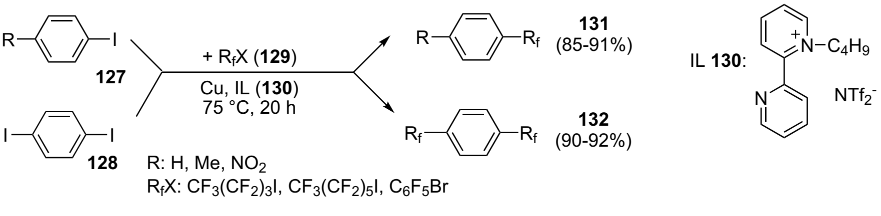
Scheme 53. Selected examples utilizing building-block approach for synthesis of halogenated organic molecules in IL media.

unsaturated ketone (**116**) as a chiral auxiliary in the DABCO–IL system, in [emim][OTf], [bmim][BF_4], and [bmim][PF_6] (Scheme 53, example 2).[127] Furthermore, they performed the reaction of fluoromethylated imines (**119**) with enamines generated from acetone derivatives (**118**) and L-proline in [emim][OTf] in the presence of the Lewis acid Sc$(OTf)_3$, providing the fluoromethylated carbinols (**120**) (Scheme 53, example 3). In further studies, trifluoromethylated materials (**123**) derived from 2-trifluoromethylacrylic acid phenethyl ester (**121**) were synthesized via an L-proline-catalyzed Michael addition reaction of **121** and ketone (**122**) in [emim][OTf], [bmim][BF_4] and [bmim][PF_6] (Scheme 53, example 4).[128] The dual role of [bmim][BF_4], as a solvent and promoter, was highlighted in the synthesis of halo-containing *N*-arylphthalimides (**126**) from various halo-aromatic amines (**125**) and phthalic anhydride **124** (Scheme 53, example 5).[129] The perfluoroalkyl group, providing **131** and **132**, could be introduced via copper-catalyzed cross-coupling reactions between perfluoroalkyl halides (**129**) and iodoaromatics (**127**, **128**) in a 2,2′-bipyridine-based IL (**130**), which in addition to acting as a solvent, also assisted the reaction by acting as a ligand for the fluoroalkylcopper intermediate (Scheme 54).[130]

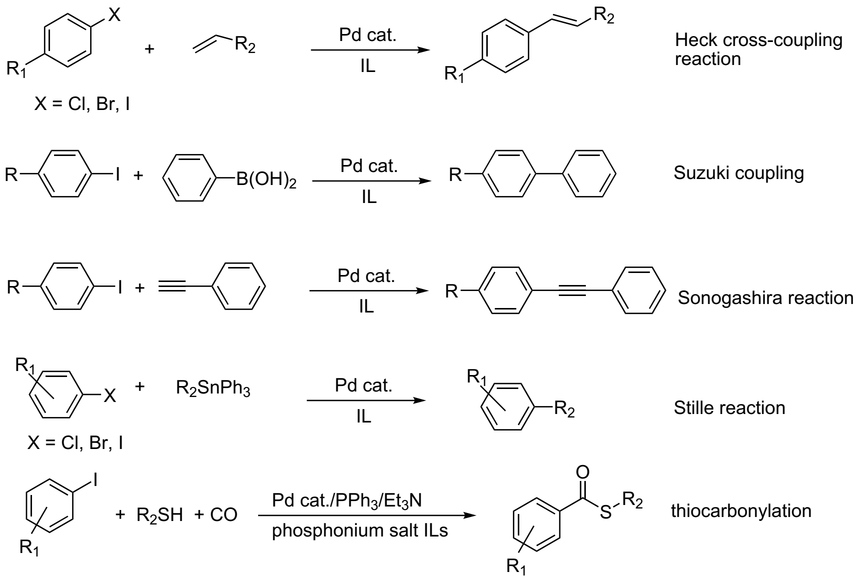
6.3. Transformations of halogenated organic compounds in ILs

Application of halogenated organics for further conversion into compounds with utility and importance in ionic liquids is a broad topic, the coverage of which is outside the scope of this review. The inclusion of some lead information and references is, however, deemed to be relevant.

