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Reactions of carbon acids and 1,3-dipoles in the presence of ionic liquids †

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Abstract. The review is devoted to the use of ionic liquids as solvents, immobilized organocatalysts and reagents in reactions involving carbon acids and 1,3-dipoles, which are widely used to prepare practically valuable organic compounds of various classes. The characteristic features of processes in the presence of ionic liquids, the effects of the structure of cations and anions on the regio-, stereo- and enantioselectivities of reactions and methods of recovery of ionic liquids are considered. The bibliography includes 333 references.

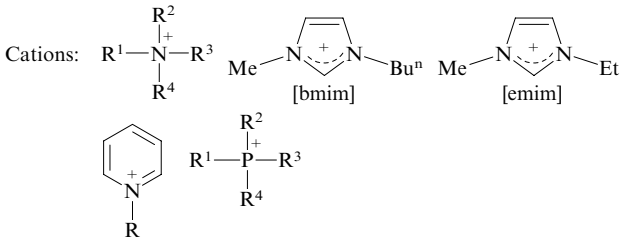
I. Introduction

The importance of increasing the efficiency of chemical processes has big economical and environmental reasons, including decumulation of reserves and, hence, increase in the cost of non-renewable natural resources (oil and gas) and environmental pollution by industrial wastes and biowastes.[1] Among the most resource-consuming processes, noteworthy are, in particular, multistep low-tonnage chemical processes used to prepare complex polyfunctional organic compounds (medical drugs, crop protection agents and so on) the amount of wastes in which reaches tens or even hundreds of tonnes per tonne of the product.[2,3] It is necessary to develop fundamentally new implementation techniques for chemical reactions providing the maximum possible transformation of the starting compounds to final products and the use of recoverable solvents and catalysts adapted to the particular (substrate-specific) reaction.[4,5]

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A promising approach for solving these problems is the use of ionic liquids (IL) in chemistry and chemical engineering; these are salts of organic bases with organic or inorganic, often fluorine-containing acids, the melting points of which do not exceed 100 – 150 °C.[6–9] The cations and anions of some commercially available IL are presented below.



Anions: BF_4^-, PF_6^-, $CF_3CO_2^-$ (TFA), $CF_3SO_3^-$ (OTf), $(CF_3SO_2)_2N^-$ (NTf_2), HSO_4^-.

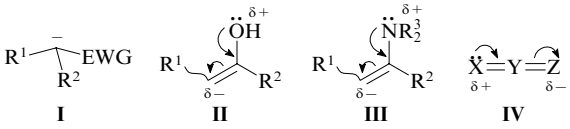
These compounds have become a usual tool of modern 'green' chemistry owing to useful physicochemical properties (non-flammability, low vapour pressure, possible recovery, *etc.*) and the concomitant ability to improve the environmental safety of the processes.[10–14] The implementation of IL into chemical processes can lead to fundamental results, since the unique ionic environment of the reacting molecules changes their reactivity and the selectivity of reactions.[15–18] Some chemical reactions (especially heterolytic ones) proceed in IL medium at higher rates than in other solvents; moreover, owing to their ionic structure, IL affect the reaction regioselectivity.[19,20] Ionic liquids are excellent media for various catalytic reactions.[21–23] Ionic liquids are highly promising as catalysts of chemical reactions.[24] As regards their structure, they resemble phase transfer catalysts, which provided once a breakthrough in

† This paper ends the series of published reviews reflecting the key trends of scientific reseach in the area of 'green chemistry' [see *Russian Chemical Reviews* **79** (6) (2010)].

the strategy and technology of organic synthesis.[25,26] In addition, owing to the presence of catalytically active groups in IL, they can act as acid-base catalysts or catalysts using other mechanisms of reactant activation.[27–30] Immobilization of reagents by introducing ionic groups in their molecules allows fast synthesis of libraries of organic compounds of various types; moreover, unlike the solid-phase synthesis, it is possible to determine the structures and purity of intermediates by spectroscopy.[31,32]

The ever increasing interest of researchers in IL is indicated by the considerable growth of the number of publications and patents (from 250 in 2001 to 3800 in 2009) describing the synthesis and properties of IL and also their use in chemistry and chemical engineering (Fig. 1). Different aspects of IL application in organic synthesis have been considered in a number of dedicated reviews[21,33–36] and in the second extended edition of the collection of papers edited by Wasserscheid and Welton 'Ionic Liquids in Synthesis' published in 2008.[19,20] However, strange as it may seem, the data on the features of some important types of organic reactions, in particular, classical reactions involving active methylene compounds (aldol reaction, alkylation, and the Michael, Knoevenagel, Horner–Emmons and other reactions) and 1,3-dipoles ([3+2] dipolar cycloaddition) in the presence of IL have not yet been reviewed.

These reactions proceed through highly polarized [carbanions (**I**), enols (**II**), enamines (**III**), *etc.*] or zwitterion (**IV**) intermediates the stability and the chemical behaviour of which are considerably affected by IL ions.



EWG is an electron-withdrawing group.

This review gives a systematic account of the results of studies into these reactions in the presence of IL used as solvents, catalysts or reagents. In these systems, the reactions of carbon acids and 1,3-dipoles often proceed more selectively and give products in higher yields than under classical conditions, owing to the solvation and stabilization of polar species in ionic media. Moreover, some heterolytic reactions that do not proceed under usual conditions can be performed in the presence of IL.[37]

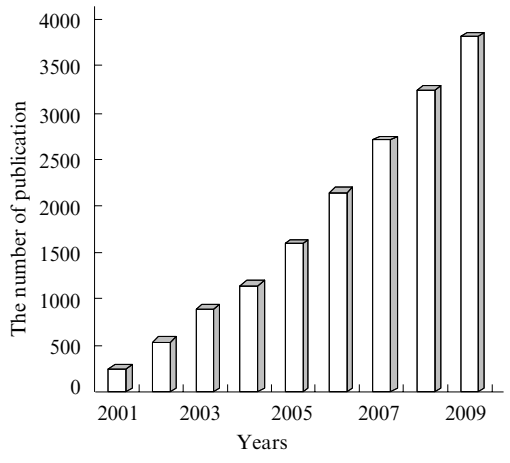


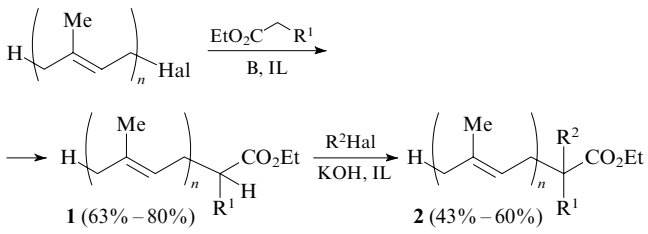
Figure 1. The number of papers and patents with 'ionic liquids' among the key words published in 2001–2009.

II. Reactions of carbon acids in ionic liquids

Many reactions of active methylene compounds are induced by bases. In the IL medium, these reactions have some specific features. On the one hand, the base accelerates deprotonation of the carbon acid, which may result in increase in the reaction rate and, in some cases, also selectivity. On the other hand, strong bases can participate in undesirable side reactions involving IL cations and anions.[38]

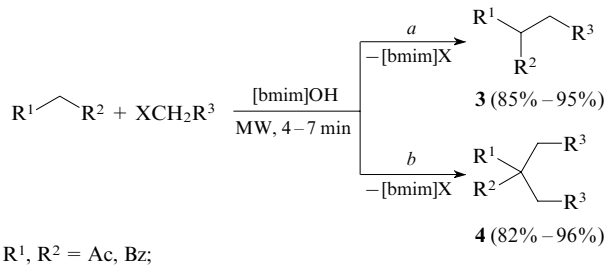
1. Alkylation

Derivatives of malonic, acetoacetic and cyanoacetic acid react with alkyl halides, in particular, those having isoprenoid structure, in 1,3-dialkylimidazolium salts as solvents in the presence of solid bases to give the corresponding C-alkylation products **1**.[39,40] There is no need to use alkali metals or anhydrous solvents; however, exhaustive alkylation of compounds **1** in IL medium can be attained only in the presence of a strong base such as KOH. Despite the fairly drastic conditions (100 °C), practically valuable compounds **2**, which are used to produce isoprenoid wound-healing agents,[41–43] were synthesized in IL medium in 10%–20% higher yields than the yields reported in the literature. Moreover, IL could be recovered and reused at least four times, although signs of IL decomposition induced by the base were noticeable in the last two cycles.



