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Ionic liquids as substrate-specific recoverable solvents and catalysts of regio-, stereo- and enantioselective organic reactions

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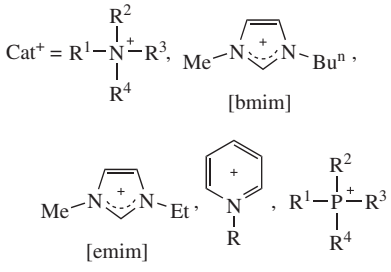
The results obtained in the past few years concerning the use of ionic liquids and their congeners in reactions of organic compounds are summarized and the new opportunities opened by the use of such liquids instead of traditional organic solvents and catalysts are demonstrated.

The need to improve the efficiency of chemical processes is caused by a decline in reserves and a rise in the cost of oil and gas along with the global pollution of the environment by industrial wastes.[1] In fact, traditional methods in the production of complex organic compounds, such as pharmaceuticals, chemical products for plant protection and some other compounds, give dozens and even hundreds tons of wastes per ton of a product.[2,3] New chemical processes are needed such that all atoms of starting compounds would be incorporated in the end products (atom-economy principle) and that selective (substrate-specific) solvents and catalysts involved in the process could be reused repeatedly.[4,5]

A promising approach to these challenges involves the use of ionic liquids (ILs) in chemistry and chemical technology, *vis.*, salts of organic bases with organic or inorganic acids, often fluorine-containing ones, with melting points not exceeding 100–150 °C (Scheme 1).[6–9] These compounds have become generally accepted in today's 'green' chemistry owing to their useful physicochemical properties (non-flammability, low vapour pressure, recovery capability, *etc*.) and the associated ability to improve the ecological characteristics of the processes.[10–14] Implementation of ILs in chemical processes may provide fundamental results, since the reactivity of molecules in a unique ionic environment is modified, as is the selectivity of the reactions involved.[15–18] The rates of certain chemical (especially heterolytic) reactions in IL solutions are higher than those in other solvents; at the same time, due to the ionic structure, they affect the regioselectivity of such reactions.[19,20] ILs are perfect environments for various catalytic transformations[21–23] and also show considerable promise as catalysts of chemical reactions.[24] They are similar in structure to phase-transfer catalysts that have once provided a 'breakthrough' in the methodology and technology of organic synthesis.[25,26] Furthermore, the presence of catalytically active groups in ILs imparts them the properties of acid-base catalysts or catalysts with other mechanisms of reagent activation.[27–30]

Taking into account the vast opportunities opened by the use of ionic liquids in organic chemistry, in 2002 we started a series of studies aimed at the development of new selective methods of organic synthesis using ionic liquids and related compounds as solvents and catalysts.[31] The results of these studies, as well as some results obtained by other scientists in this field, are summarized here.



$An^- = BF_4^-, PF_6^-, CF_3CO_2^-, CF_3SO_3^-, (CF_3SO_2)_2N^-, HSO_4^-$

Scheme 1 Cations and anions of some commercially available ILs.

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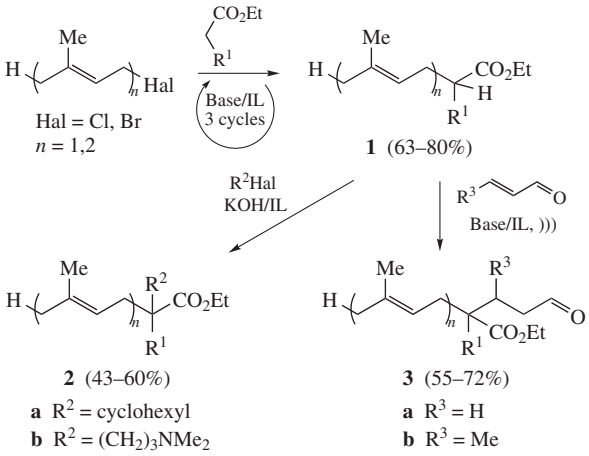
Organic syntheses in ionic liquid media

This study involved reactions with the formation of polar and zwitter-ionic intermediates. These include nucleophilic substitution and addition (alkylation, Michael reaction, Knoevenagel reaction, Horner–Emmons reaction, aldol reaction, *etc.*) involving carbanions, enols and related species, as well as nucleophiles containing heteroatoms; electrophilic addition and 1,3-dipolar cycloaddition reactions, including reactions with participation of heteroaromatic dipoles and dipolarophiles, reactions of diaziridine derivatives with generation of reactive dipolar intermediates with a nitrogen-nitrogen bond, and some others. We assumed that these reactions would occur in IL solutions more selectively and would provide higher product yields than the corresponding reactions in organic solvents owing to the stabilization of polar species in the ionic medium. ILs were studied not only in reactions involving model compounds but also in reactions that give products of practical value.