The bromo- and iodo-substituted derivatives are of paramount importance in organic synthesis for coupling reactions in the formation of C–C and C–N bonds. A wealth of data reporting on the synthetic and mechanistic aspects of these transformations, in particular those of Heck, Suzuki, Stille, Sonogashira and related protocols, have been published over the years (Scheme 55). With the greatly increased interest in ILs in the last decade, in addition to desirable higher reaction rates and yields, their potential has been seen in enabling the immobilization, recovery and higher catalytic activity of metal catalysts required for the efficiency and stereoselectivity of these coupling reactions.[131] Consequently, utilizing halogenated compounds for the synthesis of substituted olefins and



Scheme 54. Insertion of perfluoroalkyl group into aromatic ring promoted by bipyridinium-based IL.



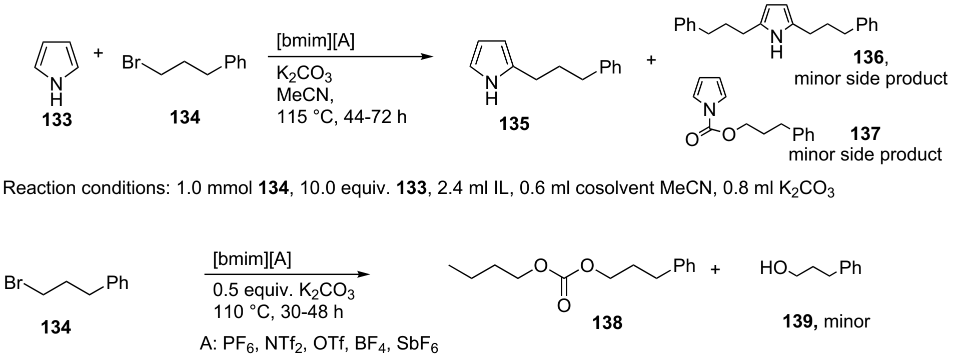
Scheme 55. General examples of transformations utilizing halogenated compounds for synthesis involving C–C bond formation.

biaryls via metal-catalyzed cross-coupling reactions has received significant attention in various ILs and has been addressed in several review articles.[3c,6a–c,7a–c,9b,11d,132] Recent papers report the use of the imidazolium-based phosphinite IL (IL–OPPh$_2$) as an effective reusable medium for C–C bond formation through Pd-catalyzed Heck coupling reactions of aryl iodides, bromides and also chlorides with styrene and *n*-butyl acrylate.[133] Such task-specific ILs function as ligand, base, and reaction medium in the Pd-catalyzed Heck C–C coupling reaction.[134] Immobilization of palladium nanoparticles in [bmim][PF$_6$] alone and without 'passivating' agents on the metallic surface leads to high catalytic activity in the Suzuki cross-coupling reaction.[135] A paper dealing with Pd-catalyzed thiocarbonylation of iodoarenes with thiols in phosphonium ILs has appeared.[136] Recently reported examples of C–N coupling include CuI-catalyzed amination reactions of aryl halides with nitrogen-containing reagents in [bmim][BF$_4$][137] and efficient heterogeneous catalysis of a novel supported task-specific IL consisting of the imidazolium cation on a modified polystyrene support with L-proline. The latter metal-soaked supported IL exhibited much higher catalytic activity in the CuI-catalyzed N-arylation of nitrogen-containing heterocycles and aryl or heteroaryl halides than free L-proline in combination with CuI in [bmim][BF$_4$], or in the corresponding homogeneous reaction conditions.[138]

Alkyl halogenides are useful alkylating reagents. Mono- and di-C-alkylation of the otherwise acid- and air-sensitive pyrrole (**133**) was achieved with various alkyl halides in [bmim][SbF$_6$], providing mono-alkylated (**135**) major product along with 2 minor side products (**135** and **137**) (Scheme 56).[139] Significantly enhanced alkylation of metal carbonates with alkyl halides (**134**) was reported in [bmim][PF$_6$], which was applied in the synthesis of symmetrical organic carbonates (**138**, Scheme 56).[140] Recently, the synthesis of enantiomerically pure masked β-amino alcohols in [bmim][BF$_4$] was reported via a fast coupling reaction between bromoketone and potassium phthalimide, followed by reduction and biocatalytic resolution, providing a facile route to this bioactive moiety.[141]

