

Advances in Contemporary Research

Potential of ionic liquids in greener methodologies involving biocatalysis and other synthetically important transformations

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This review outlines the initial history followed by the subsequent developments witnessed by the domain of the enzyme catalyzed transformations in neutral ionic liquids. Apart from that some important synthetic transformations in the first generation Lewis acidic ionic liquids are also highlighted with emphasis on the rewarding results offered by these highly solvating and generally aprotic, polar media.

Keywords: Ionic liquids, biocatalyst, Lewis acids, green chemistry

IPC Code: Int.Cl.⁸ C07C, C07D

‘Ionic liquids’, which were once very remote in the chemical literature, are now quite well-known to the chemists. This is because their existence and consequently their potential as a solvent was not recognized before. But, the ionic liquids are not very new as it appears, some of them have been known for many years now. For example, $[\text{EtNH}_3][\text{NO}_3]$, which has a melting point of 12°C, was first described in 1914 (Ref. 1). Nevertheless, one of the important developments recorded in the chemical literature about these ionic liquids and their existence was in 1940. The two US scientists, Tom Weir and Frank Hurley working on liquid electrolytes accidentally prepared chloroaluminate ionic liquid which belongs to a class of ionic liquids now referred to as the first generation ionic liquids. However, the chemists of those times hardly noticed the potential of these astoundingly important liquids. In the late 1980s, scientists working in the US Air Force Academy were instrumental in initiating the preliminary research in the realm of ionic liquids. The eminent scientists such as King and Wilkes and associates can be regarded as the beginners of the influential work on ionic liquids which involved the synthesis of structurally diverse ionic liquids, their characterization, investigation of physical properties and so on². The ground-breaking development from the point of view of an organic chemist was the investigation of Friedel-Crafts reaction in the chloroaluminate ionic liquid³. After this report, a resurgence of the rich chemistry of ionic

liquids began. The pioneering work of Seddon and his associates introduced the ionic liquids to the modern day chemists⁴. Until 2001, the chloroaluminate ionic liquids were by far the most widely explored class of ionic liquids. Later, the spotlight shifted to a class of neutral, air and moisture stable ionic liquids very frequently referred to as second generation ionic liquids. Since then the cascade of reports on investigation of different reactions in ionic liquids began to appear in the chemical literature⁵.

Ionic liquids as novel reaction media for the biocatalytic processes

Almost 20 years back, when the potential of the neutral ionic liquids as the reaction media was not even conceptualized, Adams *et al.* (in 1984) demonstrated the stability of alkaline phosphatase in aqueous solution of quaternary salt. This group found that the enzymes were relatively stable in a mixture of tetraethylammonium nitrate and water in ratio 4:1 (v/v)⁶. With an increasing consciousness regarding the ionic liquids, the scientists interested in enzyme mediated reactions obviously became curious about the behavior of enzymes in these neoteric solvents. This resulted in a rapid development of biocatalytic research in these ionic liquids. The area is now very well exploited, as there is a sizable number of chemists interested in exploiting the advantages of these greener unconventional reaction media for the enzyme mediated reactions which are believed to be the green alternatives to the conventional chemistry.

Lye *et al.* came out with the first report on multiphase bioprocess operation employing the present day's second generation room temperature ionic liquids as replacements for the conventional organic solvents⁷. The ionic liquid, [bmim][PF₆]/water was employed as a liquid-liquid biphase for the *Rhodococcus* R312 catalyzed biotransformations of 1,3-dicyanobenzene. The authors reported greater specific activity of the biocatalyst in [bmim][PF₆]/water system almost by an order of magnitude than in toluene/water system. Shortly thereafter, some results were published by Erbeldinger *et al.* and this was the first report demonstrating the use of isolated, cell free enzyme in the ionic liquid. As a model reaction, Z-aspartame was synthesized by a thermolysin catalyzed reaction of carbobenzoxy-L-aspartate and L-phenyl alanine methylester hydrochloride in [bmim][PF₆] which contained 5% (v/v) H₂O⁸. Besides, the authors also demonstrated that the enzyme, which otherwise required immobilization, exhibited outstanding stability in this novel medium.

Sheldon *et al.* demonstrated that *Candida antarctica* lipase is able to catalyze a range of transformations such as transesterifications, aminolysis and perhydrolysis in ionic liquids, [bmim][PF₆] and [bmim][BF₄] in absence of water⁹. The reactions were catalyzed by free (NOVO SP525) or immobilized enzyme (Novozyme 435). The reaction rates were as good as or better than those observed in the conventional organic media. As an example, the reaction of octanoic acid with ammonia in [bmim][BF₄] at 40°C gave complete conversion to octanamide in 4 days compared to 17 days for the same conversion using ammonium carbamate in methyl isobutyl ketone. The epoxidation of cyclohexene by peroxy octanoic acid, generated *in situ* by Novozyme 435 catalyzed reaction of octanoic acid with 60% aq. H₂O₂ proceeded smoothly in [bmim][BF₄]. Kragl and coworkers investigated the kinetic resolution of 1-phenylethanol with a number of lipases in ten different ionic liquids¹⁰. A variety of ionic liquids comprising cations such as [bmim]⁺, [mmim]⁺, [4mbpy]⁺ and anions such as [PF₆]⁻, [BF₄]⁻, [TfO]⁻, [MsO]⁻, [BzO]⁻ and [Tf₂N]⁻ were prepared and employed as the reaction media for transesterification of (±)-1-phenylethanol. Interestingly, with the lipases from *Pseudomonas* sp. and *Alcaligenes* sp., the enantioselectivity for the formation of acetate was

improved to a great extent as compared to the reaction in methyl *tert*-butyl ether (MTBE).