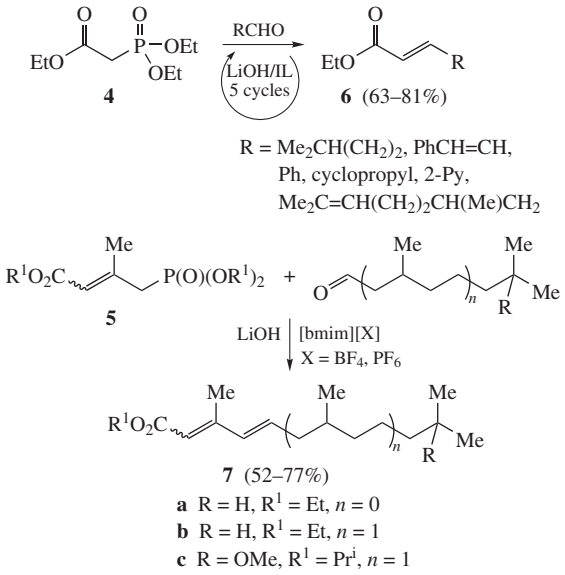
It has been found that alkylation of CH-acids with prenyl halides efficiently occurs in solutions of imidazolium salts to give isoprenoid derivatives **1** and **2**.[32,33] The method does not require applying alkali metals or anhydrous solvents. In an IL medium, CH-acids containing prenyl and geranyl groups add to α,β-enals to give adducts **3**.[34,35] The reactions are accelerated under ultrasonic treatment. The yields of compounds **2a**,**b** and **3a**, which are used in the preparation of wound-healing products Cygerol[36,37] and Methaprogerol,[38] under the suggested conditions are 10–20% higher than those cited in literature, while the ILs can be recovered and reused repeatedly (Scheme 2).



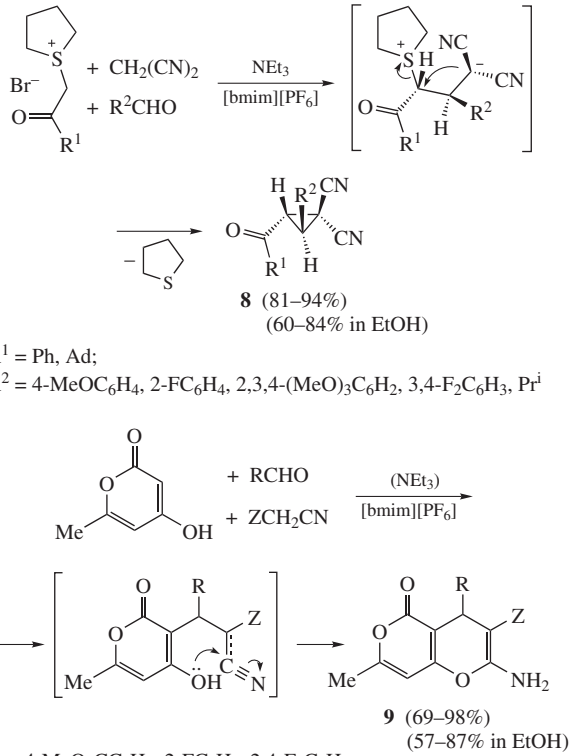
Scheme 2

Reactions of activated phosphonates **4** and allylphosphonates **5** with aldehydes in the presence of bases in an IL medium gave the corresponding acrylates **6** and diene ethers **7**,[39,40] including the sterilizing agent for spider mite (*Tetranychidae*) **7a** and analogues of juvenile insect hormones hydroprene **7b** and methoprene **7c**.[41,42] The double bond in products **6** and **7** is formed *trans*-stereoselectively. The reaction efficiency and selectivity do not decrease as the IL is used in five cycles (Scheme 3).

ILs were successfully applied in three-component stereoselective syntheses of 1,1-dicyanocyclopropane derivatives **8**[43] and in the preparation of functionally substituted 4,5-dihydropyrano-[4,3-*b*]pyrans **9**.[44] Note that the yields of compounds **8** and **9** not only fail to decrease, but even increase when the experiment is carried out in a recycled IL, apparently due to the accumulation of products resulting from the previous cycles. In certain cases, the reactions occur without addition of a base, where the role of such a base is played by the IL (Scheme 4).[44]



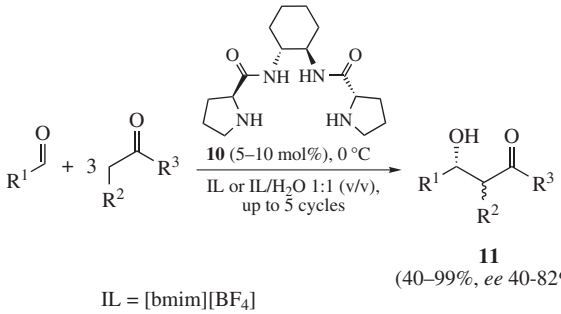
Scheme 3



Scheme 4

Not only stereoselective but also enantioselective reactions of CH-acids efficiently occur in ILs. Reactions between aldehydes and ketones catalysed by (*S*)-proline amide **10** under these conditions give chiral aldols **11** (up to 70% *ee*) that can be used as building blocks for the synthesis of chiral biologically active compounds.[45] In such case, owing to a higher activity of the catalyst, hardly accessible chiral derivatives of heterocycles, isoprenoids and metallocenes can be synthesised in an IL. It is interesting that dilution of an IL with water increases the reaction rates and the yields of compounds **11**, while the *ee* remains as high and in some cases becomes even higher than in unhydrous medium (up to 82%) (Scheme 5).[46]

A number of functional derivatives of heterocyclic compounds have been obtained in ILs, whereas synthesis of these

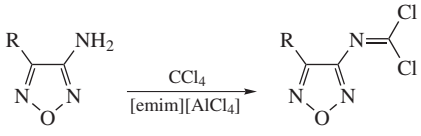


11
(40–99%, *ee* 40-82%)

IL = [bmim][BF_4]
R^1 = Ar, 5-NO_2-thienyl, 2-Py, *n*-CpMn(CO)$_3$
R^2 = H, OH;
R^3 = Me, Et, cyclopropyl, $(CH_2)_2CH{=}CMe_2$
$R_2 + R_3 = (CH_2)_n$ (n = 3, 4)