Hal = Cl, Br; n = 1, 2; R^1 = CO_2Et, Ac, CN;
R^2 = cyclo-C_6H_{11}, $(CH_2)_3NMe_2$; B = K_2CO_3, $LiOH \cdot H_2O$;
IL = [bmim][BF_4], [bmim][PF_6].

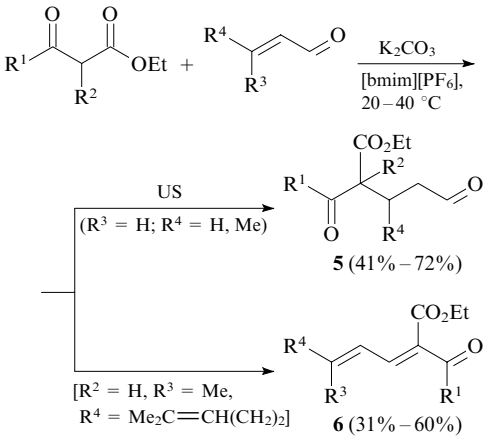
Ionic liquids having basic properties can themselves function as deprotonating agents in the alkylation of carbon acids. For example, 1,3-dicarbonyl compounds and malononitrile react smoothly with alkyl, allyl, propargyl and benzyl halides in 1-butyl-3-methylimidazolium hydroxide ([bmim]OH).[44] The reactions proceed conveniently under the action of microwave radiation (MW), which is fairly effective in ionic medium, the reaction being completed in only 4–7 min. The outcome of the reaction depends on the structure of the carbon acid: acyclic 1,3-diketones form monoalkylated products **3** under these conditions, while cyclic ketones and malononitrile derivatives give dialkylated products **4** in high yields. The reactions do not require an organic solvent (except for the product isolation stage) and the recovered IL can be reused five times. A drawback of this method is considerable consumption of the IL, which is converted to the halide [bmim]X upon the reaction.



(*a*) R^1, R^2 = Ac, Bz;
(*b*) R^1-R^2 = C(O)$(CH_2)_3$C(O), C(O)$CH_2CMe_2CH_2$C(O),
R^1, R^2 = CN, CO_2Et; R^3 = H, Pr^n, CH=CH_2, C≡CH, Ph; X = Br, I.

2. The Michael reaction

In the presence of metal carbonates, α,β-enals containing not more than one substituent at the β-carbon atom of an activated double bond add carbon acids in the [bmim][PF_6] medium to give the Michael adducts **5**.[45,46] However, in the reaction of 3,7-dimethylocta-2,6-dienal (citral) in which the β-carbon atom bears two alkyl groups 1,2-addition products **6** are formed irrespective of the nature of the carbon acid. Sonication during the reaction has a beneficial effect on the yields of the Michael products **5**.

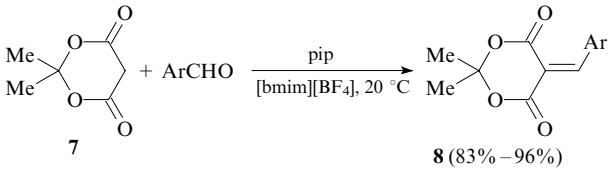


R^1 = Me, OEt; R^2 = H, Me_2C=$CH(CH_2)_2C(Me)$=$CHCH_2$;
R^3 = H, Me; R^4 = H, Me, Me_2C=$CH(CH_2)_2$.

In some cases, the Michael reactions with carbon acids take place in IL containing 1,3-dialkylimidazolium cations without addition of a basic catalyst.[47] A possible explanation is that IL contain an impurity of *N*-methylimidazole, the base used to prepare them, which is difficult to separate. According to kinetic measurements, the basicity of *N*-methylimidazole and piperidine in IL is higher than in usual organic solvents, which naturally affects the reactions carried out in this medium.

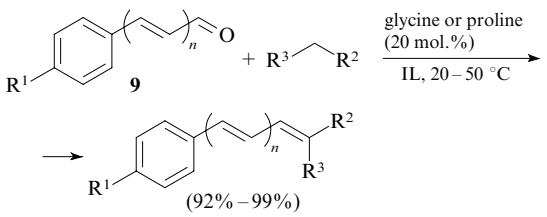
3. The Knoevenagel condensation

The condensation of carbon acids with aldehydeas (the Knoevenagel condensation) is one of the best known and widely used reactions. In organic solvents, this reaction is carried out in the presence of basic catalysts. However, when this reaction was performed in [bmim][PF_6] under the action of a strong base KOH, a considerable portion of the latter (up to 80%) was spent for deprotonation of the 1,3-dialkylimidazolium cation (at C-2), which required the use of a large excess of alkali and made this process non-catalytic.[48] It was found that in polar IL, the Knoevenagel reaction proceeds under milder conditions than in organic solvents with relatively weak deprotonating agents or without a catalyst. For instance, Meldrum's acid (**7**) reacts with aromatic aldehydes in [bmim][BF_4] at room temperature in the presence of a catalytic amount of piperidine (pip) to give the corresponding arylidene derivatives **8** in high yields, and after product isolation, the IL can be reused.[49]



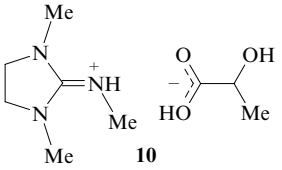
Ar = C_6H_4X (X = 2-Cl, 4-Cl, 2-NO_2, 2-OMe, 4-OMe, 4-OH), PhCH=CH, 2-furyl.

The condensation of benzaldehyde derivatives[50] and their vinylogues[51] **9** with esters of malonic and cyanoacetic acids selectively proceeds in the presence of glycine to give alkenes or dienes. Suitable ionic liquids are 1,3-dimethylimidazolium methyl sulfate ([mmim][$MeSO_4$]) and 1-hexyl-3-methylimidazolium hexafluorophosphate ([hmim][PF_6]). The glycine–IL system is readily separated from the products and can be reused at least 15 times without decrease in the process rate and efficiency. The reaction in the IL [bmim][BF_4] is also catalyzed by another amino acid, proline.[52]

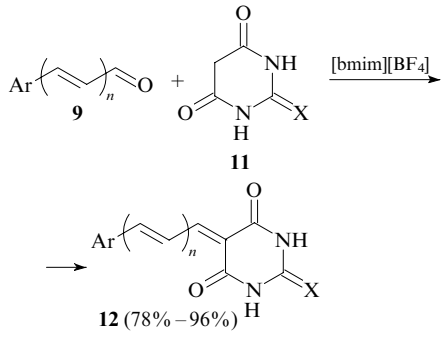


R^1 = H, Cl, Me, OMe, NMe_2; R^2, R^3 = CN, CO_2Me; *n* = 0, 1;
IL = [hmim][PF_6], [mmim][$MeSO_4$].

In some cases, the Knoevenagel condensation proceeds in IL without addition of a catalyst, which may be attributed to the increase in the dissociation constant of the CH acid in IL compared with that in conventional organic solvents.[53] In addition, IL can have catalytic properties due to structural fragments they contain. For example, aromatic aldehydes react with Meldrum's acid (**7**)[54] and with acyclic active methylene compounds[55] in ethylammonium nitrate at room temperature without a base giving rise to the corresponding condensation products in nearly quantitative yields. The Knoevenagel reaction between the aromatic aldehydes **9** (*n* = 0) and malonic or acetoacetic acid derivatives (esters and nitriles) occurs efficiently in a melt of cyclic guanidinium derivative **10**.[56] The procedure of isolation of the products, which are formed selectively and, most often, do not require additional purification, is very simple and the IL can be reused after removal of water (drying *in vacuo*) without decrease in the reaction rate or product yield.