Itoh *et al.* demonstrated lipase-catalyzed enantioselective acylation of allylic alcohols in ionic liquids using vinyl acetate as an irreversible acyl donor¹¹. They observed that the rate of acylation was strongly dependent on the anionic part of the ionic liquid. While the *Candida antarctica* catalyzed acylations proceeded with high enantioselectivity in all the solvents tested, the reaction rates in [bmim][BF₄] were nearly equal to that observed in diisopropyl ether. Kim and coworkers observed distinctly enhanced enantioselectivities in the lipase *Pseudomonas cepacia* and *Candida antarctica* catalyzed transesterifications of various secondary alcohols in ionic liquids [emim][BF₄] and [bmim][PF₆]¹². Upon comparison of the enantioselectivities in ionic liquids and organic solvents such as toluene and THF, it was found that lipases were up to 25 times more enantioselective in ionic liquids in relative terms. In the best experiment, the enantiomeric ratio greater than 1000 was observed in *Pseudomonas cepacia* catalyzed reactions in [bmim][PF₆]. The lipase activity in ionic liquids was found to be as good as or sometimes slightly lower than in organic solvents.

Kim *et al.* extended their investigation concerning the enantioselectivities of the lipase catalyzed reactions in ionic liquids. In a different strategy, a new type of immobilization protocol was devised wherein the ionic compound, 1-(3'-phenylpropyl)-3-methylimidazolium hexafluorophosphate, which is liquid above 53°C was mixed with the enzyme in its liquid state and then solidified. The preparation so obtained was identified as Ionic Liquid-Coated Enzyme (ILCE) and was used in organic solvents for the enantioselective acylation of alcohols. This preparation of *Pseudomonas* lipase exhibited strikingly enhanced enantioselectivities in almost all the cases when compared with the native form of the enzyme¹³.

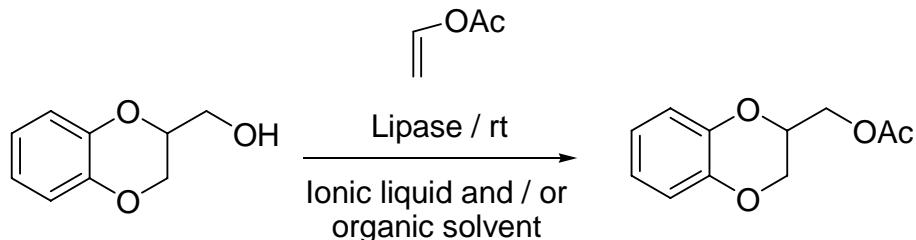
The ionic liquid, 1-ethylpyridinium trifluoroacetate, [epy][CF₃COO] was employed by Malhotra and coworker for the protease catalyzed kinetic resolution of *N*-acetyl amino acid esters¹⁴. The products with *ee* between 86-97% were realized in an optimized protocol. Kazlauskas *et al.* reported an improved method for the preparation of ionic liquids and the ionic liquids prepared by this method were found to be more suitable for the lipase catalyzed

biotransformations¹⁵. The lipase-catalyzed reactions that previously did not occur in untreated ionic liquids, now occur at the rates comparable to those observed in the non-polar organic solvents such as toluene. The acetylation of 1-phenylethanol catalyzed by lipase from *Pseudomonas cepacia* was as fast and as enantioselective in ionic liquids as was in toluene. The acetylation of glucose mediated by CAL was attempted in ionic liquids since it was found to be almost 100 times more soluble in ionic liquids than in the organic solvents.

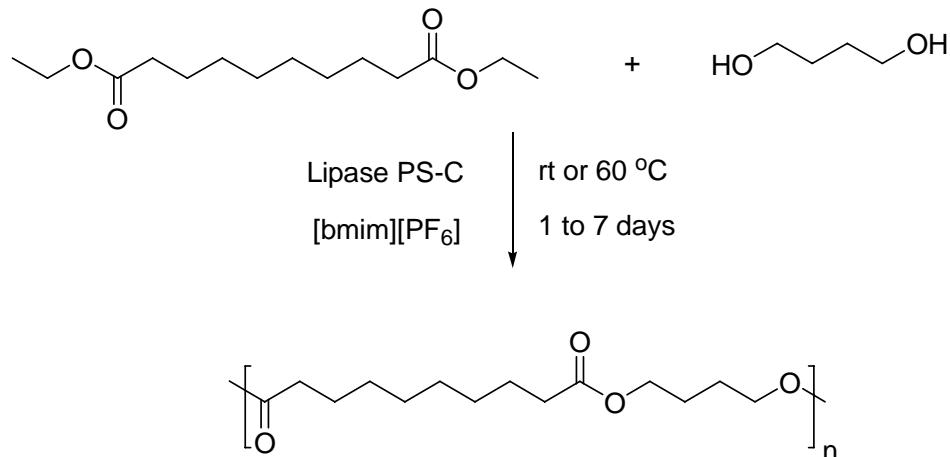
The lipase-catalyzed transesterifications of 2-hydroxymethyl-1,4-benzodioxane in two different ionic liquids, 1-butyl-3-methylimidazolium hexafluorophosphate, [bmim][PF₆] and 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim][BF₄] and organic solvents were investigated by this group in order to decipher the influence of these neoteric solvents on lipase activity (**Scheme I**)¹⁶. The hydrophobic and hydrophilic properties of ionic liquids influenced the lipase activity as gauged in terms of the rate of transesterifications. The influence of the ionic liquid as an additive in an organic solvent

on this reaction has been investigated. The supported lipase and [bmim][PF₆] ionic liquid was found to be the best combination for the said reaction. The enzyme/ionic liquid in combination were recycled for several runs without diminution in the lipase activity.