Scheme 5

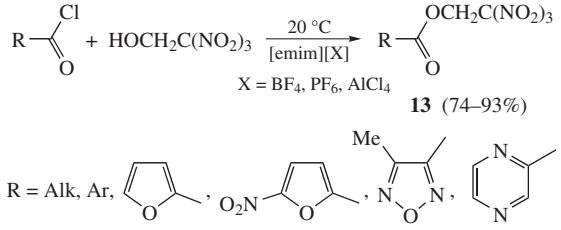
derivatives in common organic solvents is problematic. In fact, dichloroiminofurazans **12** that serve as building blocks for the preparation of functionally substituted furazan derivatives have been synthesized from aminofurazans and CCl_4 in a 3-ethyl-1-methylimidazolium tetrachloroaluminate ([emim][$AlCl_4$]) medium[47] in higher yields than those obtained in the 'organic solvent–$AlCl_3$' system commonly used for this purpose. Furthermore, performing this reaction in an IL noticeably simplifies the isolation of the products, since it becomes unnecessary to purify the reaction mixture from excess $AlCl_3$ (Scheme 6).



R = Me, Ph, CO_2Me, NO_2 **12** (81–87%)

Scheme 6

ILs accelerate the reactions of alkyl-, aryl- and hetaryl-substituted acyl chlorides with trinitroethanol to give trinitroethyl esters **13** (Scheme 7).[48] The known methods for the synthesis of polynitro compounds **13** in organic solvents require prolonged heating of the reaction mixture,[49] whereas in ILs, the same reactions occur at room temperature, which considerably reduces explosion risks.



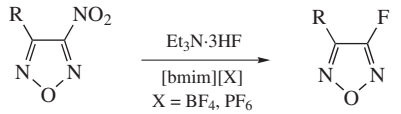
X = BF_4, PF_6, $AlCl_4$ **13** (74–93%)

R = Alk, Ar,

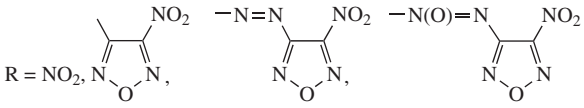
Scheme 7

In some cases, nucleophilic substitution reactions that did not occur in common organic solvents succeeded in ILs. In particular, fluorofurazans **14** could be obtained from nitrofurazans and hydrofluoric acid salts (Scheme 8).[50] Similar reactions are known in the aromatic series,[51] however previously in the case of nitrofurazans they only resulted in difurazanyl ethers.[52]

Addition of electrophiles and 1,3-dipoles to unsaturated compounds is another important example of reactions that display some specific features when carried out in ILs. In fact, highly polar ionic liquids accelerate enolization of carbonyl compounds and alter the ratio of isomeric enols **A** and **B**, which allows one

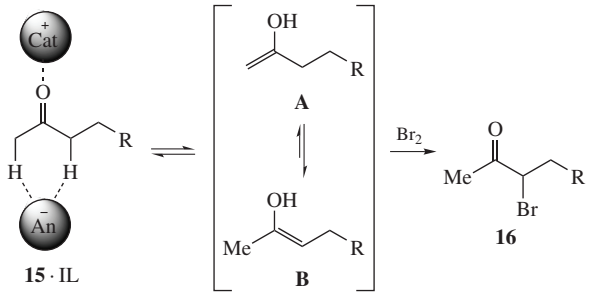


14 (50–70%)



Scheme 8

to enhance and sometimes change the regioselectivity of bromination of asymmetric methylketones **15**, including derivatives of levulinic acid, by directing the process towards the formation of internal α-bromoketones **16** (Scheme 9).[53]

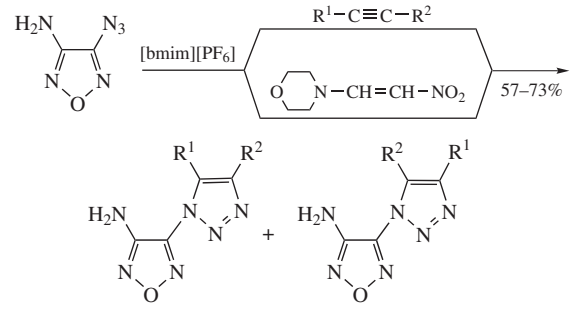


15 · IL **A** **B** **16**

R = CO_2H, CO_2R', Pr

Scheme 9

A considerable increase (3- to 5-fold) in the rate and regioselectivity of 1,3-dipolar cycloaddition of furazanyl azides to asymmetrically substituted acetylenes and morpholinonitroethylene to give 4-R-3-(1,2,3-triazol-1-yl)furazans **17a**,**b** (Scheme 10) occurs in ILs.[54] Triazolylfurazans are of interest as high-energy structural blocks and activators of the soluble form of guanylate cyclase.[56] Under the similar conditions but in another IL ([bmim][BF_4]), the reaction of phenyl azide with butynediol is accelerated threefold. In all the cases mentioned, the reactions can be carried out in ILs repeatedly without decreasing the product yields.