Under mechanical or microwave activation, barbituric and thiobarbituric acids (**11**) react with aldehydes **9** in the [bmim][BF_4] medium without addition of a catalyst to give compounds **12**. For reducing the system viscosity and for effective propagation of electromagnetic radiation, it is sufficient to add not more than 1 equiv. of IL to the reactants.[57]

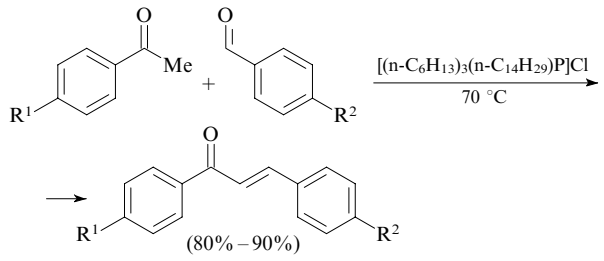


X = O, S; n = 0, 1.

The condensation of aromatic aldehydes **9** (n = 0) with Meldrum's acid proceeds without an additional catalyst in the medium of 1-methylimidazolium trifluoroacetate ([Hmim][TFA]), which has acidic properties.[58] In this case, aldehyde protonation with the IL cation, which increases its electrophilicity, is apparently the driving force of the reaction.

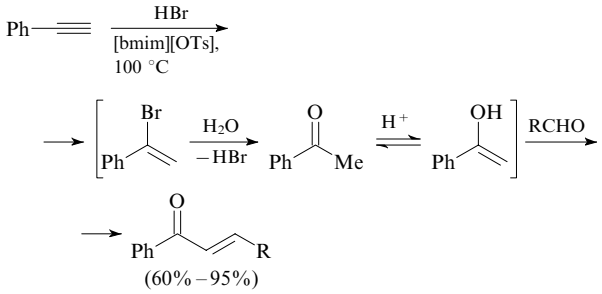
4. Aldol condensation

Exceptionally important condensation reactions of carbonyl compounds (aldol reactions) occur in IL media under mild conditions. For example, acetophenone and its derivatives react with aromatic aldehydes in tetraalkylphosphonium chloride as a solvent at 70 °C to give the corresponding chalcones in high yields.[59] No basic catalyst is required since the IL itself behaves as a base. An advantage of this method include rather mild reaction conditions, easy isolation of products and reuse of the ionic solvent.



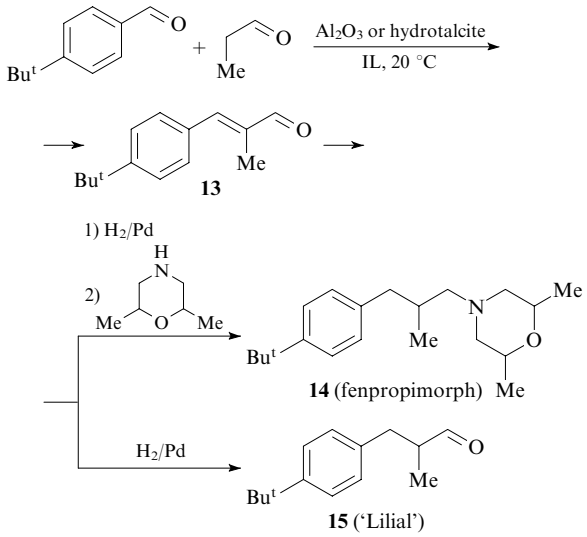
R^1 = H, Cl, NO_2, OH, OMe; R^2 = H, Cl, OH, OMe.

The HBr-catalyzed coupling of phenylacetylene with aldehydes in the [bmim][OTs] medium involves an aldol condensation step. The reaction apparently includes IL-promoted hydrobromination of the alkyne, hydrolysis of the bromoalkene formed to acetophenone, which further reacts with the aldehyde to give the corresponding chalcone.[60] This mechanism was confirmed by identification of α-bromostyrene and acetophenone in the reaction mixture by mass spectrometry. By using IL, one can carry out this reaction without applying hydrolytically unstable metal-containing Lewis acids.



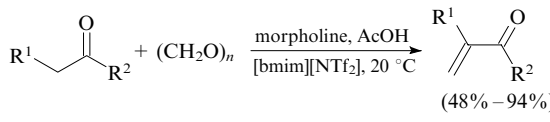
R = C_6H_4X (X = H, 2-Cl, 2-OMe, 3-OMe, 4-Me, 4-Cl, 4-Br, 4-NO_2), $PhCH_2CH_2$.

Aliphatic aldehydes can also serve as nucleophiles in aldol reactions in IL media. For instance, Al_2O_3- (Ref. 61) or hydrotalcite-catalyzed[62] condensation of 4-*tert*-butylbenzaldehyde with propanal in a melt of the [bmim][NTf_2] or [bmpyr][NTf_2] salt (bmpyr is *N*-butyl-*N*-methylpyrrolidinium) led to 3-(4-*tert*-butylphenyl)-2-methylpropenal (**13**), an intermediate for the preparation of compounds **14** and **15**, which are active components of the fungicide fenpropimorph and the perfume Lilial, respectively. The degree of conversion and the selectivity were higher than in the industrial production process of **13** in an organic solvent. It is important that the synthesis and reductive amination of intermediate **13** can be performed as one-pot processes. The IL–catalyst system was separated from amine **14** by decanting and recycled, which made the process much more economically rational.[61]

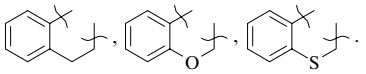


IL = [bmim][NTf_2], [bmpyr][NTf_2].

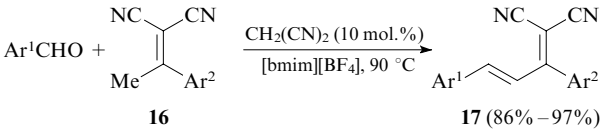
Recently, the possibility of using IL containing 1-butyl-3-methylimidazolium cations as solvents in α-methylenation of carbonyl compounds was demonstrated.[63] The best results were obtained in the [bmim][NTf_2] medium where IL could be used at least seven times without decrease in the product yield. The proposed method markedly increased the reaction rate and selectivity as compared with the known methylenation route of carbonyl compounds in acetic acid (in the absence of IL, the yields were 20%–60%). This method was used to synthesize a broad range of different α-substituted acrolein and vinyl ketone derivatives, in particular, with isoprenoid groups in the molecule.



R^1 = Ph, Bz, Bn, n-C_5H_{11}, $Me_2C{=}CH(CH_2)_2CH(Me)$; R^2 = H, Me, Et, OEt; R^1-R^2 = $(CH_2)_4$,



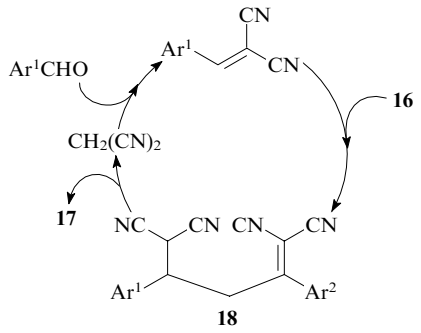
The aldol condensation occurs in the IL medium not only in the presence of acids or bases but also in the presence of other catalysts. The reaction of aromatic aldehydes with 2-(1-arylethylidene)malononitriles **16** in [bmim][BF_4] in the presence of malononitrile (10 mol.%) resulted in 2-[(*E*)-1,3-diarylallylidene)malononitrile derivatives **17**.[64]



Ar^1 = C_6H_4X (X = 2-Cl, 2-NO_2, 2-OMe, 3-NO_2), $C_6H_3Y_2$ [Y_2 = 2,4-Cl_2, 3,4-Cl_2, 3,4-Me_2, 3,4-$(OMe)_2$, 2-NO_2-4-Cl]; Ar^2 = C_6H_4X (X = H, 3-Cl, 4-Cl, 4-Br, 4-F, 4-Me, 4-OMe), 2,4-$Me_2C_6H_3$.