The supported lipase *Pseudomonas cepacia*, catalyzed aliphatic polyester synthesis in 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquid as a novel reaction medium was also investigated by the present research group¹⁷. Lipase PS-C demonstrated remarkable compatibility with the reaction medium by exhibiting excellent catalysis in the polycondensation of diethyl octane-1,8-dicarboxylate with 1,4-butanediol at room temperature (**Scheme II**). The lipase exhibited high initial rate of transesterification as indicated from the rapid initial consumption of the monomer, diethyl octane-1,8-dicarboxylate. The average molecular weight of the polymer formed was limited to around 2270 at room temperature and a relatively high molecular weight polymer was obtained in relatively shorter reaction times at 60°C. Based on the results it was apparent that to a certain extent it is possible to



Scheme I



Scheme II

exercise control over the molecular weight of the polymer obtained, by employing the ionic liquid possessing the properties streamlined for the purpose.

Russell *et al.* carried out the solvatochromic analysis of ionic liquids and the partition coefficient data obtained suggests that some ionic liquids are highly polar and hydrophilic in nature in comparison to the organic solvents such as hexane, acetonitrile and THF¹⁸. In the transesterifications studied, the activity of the free lipase was found to be greater in [bmim][PF₆] than in hexane. The conventional methods of enzyme stabilization proved to be unproductive in the hydrophilic ionic liquids. Reversible inactivation of lipase was observed in [AcO]⁻ and [MsO]⁻ based ionic liquids, whereas [NO₃]⁻ based ionic liquids were found to inactivate lipase irreversibly. Bartsch *et al.* investigated the ionic liquid-ScCO₂ combination for the execution of lipase catalyzed transesterification of vinyl butyrate and 1-butanol to butyl butyrate¹⁹. Here, the prospective advantage of ScCO₂ of differential solubilities at different pressures in ionic liquid was exploited for execution and subsequently product separation. The ionic liquids [emim][NTf₂] and [bmim][NTf₂] were employed and the enzyme used was immobilized CAL B lipase on glass wool. At lowest pressures of ScCO₂, least enzyme deactivation of about 15% was observed and greater than 99.9% *ee* was observed in the enantioselective acylation of 1-phenylethanol with vinyl propionate as acyl donor. In different approaches attempted (which included packed bed reactor and continuous flow reactor) good yields of the products were realized indicating the compatibility of the enzyme to the biphasic ionic liquid-ScCO₂ system which offered some practical advantages such as easy product separation, recyclability and potential large scale commercial applications. Iborra *et al.* demonstrated that the *Candida antarctica* lipase B dissolved in the ionic liquids [emim][NTf₂] and [bmim][NTf₂], combined with ScCO₂ displayed good catalytic activity, enantioselectivity and operational stability for both butyl butyrate synthesis and kinetic resolution of 1-phenylethanol by transesterification under anhydrous conditions²⁰. The authors suggested that the ionic liquids provide the enzyme with an adequate microenvironment allowing high activity and continuous reuse as observed in the continuous packed bed reactors. The authors also established that

the activity decay was enhanced by an increase in the temperature.

Iborra *et al.* executed CAL mediated butyl butyrate synthesis in [NTf₂]⁻ based ionic liquids with 2% by volume of H₂O at 50°C²¹. Enhanced activity was observed compared to the organic solvents. The authors observed a well defined over-stabilization of enzyme in the continuous operations, which they believe is because of the ionic environment provided by the reaction media. Reetz *et al.* reported CAL catalyzed transesterification of 1-octanol and kinetic resolution of phenylethanol in ionic liquids using ScCO₂ as a mobile phase in batch wise or continuous flow operations²².

Gubicza *et al.* effectively applied ionic liquids as solvents for enantioselective esterification of 2-choloropropanoic acid with 1-butanol using *Candida rugosa* lipase²³. The role of H₂O produced during the reaction and the control of H₂O activity with per-vapouration was studied. Under the optimal conditions of H₂O activity the lipase exhibited high thermal stability in ionic liquid and it could be reused for at least 5 cycles with only a small loss in the activity. The enzymes displayed much reduced activity in hexane than in ionic liquid in the repeated runs. Howarth *et al.* reported bioreductions of a series of ketones with immobilized Baker's yeast in [bmim][PF₆]/water taken in 10/1 ratio²⁴. In terms of enantioselectivities offered by protocol, the method is similar to those known in literature.

The racemic secondary alcohols were resolved using lipase *Pseudomonas cepacia* (supported on celite, PS-C) catalyzed enantioselective acylation. Succinic anhydride was used as acyl donor in ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF₆] (**Scheme III**)²⁵. Further, triethylamine was found to be an efficient additive in ionic liquid to enhance the rate of the said enantioselective acylation reaction.

Lipase mediated regioselective hydrolysis and alcoholysis of 3,4,6-tri-*O*-acetyl-D-glucal, have been studied in organic solvent, tetrahydrofuran and two different ionic liquids, [bmim][PF₆] and [bmim][BF₄] (**Scheme IV**)²⁶. The ionic liquids as the reaction media substantially influenced the rates and regioselectivity of enzyme catalysis. A marked regioselectivity towards the formation of 4,6-di-*O*-acetyl-D-glucal, was observed in [bmim][PF₆] with 84% product formation after 6 h with 98% selectivity in hydrolysis and 48% after 8 h with 98% selectivity

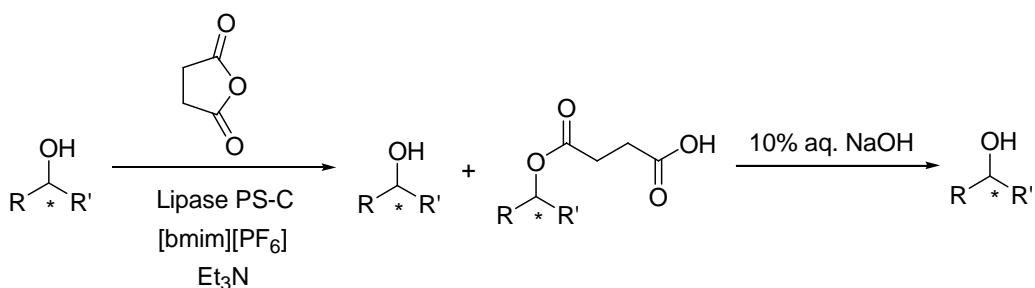
in alcoholysis. Contrary to this, the hydrophilic ionic liquid $[\text{bmim}]\text{[BF}_4\text{]}$ did not prove to be a good medium for any of these transformations.