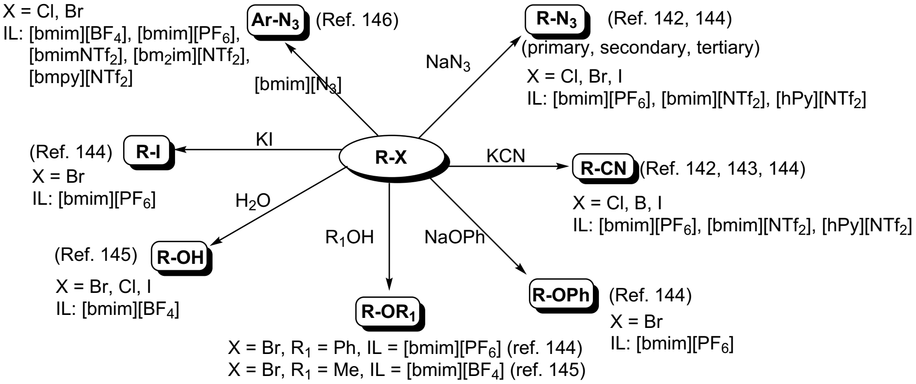
Nucleophilic displacement reactions of alkyl halides have been studied in IL media for the syntheses of azides, nitriles, ethers and hydroxylated products (Scheme 57). Chiappe et al. carried out an investigation of the nucleophilic displacement reactions of primary, secondary and tertiary halides with KCN and NaN$_3$ in [bmim][PF$_6$], [bmim][NTf$_2$] and [C$_6$Py][NTf$_2$].[142] For a given substrate, variable reactivity was observed towards a given nucleophile in the ILs by changing the cationic core or the anion of the IL under otherwise comparable reaction conditions, demonstrating that the course of reaction is not only dependent upon the nature of the leaving group and the nucleophile, but also on the properties of the reaction medium.

The IL [bmim][PF$_6$] was highlighted as a replacement for aqueous–organic phase-transfer-catalyzed biphasic systems in



Reaction conditions: 1.0 mmol **134**, 10.0 equiv. **133**, 2.4 ml IL, 0.6 ml cosolvent MeCN, 0.8 ml K$_2$CO$_3$

Scheme 56. Alkylations with alkyl bromides in IL media.



Scheme 57. Nucleophilic displacement reactions in ILs.

nucleophilic substitution reactions of alkyl halogenides with inorganic cyanide, azide, phenoxide and iodide, thus avoiding the need for a volatile organic solvent and a phase-transfer catalyst.[143,144]

Kim et al. reported enhanced nucleophilicity of water and alcohols as nucleophilic oxygen sources for nucleophilic hydroxylation and alkoxylation of alkyl halides in [bmim][BF$_4$], also forming less alkenes as elimination byproducts and thus resulting in higher yields of the substituted products than in conventional organic solvents.[145]

In a recent study, D'Anna et al.[146] studied the nucleophilic aromatic substitution (S$_N$Ar) of activated aryl and heteroaryl halides by using [bmim][N$_3$] as the solvent and nucleophile, in order to synthesis aryl azides. The reaction was also carried out in the presence of other ILs, namely [bmim][BF$_4$], [bmim][PF$_6$], [bmim][NTf$_2$], [bm$_2$im][NTf$_2$] and [bmpy][NTf$_2$]. The reactions in ILs proceeded faster and in a cleaner way than in MeOH with NaN$_3$ as the nucleophile.

7. Concluding remarks

The use of ionic liquids as solvents and/or catalysts can bring about important changes in the outcomes of many transformations, including halogenations as discussed in this review. In numerous instances, ILs have been shown to accelerate/promote reactions and offer advatanges over molecular solvents. It is clear that the structure of the ionic liquid (nature of the cation and anion) has a profound effect on the reactivity, solubility and other reaction variables. With a judicious combination of cation and anion, it is possible to tune the solvent properties in order to tailor the most suitable IL for a given application. Although an in-depth understanding of the relationship between chemical reactivity and physical/chemical characteristics of the ILs has not yet been fully realized, notable progress has been made in recent years to better understand their physico-chemical properties and to delineate how chemical reactivity is influenced in different ILs. Other issues that deserve more studies are toxicity, development of improved methods for product isolation, more efficient purification methods, recycling and cost-related issues. There is no doubt that ILs offer great potential as designer solvents and catalysts, and intense worldwide research on these fascinating systems is bound to continue.

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Stojan Stavber was born in Maribor, Slovenia, in 1951. He studied chemistry at the University of Ljubljana and in 1987 obtained his Ph.D. in the group of Prof. M. Zupan. From 1975 he has been a member of the 'Jožef Stefan' Institute, Slovenia, and from 1995 Head of the Laboratory of Organic and Bioorganic Chemistry. Together with M. Zupan in 2000 he was awarded the Zois Award for outstanding scientific achievements. His main scientific interests are connected with organohalogen chemistry and a green chemical approach to organic synthesis. Stojan Stavber has authored and coauthored over 110 peer-reviewed scientific publications.