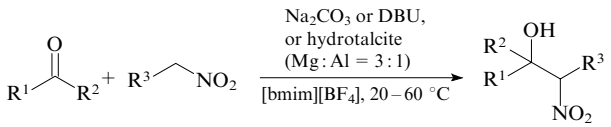
Although elucidation of the detailed reaction mechanism requires additional research, the authors proposed a possible scheme of the catalytic cycle including the Knoevenagel and Michael reaction sequence followed by elimination of malononitrile from intermediate **18** to give product **17** (Scheme 1).

Scheme 1



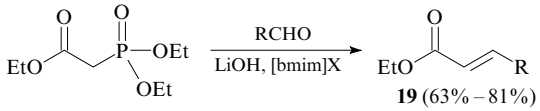
5. Reactions involving carbon acids containing a heteroatom at the active carbon atom

Ionic liquids proved to be promising solvents for nitroaldol reactions between nitroalkanes and carbonyl compounds (the Henry reaction). In the [bmim][BF_4] medium, these reactions can be induced by soft bases such as Na_2CO_3,[65] DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)[66] or basic hydrotalcites[67] to give the corresponding β-nitro alcohols in high yields. This reaction can be performed with various aldehydes and ketones; the IL can be readily separated from the products and reused (up to four cycles). Unfortunately, the nitroaldol reaction in IL is not diastereoselective: processes involving nitroethane afford a nearly equimolecular mixture of diastereomeric products (*syn* : *anti* = 44 : 56).[65] In a 1,1,3,3-tetramethylguanidinium lactate melt[68] and in IL with the chloroaluminate anions,[69] the nitroaldol reaction takes place without addition of a catalyst.

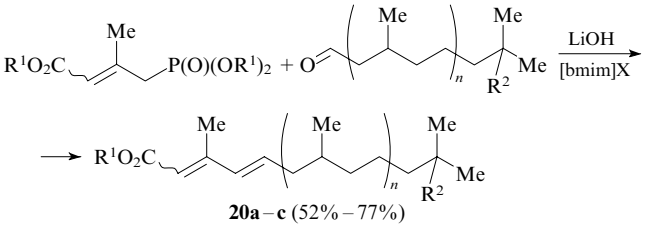


R^1 = H, Me; R^2 = Ph, 4-$NO_2C_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, Et, Bu^n; R^1-R^2 = $(CH_2)_3$, $(CH_2)_4$; R^3 = H, Me.

Yet another convenient method for the formation of carbon – carbon bonds is the Horner – Emmons reaction involving phosphorylated CH acids. Activated phosphonates and allylphosphonates react with aldehydes in the presence of LiOH in melts of 1-butyl-3-methylimidazolium salts with fluorine-containing anions to give the corresponding acrylates **19** and dienoic esters **20**.[70, 71] This method is suitable for the preparation of compounds with practically valuable properties. This was used to synthesize, in particular, the analogues of bean spider mite chemosterilant (**20a**) and insect juvenile hormone, hydroprene (**20b**) and methoprene (**20c**).[72, 73] Note that the double bond in products **19** and **20** is *trans*-confugured and the reaction selectivity and product yields do not decrease after five uses of IL.



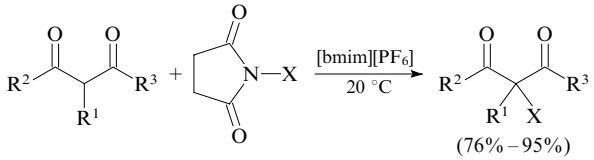
R = $Me_2CH(CH_2)_2$, Ph, PhCH=CH, cyclo-C_3H_5, 2-2-pyridyl, $Me_2C{=}CH(CH_2)_2CH(Me)CH_2$.

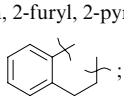


X = BF_4, PF_6; R^1 = Et, R^2 = H: *n* = 0 (**a**), 1 (**b**); R^1 = Pr^i, R^2 = OMe, *n* = 1 (**c**).

6. Halogenation reactions

α-Halogenation of carbonyl compounds can be carried out in IL. For example, 1,3-diketones or β-ketoesters reacted with *N*-halosuccinimides in [bmim][PF_6] to give the respective chlorination, bromination or iodination products in good yields.[74]



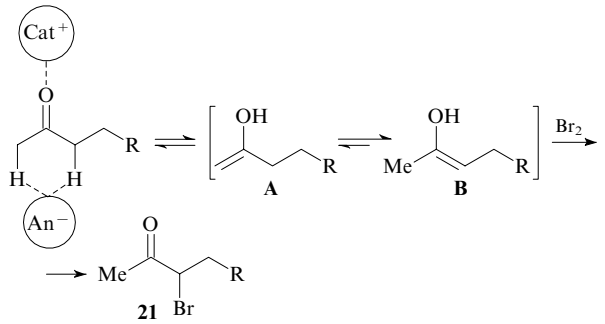
R^1 = H: R^2 = Me, Pr^i, Bu^t, Ph, 2-furyl, 2-pyridyl;
R^3 = OMe, OEt, OBn, Ph;
R^3 = OEt: R^1-R^2 = $(CH_2)_4$, ; X = Cl, Br, I.

The reactions occur at room temperature without catalyst addition. The α-halo ketones poorly soluble in hydrophobic IL were extracted with diethyl ether, the remaining IL was washed with water to remove the by-product (succinimide) and reused at least four times without noticeable decrease in

the product yield. A similar reaction was carried out for cycloalkanones.[74]

α-Chlorination and α-bromination of alkyl aryl ketones in [bmim][BF_4] proceed efficiently under the action of the *N*-halosuccinimide – urea – hydrogen peroxide system. In this case, true halogenating agents are apparently hypochlorous and hypobromous acids formed *in situ*.[75]

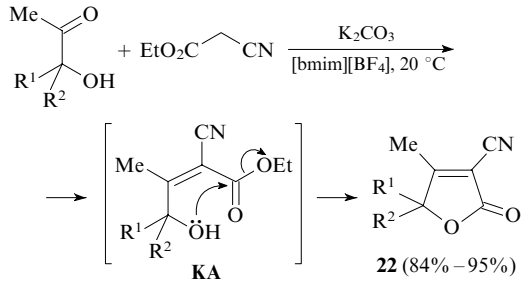
A possible explanation to the observed effect of highly polar IL on the reactions of carbonyl compounds is that they accelerate their enolization and change the ratio of enol isomers **A** and **B** in the reaction mixture. A practical outcome is the possibility to increase the regioselectivity and in some cases change the bromination site of unsymmetrical methyl ketones, including levulinic acid derivatives, with molecular bromine by directing the process towards the formation of internal α-bromo ketones **21**.[76]



R = Pr^n, CO_2H, CO_2Me, CO_2Bu^n; IL = [Cat^+][An^-].

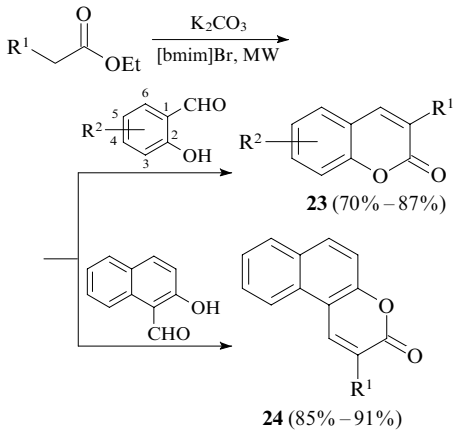
7. Domino reactions

When the reactant molecules contain appropriately arranged functional groups (in particular, hydroxy groups), transformation sequences (domino reactions) initiated by the starting reaction (usually the Knoevenagel condensation), resulting in valuable cyclic and polycyclic compounds, can be effected in IL. For instance, a one-step synthesis of 5,5-dialkyl-4-methyl-2-oxo-2,5-dihydrofuran-3-carbonitriles (butenolides) **22** by K_2CO_3-catalyzed reaction of α-hydroxy ketones with ethyl cyanoacetate in [bmim][BF_4] was described.[77] The reaction proceeds evidently through the Knoevenagel adducts (**KA**), which cyclize to the target heterocycles **22** under these conditions. The use of IL as the solvent led to higher product yields and simpler workup of the reaction mixture. The IL – K_2CO_3 system can be readily recovered and used in the reaction at least four times. This reaction is very important as the butenolide fragment is a part of many biologically active compounds, including vitamin C, acetogenins and related cardenolides.[78 – 80]