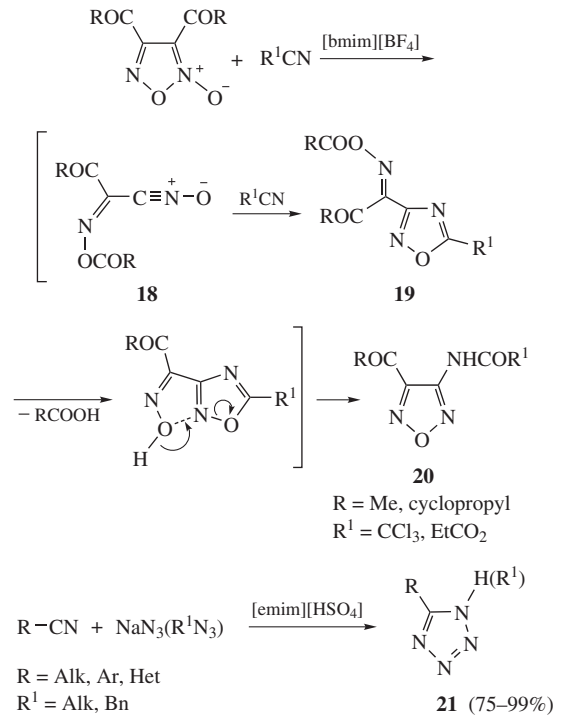
17a **17b**

17a : 17b = 4.5 : 1 (lit.,[55] 2.5 : 1)

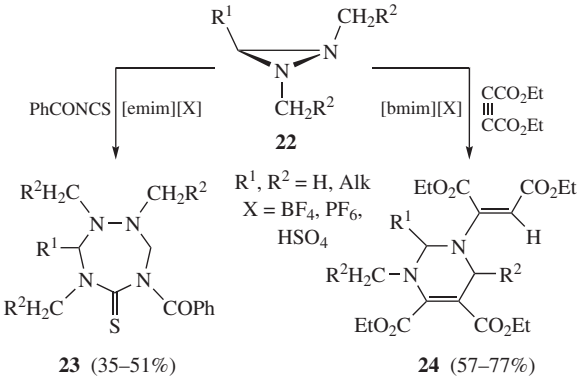
$R^1 = R^2 = CH_2OH$
R^1 = H, $R^2 = CH_2OH$
R^1 = H, $R^2 = NO_2$

Scheme 10

1,3-Dipolar cycloaddition of nitrile oxides **18**, generated *in situ* by thermolysis of 3,4-diacetyl- and 3,4-dicyclopropanoylfuroxans, to activated nitriles followed by one-pot azole–azole rearrangement of the resulting cycloadducts **19** in an IL medium gave hitherto hardly-accessible 3-acetyl(cyclopropanoyl)-4-acylaminofurazans **20**.[57] The use of 1-ethyl-3-methylimidazolium hydro-



Scheme 11



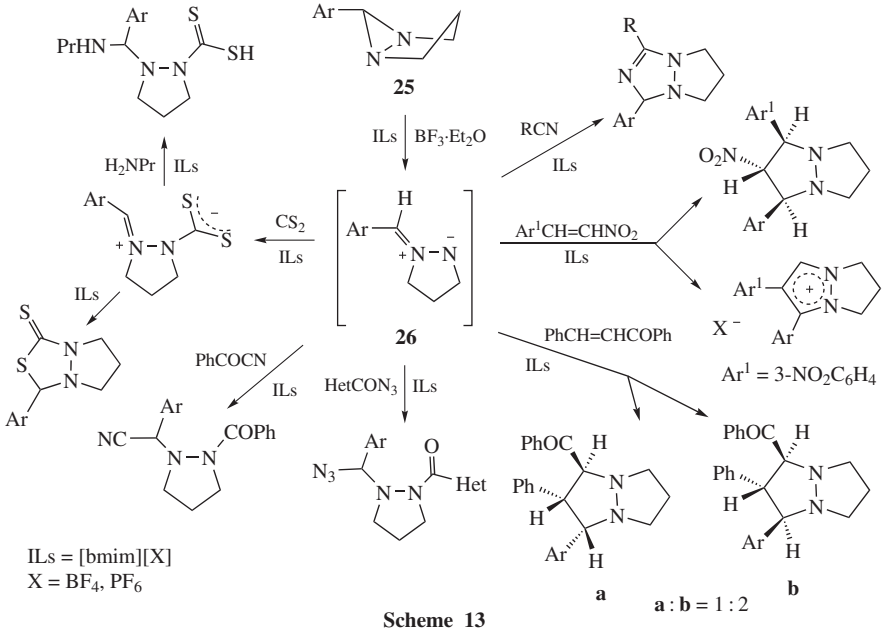
Scheme 12

sulfate ([emim][HSO_4]) as the solvent allows one to synthesise 5-aryl(hetaryl)tetrazoles **21** from aryl(hetaryl) cyanides and azides without addition of an acid as the IL acts as the acid in this reaction (Scheme 11).[58]

The effect of replacement of an organic solvent for an IL manifests itself most clearly in transformations of the diaziridine ring. It has been found that ILs not only accelerate heterolytic processes by increasing the formation rate of dipolar intermediates; they can also change the direction of such reactions due to the stabilization of intermediates in the ionic medium. In certain cases, this gives unpredictable results that are hard to achieve in common organic solvents. Based on this method, two new reactions of 1,2-dialkyldiaziridines **22** were discovered. Compounds **22** react with benzoyl isothiocyanate in an IL to yield hitherto unknown non-fused 1,2,4,6-tetrazepan-5-thiones **23**,[59] whereas their treatment with diethyl acetylenedicarboxylate results in tetrahydropyrimidine derivatives **24** (Scheme 12).[60] 1,2,3-Trialkyldiaziridines undergo similar reactions, which in this case are carried out in an IL comprising the hydrosulfate anion; this IL serves both as the solvent and catalyst.[60]

Reactions of 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **25** with dipolarophiles (carbon disulfide,[61,62] activated nitriles[62,63] and olefins, including chalcone and β-nitrostyrenes[64]) that do not occur in organic solvents succeeded in an IL medium in the presence of a Lewis acid (BF_3·Et_2O) (Scheme 13). These reactions lead to fused heterocyclic systems, in which the pyrazolidine ring is annelated with thiadiazolidine, triazoline, pyrazolidine or pyrazolium moieties, including functionally substituted ones. The key intermediate is azomethine imine **26** that is formed by opening of the diaziridine ring on treatment with a Lewis acid and further reacts with the corresponding dipolarophile. The reactions discovered manifest high regio- and stereoselectivity. It has also been found that reactions with CS_2 and activated nitriles do not proceed synchronously but involve the formation of new dipolar intermediates, which then undergo cyclisation to give the final bicyclic systems. Some of the intermediates, including the azomethine imine one, were isolated or detected spectroscopically or by chemical methods, namely, as adducts with nucleophiles or acylating reagents.