The *Candida rugosa* lipase-catalyzed enantioselective hydrolysis of butyl-2-(4-chlorophenoxy)propionate has been carried out in aqueous buffer with ionic liquid as co-solvent (**Scheme V**)²⁷. The markedly enhanced enantioselectivity towards the *R*-enantiomer of the substrate was observed under the optimal additive conditions (1:1 composition of ionic liquid and buffer). The hydrophobic ionic liquids offered almost quantitative conversions with $ee \geq 99\%$.

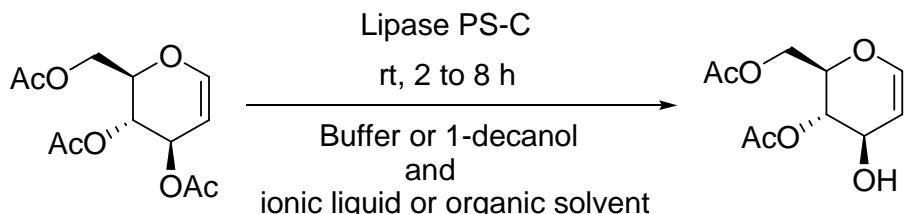
In one of the recent endeavors, the present group has conceptualized the idea of using the ionic liquid as a vehicle for the substrate of interest for the lipase catalyzed kinetic resolution. The idea is to use the ionic liquid as a support in the enzyme mediated reactions. The ionic liquid anchored-ibuprofen (**Scheme VI**) was synthesized by using the $-\text{OH}$

group appended ionic liquid and (\pm) -ibuprofen and this racemic ester underwent *Candida antarctica* lipase catalyzed hydrolysis yielding the *S*-enantiomer²⁸. The strategy facilitated easy post-resolution isolation of the enantiomers and also carries the prospect of recyclability. The idea is conceptually quite parallel to biodegradable ionic liquids²⁹, but is quite different in terms of the applied value of the principle.

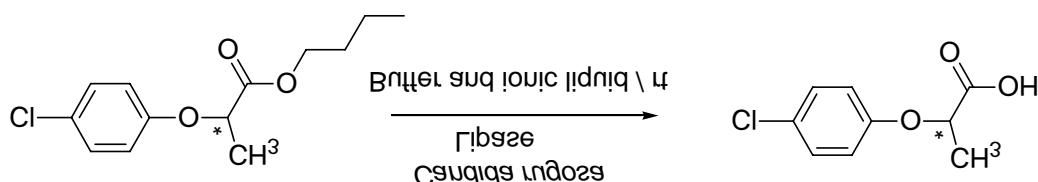
The arena of the organic biocatalytic transformations in ionic liquids has been very well reviewed earlier by the eminent chemists active in this field encompassing very fine pieces of work³⁰⁻³⁶. Apart from the examples mentioned above, the other examples of enzymatic reactions in ionic liquids include the dynamic kinetic resolution of secondary alcohols by enzyme-metal combinations³⁷, enantioselective acylation of amines³⁸, continuous flow enzymatic kinetic resolution and enantiomer separation using ionic liquid-supercritical carbon



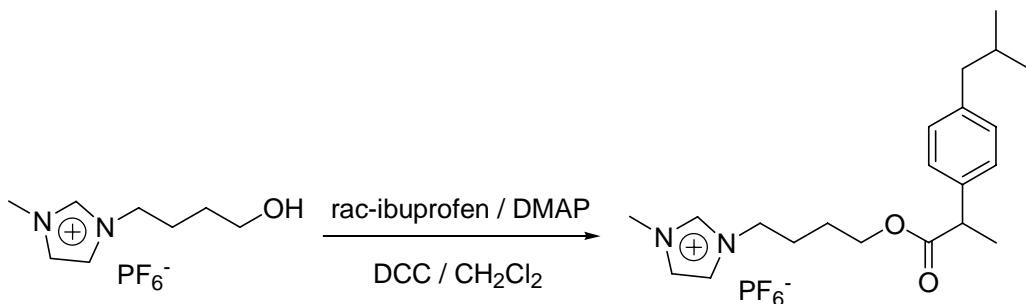
Scheme III



Scheme IV



Scheme V



Scheme VI

dioxide media³⁹, enantioselective transport of (*S*)-ibuprofen through a supported liquid membrane based on ionic liquids⁴⁰, selective acylation of glycosides⁴¹, 1-butyl-2,3-dimethylimidazolium tetrafluoroborate facilitated transesterification using vinyl acetate as acyl donor⁴², esterification integrated with pervaporation for removal of water⁴³, resolution of homophenylalanine ester⁴⁴, ester synthesis^{45,46}, use of oxidative enzyme⁴⁷, β -galactosidase catalyzed synthesis of *N*-acetyllactosamine⁴⁸, resolution of racemic *P*-chiral hydroxymethanephosphinates and hydroxymethylphosphine oxides⁴⁹, stereoconvergent hydrolysis of *trans*- β -methylstyrene oxide⁵⁰, whole cell biocatalysis^{51,52}, preparation of flavonoid derivatives⁵³, whole cells biocatalytic asymmetric reductions⁵⁴, chemoenzymatic epoxidation of olefin⁵⁵, hydrogenation of C=C⁵⁶, deracemization of (\pm)-mandelic acid⁵⁷, glucose-fatty acid ester synthesis⁵⁸, chloroperoxidase catalyzed oxidations⁵⁹, oxidase-peroxidase catalyzed sulfoxidation⁶⁰, etc.