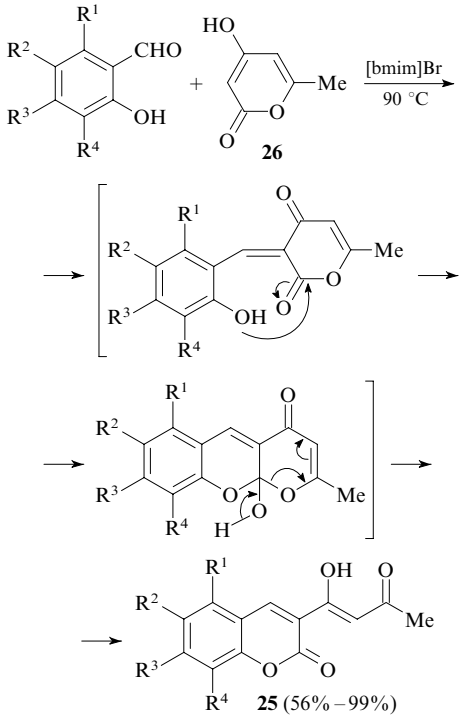
R^1 = Me, cyclo-C_6H_{11}; R^2 = Me, Et, All, Bn.

Potash-catalyzed condensation of active methylene compounds (β-diesters, β-keto esters, *etc.*) with salicylaldehyde derivatives in the [bmim]Br medium follows a similar route. This reaction proceeds under mild conditions and selectively produces substituted coumarins **23** and **24** in high yields.[81] Under microwave irradiation of the reaction mixture, the reaction time is reduced to 1 – 2 min.



R^1 = CN, Ac, CO_2Et; R^2 = H, 5-OH, 5-NEt_2, 4-OMe (the numbering is given for the starting aldehyde).

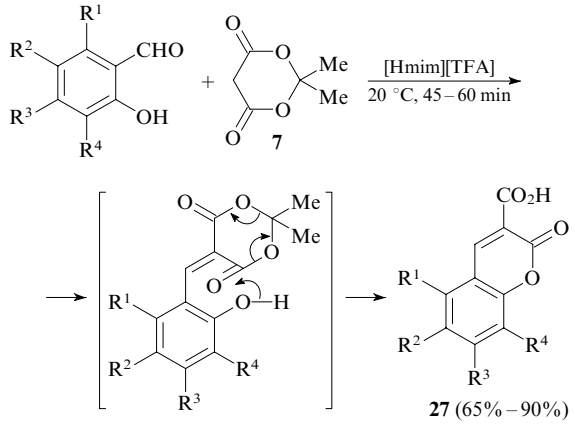
The ionic liquid [bmim]Br was successfully used in the syntheses of 3-acetoacetylcoumarin derivatives **25** based on the domino reaction of substituted 2-hydroxybenzaldehydes with 4-hydroxy-6-methyl-2*H*-pyran-2-one (**26**). This reaction takes place without a basic catalyst, which is apparently caused by high dissociation constant of carbon acid **26** in ionic medium.[82] Unfortunately, the procedure proposed by the authors does not imply recovery and reuse of the IL.



R^1, R^2, R^3, R^4 = H, Cl, Br, OMe, Me, Bu^t.

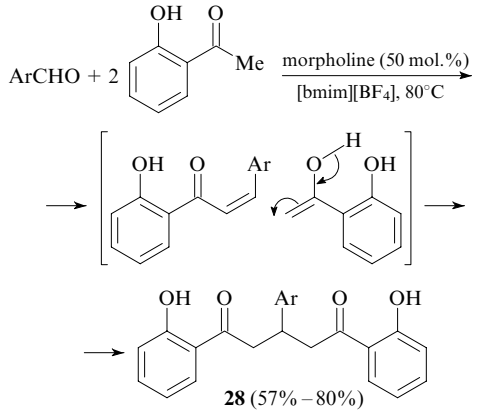
Yet another example of application of IL in domino reactions that include the condensation, cyclization and ring

transformation steps is the synthesis of 3-carboxycoumarin derivatives **27** from 2-hydroxybenzaldehydes and Meldrum's acid (**7**).[83] In this case, the reaction rate and the product yields are maximum when the IL used is the 1-methylimidazolium trifluoroacetate exhibiting acidic properties. The aqueous solution of IL remaining after separation of precipitated products was dried *in vacuo* and the IL recovered in this way was recycled; this procedure repeated four times did not lead to any decrease in the IL activity.



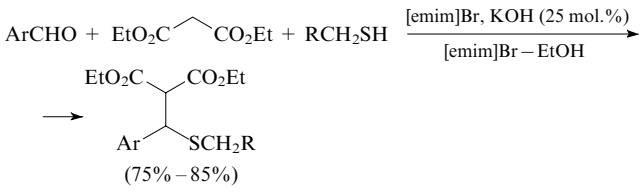
R^1, R^2, R^3, R^4 = H, OH, Cl.

Ionic liquids are effective not only for two-component but also for multicomponent domino reactions of CH acids, which allow one-pot syntneses of complex polyfunctional, in particular, cyclic and heterocyclic compounds. Chinese researchers developed a convenient method for the synthesis of 1,3,5-triarylpentane-1,5-dione derivatives **28** containing hydroxy groups in the *ortho*-positions of two of the three aromatic nuclei by the morpholine-catalyzed domino reaction of aromatic aldehydes with two 2-hydroxyacetophenone molecules in [bmim][BF_4].[84] The process includes successive aldol condensation and the Michael reaction. Products **28** are valuable starting compounds for the preparation of practically important 2,4,6-triarylpyridines.



Ar = C_6H_4X (X = 2-Cl, 2-Br, 2-OMe, 3-NO_2, 4-Cl, 4-Br, 4-Me, 4-OMe, 4-CN, 4-NO_2).

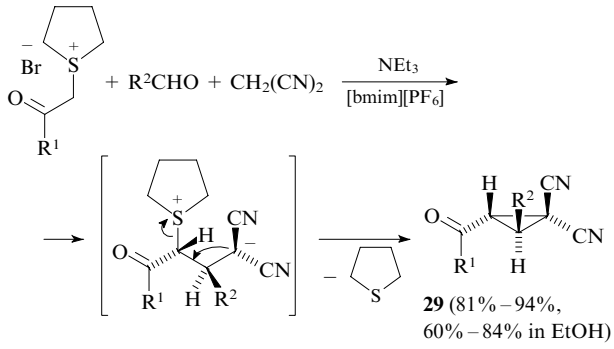
1-Ethyl-3-methylimidazolium bromide proved to be an excellent solvent in a three-component synthesis of sulfur-containing derivatives of malonic acid from aldehydes, diethyl malonate and alkanethiols in the presence of KOH.[85]



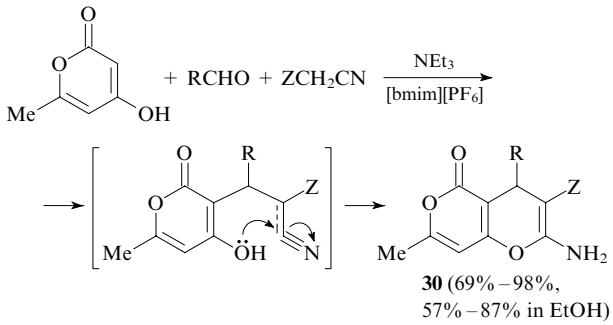
Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 2-furyl; R = CH_2CO_2Me, 2-furyl.

Presumably, the reaction starts from the formation of the Knoevenagel adduct from diethyl malonate and aldehyde followed by the Michael addition of the adduct to the thiol present in the system. In the author's opinion, the true catalyst is 1-ethyl-3-methylimidazolium hydroxide ([emim]OH) generated *in situ* from the corresponding bromide and KOH. Note that the IL introduced in the reaction was diluted with ethanol (2 : 1 by volume), probably, to reduce the viscosity of the reaction mixture.