The bicyclic compounds thus obtained belong to heterocycle classes of practical value, and representatives of these classes have been patented for use in medicine (anti-HIV agents,[65,66] NO-synthase inhibitors,[67] antidiabetic agents[68]), in agriculture (herbicides, fungicides[69,70]) and in other areas (lubricant addi-



Scheme 13

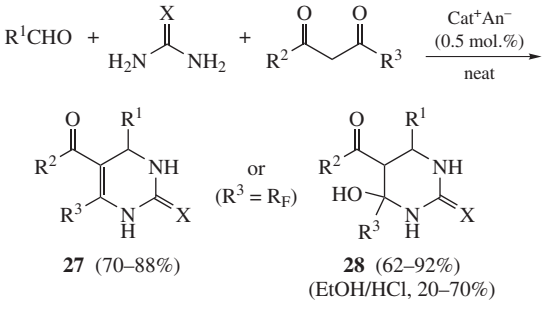
tives,[71] semiconductors, sorbents[72] *etc*.). In all cases, the ILs were recovered and reused many times in the reactions without any loss in efficiency. Unlike these methods, the known methods for the synthesis of the above heterocycles[73–75] involve multiple stages and cannot be considered as a basis for the development of efficient resource-saving chemical processes.

Obviously, the discovered ability of ILs to stabilise dipolar intermediates is highly promising as a new approach to the synthesis of compounds of practical value, based not only on reactions of diaziridine derivatives with dipolarophiles, but also on other reactions involving intermediate dipolar species.

Reactions of organic compounds catalysed by ionic liquids and their congeners

As noted above, certain ILs are both solvents and catalysts of chemical reactions carried out in their media. In some cases, as little as 0.5–30 mol% of an IL with respect to the reagents is required to achieve a pronounced catalytic effect, which, taking into account that the catalyst can be recovered, enhances considerably the cost efficiency of using these compounds that are as yet relatively expensive. ILs usually play the role of acid-base or phase-transfer catalysts; however, if the corresponding structural fragments are present, ILs exhibit other types of catalytic activity as well.

In fact, alkylamine and alkylimidazole salts with BF_4^-, PF_6^-, $AlCl_4^-$ and $Al_2Cl_7^-$ anions were identified as mild acid catalysts in the three-component reaction of β-dicarbonyl compounds, including fluorinated ones, with aldehydes and urea (thiourea) (Biginelli reaction) (Scheme 14). The use of these catalysts (0.5 mol%) allowed one to synthesise various derivatives of di-**27**[76] and tetrahydropyrimidine **28**,[77] *i.e*., heterocycles among which antitumour compounds[78,79] and selective antagonists of α_{1a} adrenoreceptors[80] have been discovered. The yields of products **27** and especially **28** are much higher than those achieved previously.



27 (70–88%)

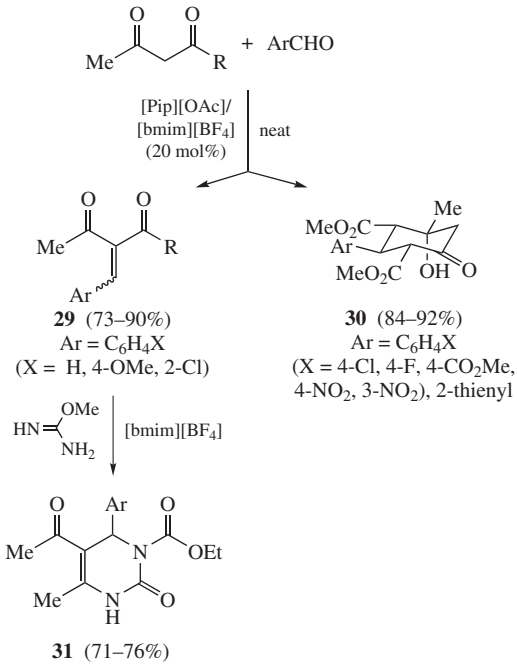
28 (62–92%)
(EtOH/HCl, 20–70%)

Cat = $HNEt_3$, $BnNEt_3$, NBu_4, bmim
An = BF_4, PF_6, $AlCl_4$, Al_2Cl_7
R^1 = Ar, 3-thienyl
R^2 = Me, OEt, CF_3, Ph
R^3 = Me, CF_3, CF_2CHF_2
X = O, S

Scheme 14

The system [bmim][BF_4]/piperidinium acetate ([Pip][OAc]) (1:1) efficiently catalyzes the Knoevenagel reaction between aromatic aldehydes and β-dicarbonyl compounds under neat conditions. Depending on aldehyde structure the reaction yielded either enones **29** or cyclohexanone derivatives **30**.[81] Apparently, the two ILs complement each other: [Pip][OAc] serves as a mild base whereas [bmim][BF_4] stabilizes the carbon acid anion. Compounds **29** were then applied to the synthesis of dihydropyrimidines **31** by the reaction with *O*-methylurea in the IL (Scheme 15).