Lewis acidic ionic liquids as solvents and catalysts

The chloroaluminate ionic liquids or the first generation ionic liquids are prepared by mixing the quaternary ammonium salts such as 1-butyl-3-methylimidazolium chloride with AlCl₃ (Ref. 61). The apparent mole fraction of AlCl₃, *N* in these liquids dictates the behavior of the liquid as a Lewis acid catalyst. The mole fraction of AlCl₃, *N* between 0.33 to < 0.5 furnishes basic, 0.50 gives neutral and > 0.50 to 0.67 or higher yields the Lewis acidic ionic liquid. It is the later variety of chloroaluminates that is useful for driving the Lewis acid catalyzed reactions. The liquidus range (the range of temperatures in which the compound exists in liquid state) depends on the structure of the cation and the mole fraction of AlCl₃. The interesting property of these liquids is that they provide a distinctly homogenous Lewis acidic

medium in contrast to the conventional Lewis acid, AlCl₃ that is used for the reactions. After the execution of the Friedel-Crafts reactions by Wilkes *et al.*, several electrophilic substitution reactions such as acylation of ferrocene, chlorination, nitration, etc. were investigated¹.

Among the other reactions investigated, the Fries rearrangement, a typically Lewis acid catalyzed reaction was also executed in these ionic liquids. In order to realize the advantages of the chloroaluminate ionic liquids in the Fries rearrangement reaction, 1-butyl-3-methylimidazolium chloroaluminate, [bmim]Cl_xAlCl₃ (*x* = 1–2) was used as a solvent and Lewis acid catalyst for Fries rearrangement reaction of phenyl benzoates (**Scheme VII**)⁶². The [bmim]Cl₂AlCl₃ ionic liquid fetched good yields of the products at 120°C within 2 h. The interesting feature observed was that the variation in the Lewis acidity of the ionic liquid and temperature influenced the overall yields as well as the *ortho* to *para* ratio (*o/p*) of the product formed in the reaction. The extent of conversion of phenyl benzoate was found to be the function of the Lewis acidity of the ionic liquid. An increase in the Lewis acidity of the ionic liquid favored the *para* product. The kinetic investigations revealed that the rate of consumption of phenyl benzoate obeyed the first-order kinetics. Higher regioselectivities were observed in [bmim]Cl₂AlCl₃ at different temperatures.

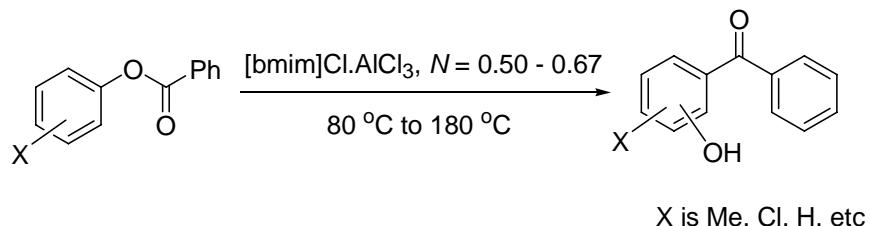
The Friedel-Crafts sulfonylation reaction of benzene and substituted benzenes with 4-methyl benzenesulfonyl chloride in [bmim]Cl_xAlCl₃ was reported (**Scheme VIII**)⁶³ by the present group. The substrates exhibited enhanced reactivity, furnishing almost quantitative yields of diaryl sulfones, under ambient conditions. Studies concerning the effect of Lewis acidity of the ionic liquid on the initial extent of conversion of this reaction, revealed a progressive

increase in the initial rates of the reactions, due to consequent increase in the concentration of the catalytic species in the ionic liquid. The interesting insights into the mechanistic details of the reaction in these liquids were investigated with the aid of ^{27}Al NMR spectroscopy. The studies reveal that the reaction takes place between the Lewis acidic species, $[\text{Al}_2\text{Cl}_7]^-$ and HCl formed during the course of electrophilic substitution. Due to this, the catalytic species is converted to $[\text{AlCl}_4]^-$ and is no more available for catalysis. Some preliminary attempts to prevent this reaction in order to make these ionic liquids recyclable did not succeed. However, it is believed that if a suitable way is devised to prevent this reaction, the chloroaluminate ionic liquids could very well revolutionize the Friedel-Crafts chemistry.

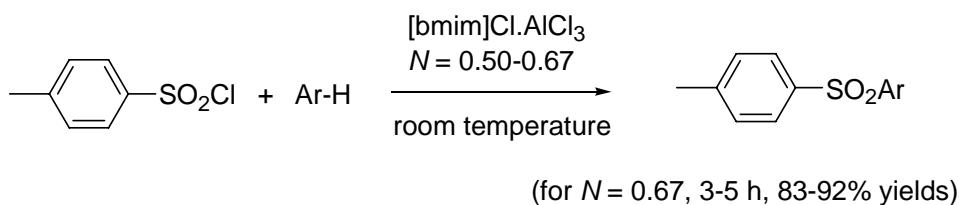
The Knoevenagel condensation, a useful reaction for the synthesis of electron deficient olefins, was found to work efficiently and expeditiously in $[\text{bmim}]\text{Cl} \cdot 2\text{AlCl}_3$, and $[\text{bpy}]\text{Cl} \cdot 2\text{AlCl}_3$ ionic liquids.