We successfully used imidazolium ionic liquids in the three-component stereoselective syntheses of 1,1-dicyanocyclopropane derivatives **29** (Ref. 86) and for the preparation of functionally substituted 4,5-dihydropyrano[4,3-*b*]pyrans **30**.[87] The yields of compounds **29** and **30** were noticeably higher in [bmim][PF_6] than in EtOH; moreover, IL became more efficient after the recovery, apparently, due to product accumulation in it. In some cases, the reactions took place without addition of a base, IL itself functioning as the catalyst.[87]



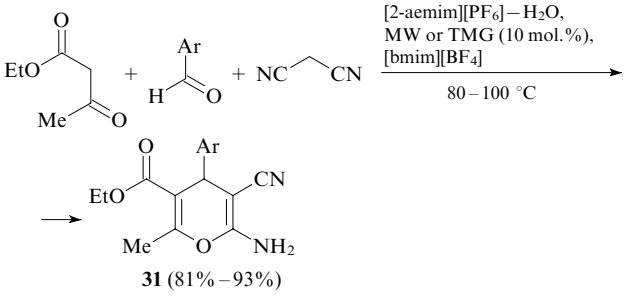
R^1 = Ph, 1-adamantyl; R^2 = 4-$MeOC_6H_4$, 2-FC_6H_4, 3,4-$F_2C_6H_3$, 2,3,4-$(MeO)_3C_6H_2$, Pr^i.



R = 4-$MeO_2CC_6H_4$, 2-FC_6H_4, 4-$CF_3C_6H_4$, 2,4-$F_2C_6H_3$, 3,4-$F_2C_6H_3$, 4-$CF_3SC_6H_4$; Z = CN, CO_2Et.

The catalytic properties of IL in multicomponent reactions of carbon acids were demonstrated also in a number of later publications. Chinese researchers developed an effective environmentally safe method for the synthesis of 4*H*-pyran derivatives **31** by three-component condensation of ethyl acetoacetate, malononitrile and aromatic aldehydes in an aqueous solution of 1-(2-aminoethyl)-3-methylimida-

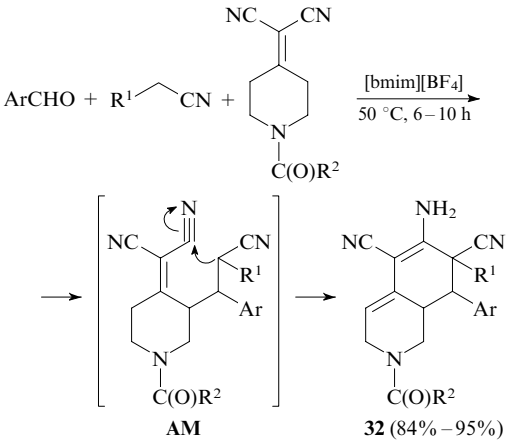
zolium hexafluorophosphate ([2-aemim][PF_6]) (40 vol.% H_2O) under microwave radiation.[88] This reaction can also proceed in the commercially available IL [bmim][BF_4]; however, in this case, the addition of a catalyst, 1,1,3,3-tetramethylguanidine (TMG), to the system is required.[89]



31 (81% – 93%)

Ar = C_6H_4X (X = H, 3-NO_2, 4-CN, 4-Cl, 4-OH, 4-OMe), 2,4-$Cl_2C_6H_2$.

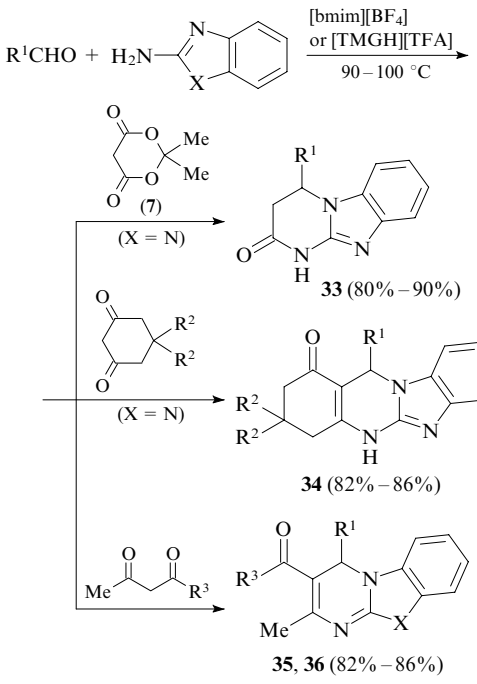
A series of new polyfunctional isoquinoline derivatives **32** were prepared by the reaction of 2-(piperidin-4-ylidene)-malononitrile derivatives with aromatic aldehydes and malononitrile or methyl cyanoacetate in the [bmim][BF_4] medium.[90] The proposed method differs from the known methods by the use of IL as both the solvent and the promoter and by the fact that the reaction gives rise to a carbocyclic rather than a pyridinium fragment of isoquinoline. As in the syntheses of compounds **29** – **31**, the reaction occurs without addition of a basic catalyst, IL acting as such. On the basis of experimental data, a possible reaction mechanism including the formation of a Michael adduct (**MA**) and its cyclization to isoquinoline derivative **32** was proposed.



AM **32** (84% – 95%)

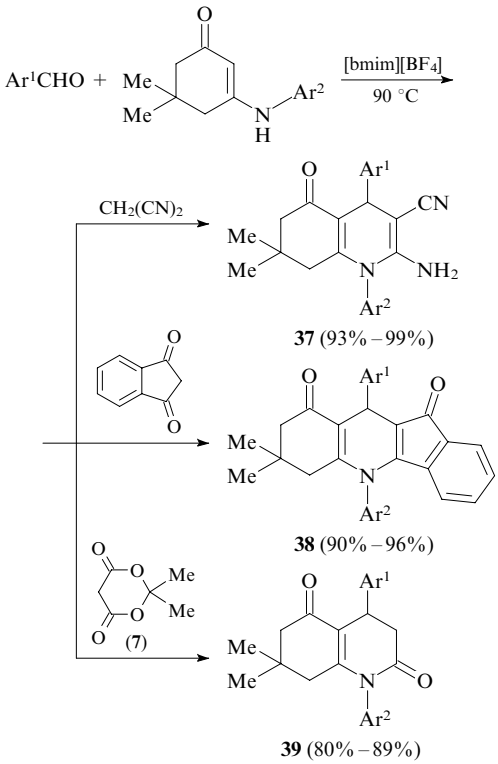
Ar = C_4H_4X (X = H, 2-F, 2-Cl, 2-Br, 2-CN, 3-Cl, 3-Br, 4-Cl, 4-Br, 4-F, 4-NO_2); $C_6H_3Y_2$ [Y_2 = 2,4-Cl_2, 2,3-Cl_2, 3,4-Cl_2, 2,3-$(OMe)_2$]; R^1 = CN, CO_2Me; R^2 = OEt, 3-ClC_6H_4.

Ionic liquids [bmim][BF_4] (Ref. 91) and [TMG][TFA] (TMG is 1,1,3,3-tetramethylguanidinium[92]) were used as reaction media in the facile and efficient syntheses of benzimidazole **33** – **35**[91] and benzothiazole **36** derivatives[92] by three-component condensation of aromatic aldehydes, 1,3-dicarbonyl compounds and 2-aminobenzimidazole (-thiazole). The precipitated products are readily filtered off to be separated from the IL, which can be recycled after vacuum drying.



R^1 = C_6H_4Y (Y = H, 2-F, 3-Br, 3-NO_2, 4-NO_2, 4-Me, 4-OMe, 4-F, 4-Br), 3,4-$(OCH_2O)C_6H_3$, 3,4,5-$(OMe)_3C_6H_2$, 2-furyl; R^2 = H, Me; R^3 = Me, OEt; X = NH (**35**), S (**36**).