Efficient phase-transfer catalysts for reactions involving the formation of carbon acid anions were found among organic salts



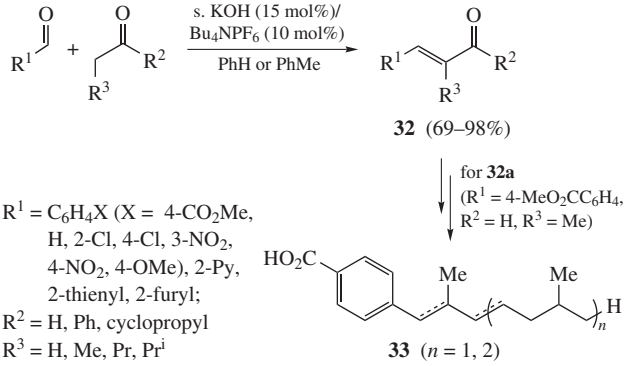
29 (73–90%)
Ar = C_6H_4X
(X = H, 4-OMe, 2-Cl)

30 (84–92%)
Ar = C_6H_4X
(X = 4-Cl, 4-F, 4-CO_2Me, 4-NO_2, 3-NO_2), 2-thienyl

31 (71–76%)

Scheme 15

with BF_4^- and PF_6^- anions. The aldol reaction between aromatic (heteroaromatic) aldehydes and various carbonyl compounds occurs in the catalytic system (Bu_4NPF_6)/s.KOH/PhH (PhMe) with a remarkable selectivity yielding the condensation products **32**.[82] Among them, the key intermediate **32a** for the synthesis of *para*-(*nor*-polyprenyl)benzoic acid derivatives **33** possessing anti-cancer,[83] hypolipidemic[84] and anticoagulant activities,[85] was prepared in 98% yield (Scheme 16).



32 (69–98%)

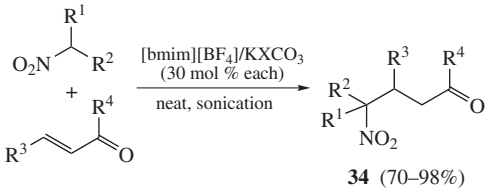
R^1 = C_6H_4X (X = 4-CO_2Me, H, 2-Cl, 4-Cl, 3-NO_2, 4-NO_2, 4-OMe), 2-Py, 2-thienyl, 2-furyl;
R^2 = H, Ph, cyclopropyl
R^3 = H, Me, Pr, Pr^i

33 (*n* = 1, 2)

Scheme 16

The IL [bmim][BF_4] (30 mol%) efficiently accelerates reactions of nitroalkanes or α-nitroesters with electron-deficient alkenes under solvent-free conditions in the presence of a solid base.[86] It is advisable to apply sonication to increase the solid base dispersion and intensify mass transfer. This procedure was employed for the synthesis of δ-oxocarboxylic and glutaric acid α-nitro derivatives **34** bearing prenyl moieties which are intermediates for producing isoprenoid amino acids, in particular, analogues of wound-healing medications (Scheme 17).[87]

The salt Bu_4NPF_6 used as a phase-transfer catalyst (1 mol%) allows one to increase selectivity and product yield, as compared to the existing procedures, in heterogeneous reactions that run through the steps where the CCl_3^- anion **35** or dichlorocarbene **36** are generated from $CHCl_3$ under the action of solid base. The reaction pathway depends on the reagent structure. Electron-deficient alkenes and aldehydes react with anion **35**, affording the corresponding trichloromethyl derivatives **37** and **38**. In the

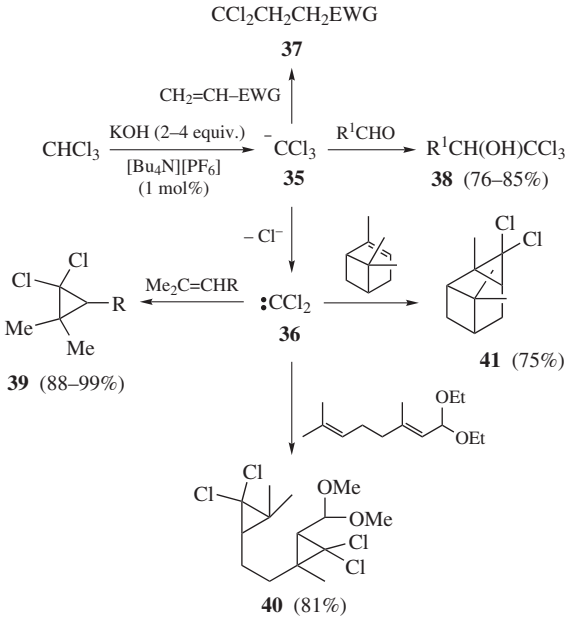


34 (70–98%)

X = H, K
R^1, R^2 = H, Me; H, CO_2Me; Me, Me; $(CH_2)_4$;
$H[CH_2C(Me)=CHCH_2]_n$ (n = 1, 2), CO_2Me
R^3 = H, Me, Ph, $Me_2C=CH(CH_2)_2CH(Me)CH_2$
R^4 = H, Me, Ph, cyclopropyl, OMe

Scheme 17

absence of an electrophile, dichlorocarbene **36** reacts with alkenes yielding 1,1-dichlorocyclopropane derivatives **39**–**41** (Scheme 18).[88] Some hitherto unknown isopropenoid and terpene derivatives are obtained using the developed procedure.