The condensations of benzaldehyde and substituted benzaldehydes with diethyl malonate gave benzylidene malonates (**Scheme IX**)⁶⁴. The optimized protocol fetched almost quantitative conversions with respect to decay of benzaldehydes. However, the benzylidene malonates subsequently underwent Michael additions with diethyl malonate. This side reaction was more pronounced in case of aldehydes with an electron releasing group at *para* position. Higher molar proportions of the ionic liquid favors the formation of the Knoevenagel over the Michael product. The declined K/M was observed as the Lewis acidity of the ionic liquid increased. An increase in the proportion of the ionic liquid increased the K/M ratio. The conversions in $[\text{bpy}]\text{Cl} \cdot 2\text{AlCl}_3$, ionic liquid were relatively less with relatively lower K/M ratios than what were observed in $[\text{bmim}]\text{Cl} \cdot 2\text{AlCl}_3$.

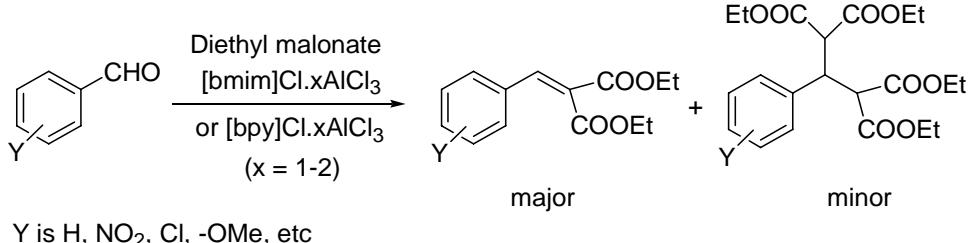
The coumarin synthesis was extended in these liquids *via* Pechmann condensation route⁶⁵. The protocol was found to be the most expeditious route



Scheme VII



Scheme VIII



Scheme IX

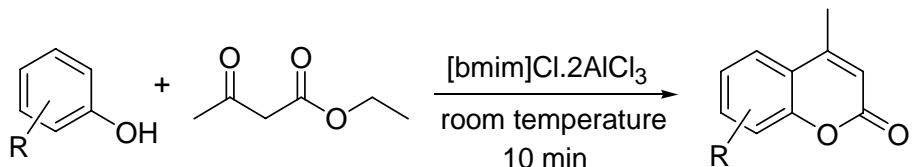
(10 min), overcoming the disadvantage of demethylation in case of methoxy phenols, which is often observed in the protocol using AlCl_3 (**Scheme X**). Further, we also demonstrated their synthesis in neutral ionic liquids, circumventing the limitations of the protocol involving Lewis acid.

A search for a suitable catalyst to induce direct synthesis of sulfoxides from arenes and thionylchloride, avoiding side reactions such as chlorination has been scarcely successful. The ionic liquid, $[\text{bmim}]Cl.2\text{AlCl}_3$ mediated protocol proved to be a useful and advantageous addition to the reported methods⁶⁶. The experimental procedure is simple and time saving, furnishing the diaryl sulfoxides in near quantitative yields within 5 min (**Scheme XI**).

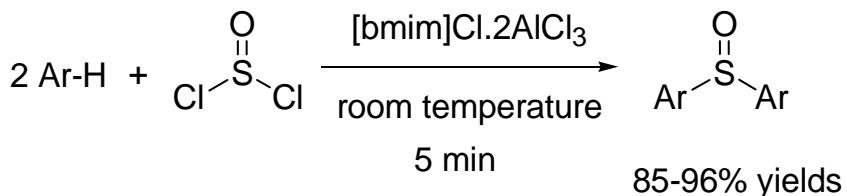
Few of the many interesting reports published pertaining to the usefulness of chloroaluminate ionic liquids for several organic transformations involve a practical and convenient protocol using $[\text{emim}]Cl.\text{AlCl}_3$, $N = 0.67\text{--}0.75$ for the synthesis of the novel 3-acylated indoles starting with the *N*-unprotected indoles⁶⁷. Deng *et al.* reported a novel cyclization reaction of 1-dodecene to cyclodecane with high selectivity under moderate pressure in chloroaluminate ionic liquid⁶⁸. It was demonstrated that the solvent duo of EtOH and chloroaluminate ionic liquid provides a homogenous catalytic medium for the reaction, from which the products can be separated by merely raising the temperature of the reaction mixture, which is required for the separation of phases. The use of 1-butyl-pyridinium chloroaluminate ionic liquid for Fischer-Indole

synthesis of ketones with aryl hydrazones has been demonstrated⁶⁹. The amount of ionic liquid required for the process is equimolar with respect to the ketone used for the reaction. In addition to this, the method does not require the catalyst in high concentrations as is often required in the protocols employing PPA and ZnCl_2 . Wasserscheid *et al.* demonstrated the use of the buffered chloroaluminate ionic liquid as solvent for the catalyst, $[(\text{cod})\text{Ni}(\text{hfacac})]$ known to produce the linear dimers from 1-butene⁷⁰. The dissolution of the catalyst resulted in the enhancement of the activity of the catalyst. The buffered chloroaluminate also takes care of the dimer selectivity and product linearity. An added advantage of the method is that being a biphasic process, easy catalyst recovery and recyclability is possible. Singer *et al.* used $[\text{emim}]I.\text{AlCl}_3$ as a solvent and catalyst for the acylative cleavage of cyclic and acyclic ethers in presence of benzoyl chloride as an acylating agent⁷¹. Bifunctionalised α,ω -iodobenzoates have been isolated as the products from the reaction mixture from the cleavage of the cyclic ethers. The Lewis acidic 1-butyl-3-methylimidazolium chloroaluminate ionic liquid $[\text{bmim}]Cl.\text{AlCl}_3$, $N = 0.67$, has also been employed by the present group as a catalyst as well as the solvent for the quick and efficient syntheses of aryl keto acids by Friedel-Crafts acylation and aroylation of aromatic hydrocarbons using cyclic acid anhydrides⁷².