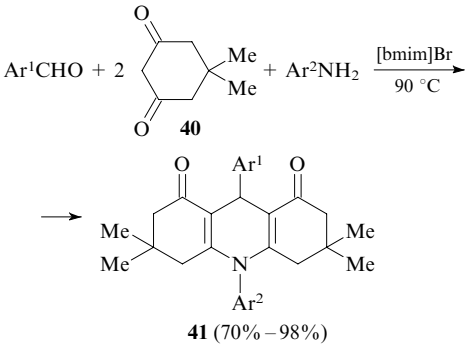
Three-component condensation of aromatic aldehydes, 3-arylamino-5,5-dimethylcyclohex-2-enone and active methylene compounds (malononitrile or 1,3-dicarbonyl compounds) in the [bmim][BF_4] medium at 90 °C resulted in *N*-arylquinoline derivatives **37** – **39**, representatives of the class of heterocycles having diverse biological activities.[93,94]



Ar^1 = C_6H_4X (X = H, 2-Cl, 3-Cl, 3-NO_2, 4-Cl, 4-Br, 4-F, 4-Me, 4-OH, 4-NO_2); $C_6H_3Y_2$ [Y_2 = 2,4-Cl_2, 3,4-Cl_2, 3,4-$(OMe)_2$, 2-NO_2-4-Cl]; Ar^2 = C_6H_4X-4 (X = H, Br, Me).

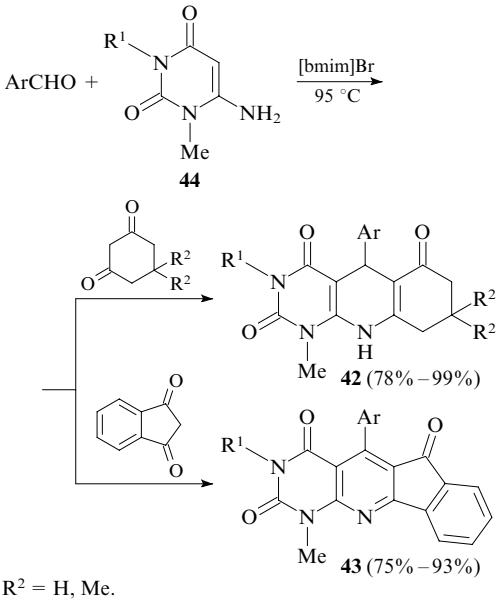
By performing these reactions in IL, it was possible to implement them as one-pot processes and synthesize the target products in high yields. In all cases, reactions proceeded without a base.

In some cases, IL with halide anions were used as solvents in multicomponent reactions of carbon acids. For example, 1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione derivatives **41**, which like compounds **37**–**39** are of interest for their biological activities, were prepared in one experimental stage by four-component reaction of aldehydes with aniline derivatives and two dimedone molecules (**40**) in a [bmim]Br melt.[95] Products **41** were filtered off and the IL was purified from wash water by heating *in vacuo* and reused.



Ar^1 = C_6H_4X-4 (X = Br, Cl, Me, OMe, NMe_2), $C_6H_3Y_2$ [Y_2 = 3,4-Cl_2, 3,4-$(OMe)_2$, 3,4-OCH_2O], 2-thienyl, 3-pyridyl; Ar^2 = C_6H_4X (X = 2-Me, 4-Cl, 4-F, 4-OMe).

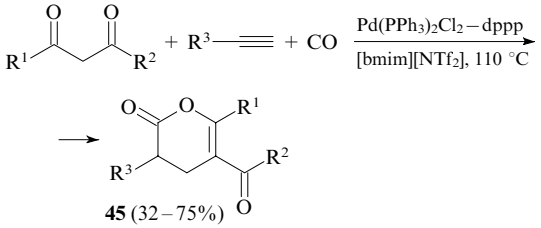
1-Butyl-3-methylimidazolium bromide proved to be an effective medium for the synthesis of pyrimido[4,5-*b*]quinoline derivatives **42** and indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine **43** by means three-component condensation of aromatic aldehydes, 6-aminopyrimidine-2,4-diones **44** and cyclic 1,3-diketones.[96] Under the proposed conditions, a one-pot cascade of transformations takes place resulting in the target heterocycles **42** or **43** in 99% overall yield. These products can be considered as derivatives of uracil, a component of ribonucleic acids.



R^1, R^2 = H, Me.

8. Reactions catalyzed by metal complexes

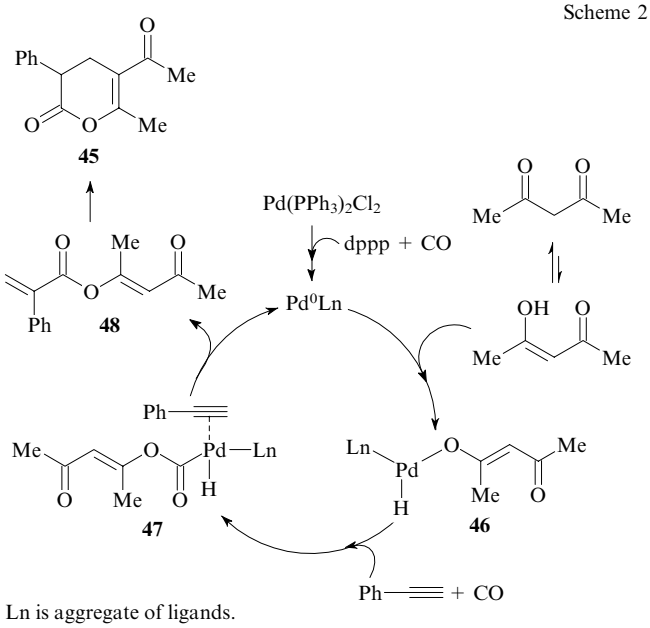
There are only a few examples of using metal complex catalysts in the reactions of 1,3-dicarbonyl compounds in the IL medium. One example is three-component synthesis of substituted lactones **45** from β-dicarbonyl compounds, alkynes and carbon oxide catalyzed by Pd phosphine complex.[97] It was found that in the [bmim][NTf_2] medium, this reaction is highly regioselective and gives products **45** in reasonable yields; these products are valuable intermediates in organic synthesis and the source of important structural fragments of natural compounds. In organic solvents, in particular, in dichloroethane, DMF and MeCN, the yields of lactones **45** were substantially lower (< 26%). Moreover, unlike these solvents, the catalyst–IL system was recycled 5 times without decreasing the product yield, although to attain the same result with the recycled catalyst, longer reaction time was required, *i.e.*, the catalyst activity gradually decreased.



R^1, R^2 = Me, Ph; R^3 = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 2-$CF_3C_6H_4$, Bn, $AcO(CH_2)_4$, $NC(CH_2)_3$; dppp is 1,3-bis(diphenylphosphino)propane.

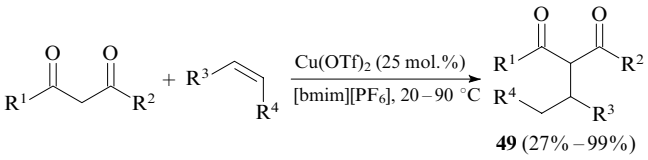
It is assumed that the catalytic reaction cycle includes the reduction of $Pd(PPh_3)_2Cl_2$ to Pd^0, oxidative addition of the enol form of 1,3-diketone to the Pd^0 complex to give intermediate **46**, which is converted to complex **47** upon coordination to the alkyne triple bond and insertion of CO. The regioselective intramolecular acylpalladation of the latter followed by reductive elimination furnish linear intermediate **48** and recover the catalyst active form. The intramolecular cyclization of vinyl acetate **48** involving the activated double bond results in six-membered lactone **45** (Scheme 2).

Scheme 2



Ln is aggregate of ligands.

The $Cu(OTf)_2$–[bmim][PF_6] system permitted regioselective addition of β-diketones to alkenes, in particular, to styrene, norbornene, cyclic enol and diene to give adducts **49** in moderate to high yields.[98]

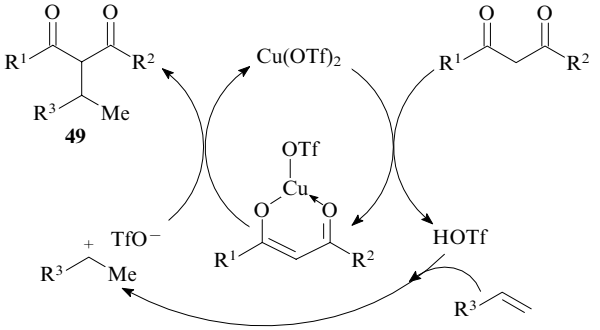


49 (27%–99%)

R^1, R^2 = Me, Ph, OMe; R^3 = Ph, 4-MeC_6H_4, 4-ClC_6H_4; R^4 = H; R^3–R^4 = $O(CH_2)_3$, CH=CHCH_2, pentane-1,3-diyl.