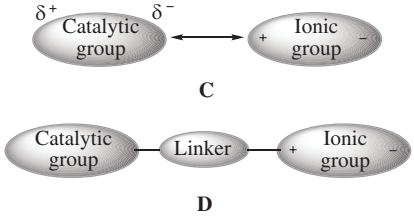
EWG = CN, CO_2Et
R = $(CH_2)_2C(Me)CH_2CH(OEt)_2$, $(CH_2)_2C(Me)(OH)CH=CH_2$, $(CH_2)_2C(Me)=CHCH_2OAc$
R^1 = Ar, CH=CHAr, $CH=C(Me)(CH_2)_2CH=CMe_2$

Scheme 18

A particular feature of the catalytic systems developed, which differs them from traditional halide salts-based phase-transfer catalysts, is that anion metathesis occurs in these systems, which recovers fluorine-containing catalysts poorly soluble in the organic phase and in water.[88,89] The recycling procedure is extremely easy. Following removal of the organic phase, fresh portions of reactants are added to the remaining base and phase-transfer catalyst mixture, and the process is re-performed with the same rate and selectivity. The catalysts are available, convenient in handling, and are likely to find applications in low-tonnage chemical processes.

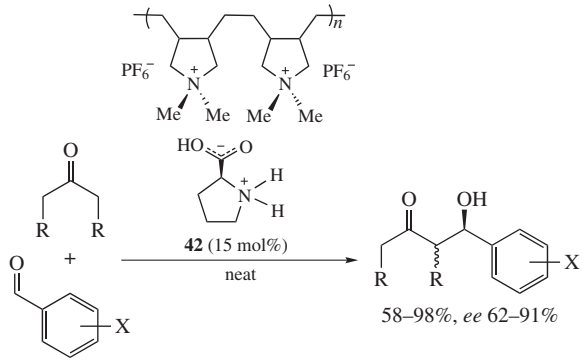
Fundamentally important results were obtained upon the use of ILs in asymmetric organocatalysis, which is among the areas developing most dynamically in today's organic chemistry.[90–96] In some cases, incorporation of IL fragments with certain electronic and spatial configurations in chiral organocatalysts increases their substrate specificity and hence selectivity of reactions catalysed.[97,98] Furthermore, such a combination of structural fragments allows the ratio of hydrophilic and hydrophobic properties of the catalyst to be adjusted over a wide range, thus gaining the maximum catalytic efficiency under the reaction conditions. Moreover, this approach ensures that the catalyst can be recovered.

Recently, original approaches to the synthesis of such catalysts have been suggested, which involve combining a chiral inductor, *e.g.*, a natural α-amino acid, with an ionic fragment by electrostatic forces (Scheme 19, **C**)[99–102] or integrating them within a single molecule by means of a spacer group (Scheme 19, **D**).[103]



Scheme 19 Immobilized organocatalysts containing ionic groups.

The former approach was implemented for designing proline-based organocatalyst **42** supported on organic polyelectrolyte poly(diallyldimethylammonium) hexafluorophosphate, which may be considered as an IL analogue. This catalyst showed high activity and good enantioselectivity in the aldol reaction carried out in the medium of the reagents, and these properties remained effective after the catalyst had been reused six times (Scheme 20).[99] The method of ionic immobilizing allows some organometal catalysts to be regenerated as well.[104]