Recently, a new protocol was developed for the synthesis of *N*-substituted thioamides employing arenes and isothiocyanates in $[\text{bmim}]Cl.2\text{AlCl}_3$ as a



Scheme X



Scheme XI

homogenous Lewis acid catalyst and solvent (**Scheme XII**)⁷³. Studies reveal that a progressive increase in yields was observed with increasing Lewis acidity and two equivalents of [bmim]Cl₂AlCl₃ was optimal amount for the reaction. A distinct *para*-selectivity for the incoming thioamido group on activated arenes was observed under ambient conditions. The protocol eliminates the use of conventional obnoxious or volatile solvents such as halogenated hydrocarbons, nitromethane and carbon disulphide. Homogenous catalysis, reduced reaction times, and ambient conditions are some of the distinctively notable advantages offered by the novel procedure.

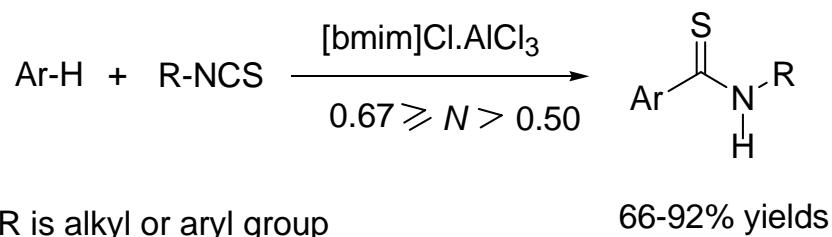
Further the ionic liquid, [bmim]Cl.AlCl₃, $N = 0.67$ mediated syntheses of aromatic sulfonamides via electrophilic substitution of arenes has been investigated (**Scheme XIII**)⁷⁴. The protocol serves as a distinctly expeditious and ambient route towards the syntheses of these pharmaceutically useful compounds, yielding quantitative conversions at room temperature within 5-30 min in most of the cases. The method has been used for the syntheses of a diverse range of sulfonamides by variation of arenes and sulfamoyl chlorides. With monosubstituted benzenes, the protocol offers an added advantage of exclusive selectivity towards the formation of *para*-substituted sulfonamides over the *ortho* products.

To list a few of many other applications where the chloroaluminate ionic liquids have been used include their application in one-pot synthesis of α -amino

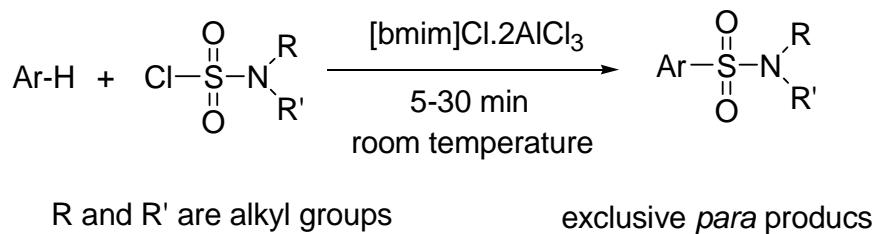
phosphonates⁷⁵, Henry reaction⁷⁶, arene carbonylation⁷⁷, alkylation of isobutene and butane⁷⁸, cleavage of methyl esters of flavones⁷⁹, DABCO-catalyzed Baylis-Hillman reactions⁸⁰, *endo*-selective Diels-Alder reaction⁸¹, the dimerization of 1,3-cyclopentadiene⁸², Baeyer condensation⁸³, Prins cyclizations⁸⁴, cleavage of aromatic methyl ethers⁸⁵, oligomerisation of olefins⁸⁶, ring-opening polymerization of ethylene carbonate⁸⁷, Nickel(II) heterocyclic carbene complexes mediated olefin dimerization⁸⁸, selective hydrogenations⁸⁹, synthesis of transition metal cyclophane complex⁹⁰ and synthesis of organometallics⁹¹.

Over the last few years there has been much emphasis on the design of the ionic liquids by structural manipulations so as to make them suitable for specialized applications. There is also an increasing awareness in the community of chemists not only to device more greener ionic liquids but also to synthesize them in a greener way. Besides this the development of synthetic methodologies continues to be an escalating area of chemical research. This group has been involved in development of the synthetic methodologies in the area of neural ionic liquids as well, which are not just green but also offer the advantage of being reusable.

The ionic liquid 1-methoxyethyl-3-methyl-methanesulfonate [MOEMIM][OMs] was prepared by a novel methodology in which the mesylate esters are treated with 1-methylimidazole. This can be carried



Scheme XII



Scheme XIII

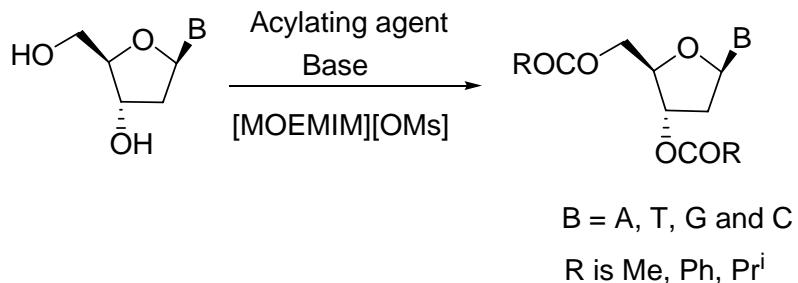
out either by direct heating or by microwave heating. The insolubility of the nucleosides in many organic solvents is a major obstacle in the development of new methodologies. The ether linkage containing ionic liquids were designed with an intention to serve as solvents for nucleoside chemistry. The ionic liquid, [MOEMIM][OMs] was used for the execution of acetylation of various 2'-deoxyribonucleosides (**Scheme XIV**)⁹².