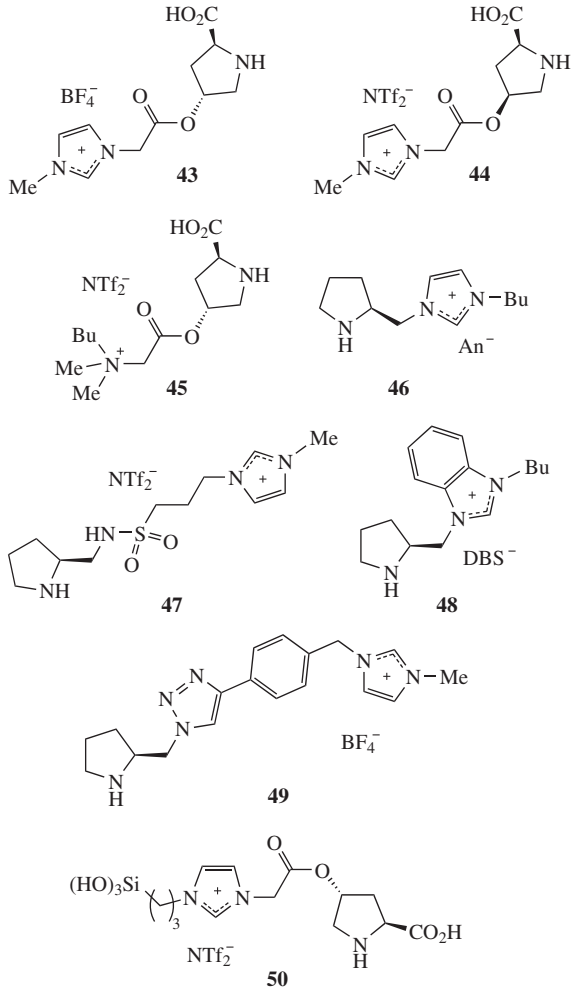


R = H
R + R = $(CH_2)_2$, $(CH_2)_3$
X = 3-NO_2, 4-NO_2, 2-Cl, 4-Cl, 4-CO_2Me, 4-CHO

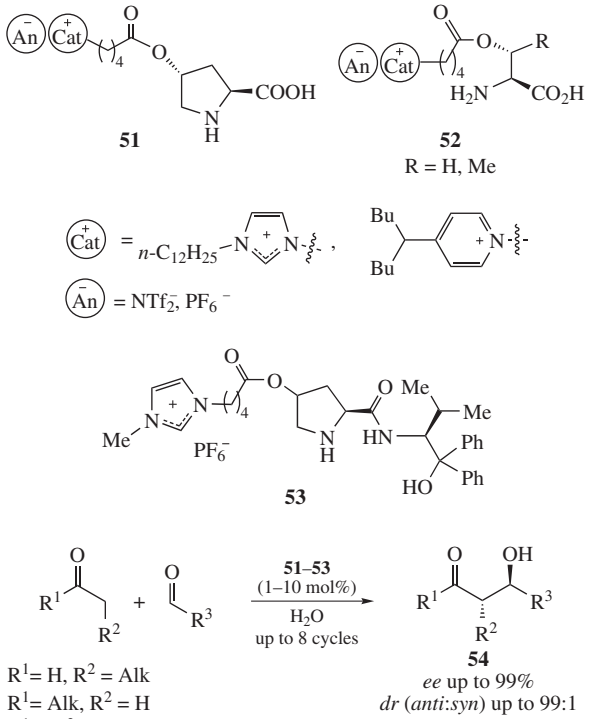
Scheme 20

Implementation of the second approach resulted in the synthesis of a series of chiral pyrrolidine derivatives **43**,[105] **44**,[106] **45**,[107] **46**,[108–110] **47**,[111] **48**,[112] **49**,[113] and **50**,[114] containing ionic groups, which efficiently catalysed asymmetric aldol reactions and Michael reactions in organic solvents, ionic liquids, and in some cases in water (Scheme 21). It should be noted that water, which is an available and environmentally friendly solvent, finds increasingly wide use in organic synthesis.[115,116]

A specific feature of the catalysts of this type that we developed, namely, **51**,[117,118] **52**[118] and **53**,[119] is that they comprise lipophilic alkyl or aryl groups with a large number of carbon atoms and hydrophobic anions (Scheme 22). Such a structure of compounds **51**–**53** makes it much easier to perform aldol reactions catalysed by them in water, allowing one to obtain aldols **54** under simple experimental conditions in quantitative yields and with exceptionally high diastereo- (*dr* up to 99:1) and enantioselectivity (*ee* up to 99%). Using this approach, linear chiral aldols **54**[119] as well as compounds of carbo-[117,118] and heterocyclic series[120] have been obtained. The procedure is scalable, while the catalysts are easy to regenerate



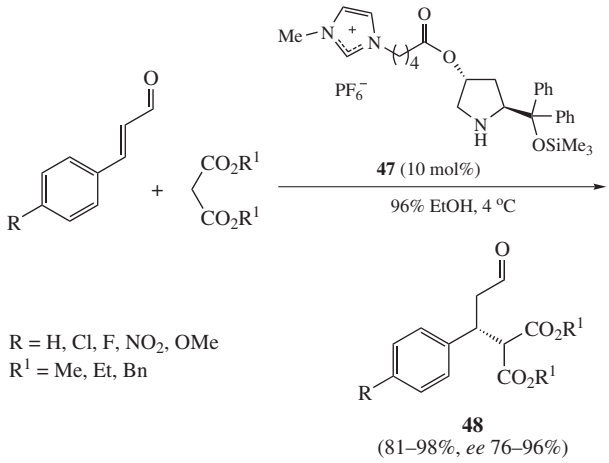
Scheme 21



Scheme 22 Chiral organocatalysts for asymmetric aldol reactions in water.

and can be reused in the reaction up to eight times with the same efficiency.

The addition of malonic esters to α,β-enals in aqueous EtOH efficiently occurs under the action of α,α-diphenyl-(*S*)-prolinol derivative **47**,[121] which is the first representative of a new family of recoverable organocatalysts for asymmetric reactions involving the formation of iminium intermediates (Scheme 23).[122] The presence of this compound increases considerably the yield and *ee* value of adduct **48a** (R = F, R^1 = Bn), a key intermediate in the synthesis of a promising antidepressant (–)-paroxetine, in comparison with the previously known method.[123] The yields and enantiometic purity of products **48** remained the same when catalyst **47** was reused four times.



Scheme 23

The catalytic activity and selectivity of compounds **43**–**45** and **47** approach those of enzymes, including aldolases that catalyse the carbohydrate biosynthesis in nature.[124–126] Actually, the approach suggested may result in the synthesis of extremely efficient and substrate-specific analogues of natural enzymes that can find use in asymmetric synthesis and catalysis.

Prospects

The results obtained contribute to the development of a promising field of 'green chemistry' concerning the use of ionic liquids and their congeners as solvents and catalysts in fine organic synthesis. Studies in this area are being carried out intensely in industrial countries (USA, Great Britain, France, Italy, Japan, Canada, China, South Korea and some others); some of these studies are performed in laboratories of the largest chemical companies (Merck KGaA, BASF, DuPont, ExxonMobil, Cytec, Degussa, *etc.*).[7] The implementation of ionic liquids at operating chemical industry requires considerable investments and a detailed assessment of the long-term ecotoxic risks.[14] However, a number of innovative technological processes using ILs have already been realised, for example, the so-called BASIL process (Biphasic Acid Scavenging utilizing Ionic Liquids) (BASF),[127] the isobutene alkylation process (PetroChina)[128] and some others.[7] In the near future one can expect that fundamentally new environmentally-friendly chemical technologies will be developed for the preparation of next-generation pharmaceuticals, chemical agents for plant protection, and compounds with other properties of practical value involving the use of ionic liquids.

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