The enantioselective Michael addition of dimethyl malonate to 1,3-diphenylprop-2-en-1-one, promoted by a quaternary ammonium salt derived from quinine as a phase transfer catalyst in different ionic liquids, [bmim][PF₆], [bpy]BF₄, [bmim]BF₄] as well as in the conventional organic solvents was studied by the present group (**Scheme XV**). The results indicated that the reversal of enantioselectivity observed upon switching from one ionic liquid to another was not due to the PTC, but can be attributed to the cation of the ionic liquid⁹³.

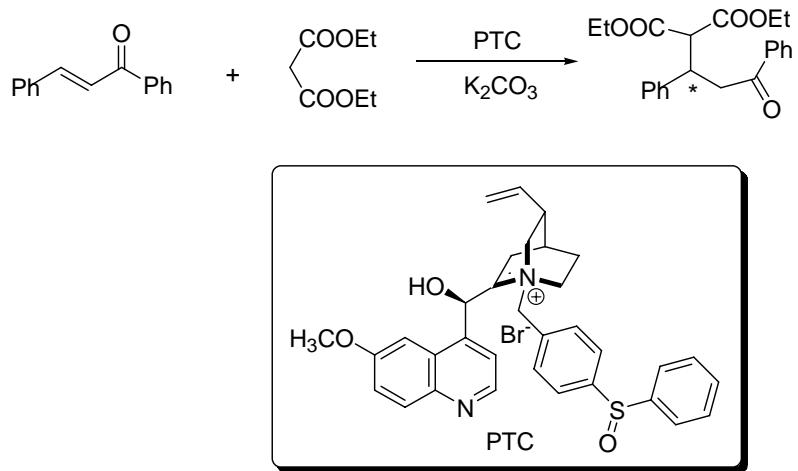
The Ferrier glucosylation of alcohols with 3,4,6-tri-*O*-acetyl-D-glucal has been investigated with several

metal nitrates and the optimal catalyst is bismuth nitrate pentahydrate (BNP)⁹⁴. Good yields of pseudoglycals were also obtained with ferric nitrate nonahydrate (FNN), heightening the catalyst dosage (50 mol%). The BNP-mediated reactions showed remarkable solvent dependency and in the optimal protocol, the amount of BNP as low as 10 mol% was effective (**Scheme XVI**), furnishing excellent yields of *O*-glucosides with good anomeric selectivity in acetonitrile. A comparison of BNP and FNN in terms of yields and selectivity of the product has been made. In comparison to the reactions in acetonitrile, the catalytic ability of BNP was found to enhance drastically in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF₆].

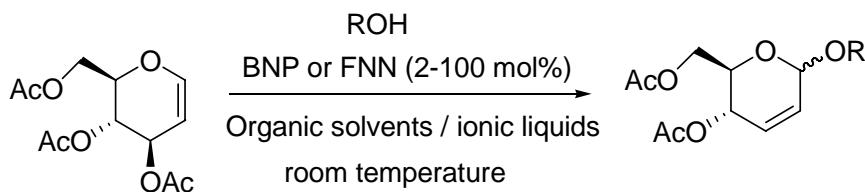
L-Proline in ionic liquid was employed for Michael addition of ketones to nitrostyrene by the present group. This asymmetric synthesis of γ -nitroketoesters fetches up to 80% yield with high *syn*-selectivity (90%) (Ref. 95). The ionic liquid has been found to enhance the enantioselectivity, wherein the *ee* approaches 75%. The system ionic liquid/catalyst has



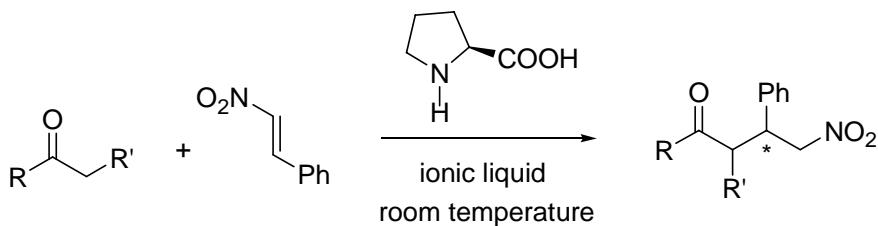
Scheme XIV



Scheme XV



Scheme XVI



Scheme XVII

proved to be an efficient and recyclable medium (**Scheme XVII**).

The Pechmann condensation of phenols and ethyl acetoacetate was revisited but under ambient conditions in neutral ionic liquids with catalytic amount of acid. The reaction was also successfully carried out at high temperature in $[\text{bmim}][\text{PF}_6]$ ionic liquid, without the use of the catalyst. The possibility of the use of Brönsted acidic ionic liquids for this reaction has also been investigated. Ionic liquids were recycled efficiently⁹⁶.

Conclusion

It is now a well proven fact that the ionic liquids are potential solvents for a varied range of applications. With the speed at which the research in this area is growing and the promising results that are already obtained with ionic liquids as the alternative media, it would not be inappropriate to predict that they will soon become common not only in the chemistry laboratory shelf but also as solvents in industrial applications. They surely are the solvents of the future and are geared up to amend the way the chemist thinks and works.

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