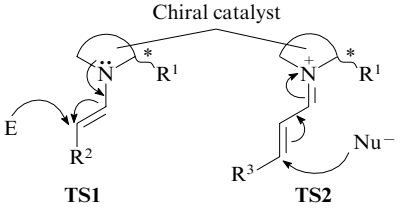
Among organic solvents, only dioxane is a satisfactory alternative to the IL in this reaction. Presumably, $Cu(OTf)_2$ activates the enol form of β-diketone and acts as a source of HOTf needed for alkene protonation. The proposed mechanism is shown in Scheme 3 for R^4 = H.

Scheme 3



9. Enantioselective reactions

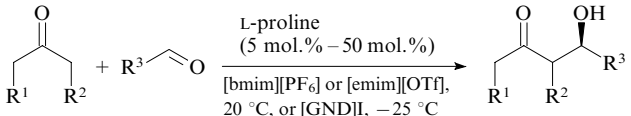
The use of IL as solvents in enantioselective reactions of active methylene, first of all carbonyl, compounds carried out in the presence of chiral organocatalysts has become a widely used practice in recent years.[22, 99, 100] These reactions usually involve transition states **TS1** or **TS2**, which include asymmetric enamine or iminium intermediates formed from the carbonyl compound and a chiral catalyst (an amino acid, amino alcohol, amine, *etc*.) and an electrophile or nucleophile, respectively, present in the system.[101–107] The IL that specifically solvate polar associates **TS1** and **TS2** usually increase the reaction rates, while retaining or slightly decreasing their enantioselectivities.[108] In addition, many organocatalysts are readily soluble in IL and are not 'washed out' to the organic phase during the isolation of products, which allows the recovery of the catalyst–IL system.[33, 109]



TS1 **TS2**

a. Enantioselective aldol reactions

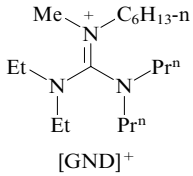
The asymmetric aldol reactions in an IL medium proceeding through transition state **TS1** in which one of the two reactants acts as the electrophile are best studied. In 2002, Slovak [110] and Chinese researchers [111] found independently that acetone and cycloalkanones react with aromatic aldehydes in the presence of L-proline in molten 1,3-dialkylimidazolium salts containing BF_4^- and PF_6^- anions to give aldols **50** in 55%–94% yields and enantiomeric excess of up to 93% *ee*, which is comparable with characteristics of these reactions in DMSO. In the case of cycloalkanones, the reaction was highly *anti*-diastereoselective: the *anti*:*syn*-diastereomer ratio in aldols **50** was in some cases more than 20:1.



50 [55%–94%, *dr* (*syn*:*anti*) = (1:1)–(>20:1), (*anti*) 46%–99% *ee*]

R^1 = H: R^2 = H, OH, OMe, Cl, F; R^1 = Me, R^2 = H; R^1–R^2 = $(CH_2)_n$, (n = 1–3); R^3 = C_6H_4X (X = H, 3-NO_2, 4-NO_2, 4-F, 4-CN, 4-CF_3, 4-OMe), 2-pyridyl, 3-pyridyl, 4-pyridyl, Pr^i, Bu^t.

Heteroaromatic aldehydes also enter this reaction.[112] An important role is played by the IL nature: the yield and enantiomeric excess of aldols **50** (R^1 = R^2 = H) in proline-catalyzed reactions of acetone with aldehydes increased (up to 99%) when the reactions were conducted in hexa- and pentaalkylguanidinium salts, for example, [GND]I.[113]

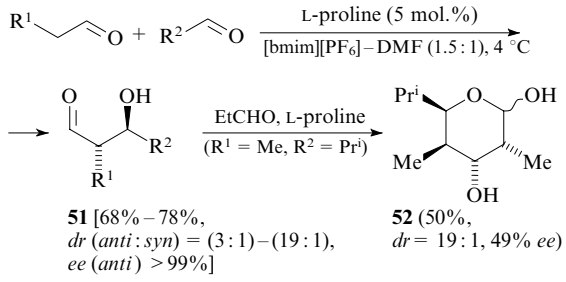


[GND]$^+$

Minor amounts of salts of trifluoroacetic acid and/or water (up to 10 equiv.) added to the system may have beneficial effect on the reaction diastereoselectivity.[114]

The regiodirection of the proline-catalyzed aldol reactions involving unsymmetrical ketones in IL depends on their structure: butan-2-one reacts at the methyl group,[110] while ketones containing a heteroatom in the α-position to the carbonyl group react at the heteroatom-linked methylene group.[115] In the latter case, the best results were attained in the [emim][OTf] medium.

In the presence of IL, proline-catalyzed cross-aldol reactions between aliphatic aldehydes are markedly accelerated and have exceptionally high enantioselectivity (up to 99% *ee*).[116] Indeed, the yields of aldols **51** in the [bmim][PF_6]–DMF system (1.5:1 by volume) are 10%–20% higher than in the reactions carried out without IL. Under the found conditions, aldols can react with a third aldehyde molecule to give, for example, hydroxy pyran **52**. The proline–[bmim][PF_6]–DMF system was used five times without decrease in the reaction yields and selectivities.

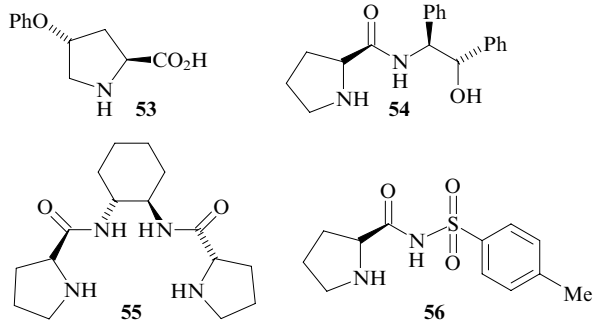


51 [68%–78%, *dr* (*anti* : *syn*) = (3 : 1)–(19 : 1), *ee* (*anti*) >99%]

52 (50%, *dr* = 19 : 1, 49% *ee*)

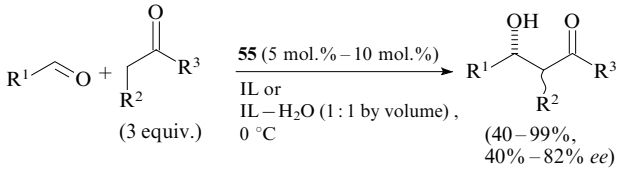
R^1 = Me, Bu^n; R^2 = Me, Et, Pr^i, Bu^i, cyclo-C_6H_{11}.

The aldol reactions carried out in [bmim][BF_4] or [bmim][PF_6] can be catalyzed by proline derivatives, including *trans*-4-phenoxy-L-proline (**53**),[117] and proline amide **54**,[118] bisamide **55**[119] and sulfonylated amide **56**.[120] The use of highly effective amide catalysts **54** and **55** resulted in increase in the reaction rate and extended the scope of the reaction.



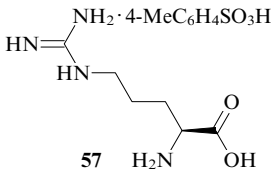
53 **54** **55** **56**

For example, the bisamide **55**-catalyzed aldol reactions between aldehydes and ketones in [bmim][BF_4] require a much lower excess of the donor ketone (3 equiv. instead of 30 equiv. in proline-catalyzed reactions) and allow the synthesis of chiral derivatives of heterocycles, isoprenoids and metallocenes difficult to prepare by other methods.[119] It is of interest that dilution of IL with water (1 : 1 by volume) increases the reaction rates and product yields, the enantioselectivity being retained or even becoming higher (up to 82% *ee*).[121]



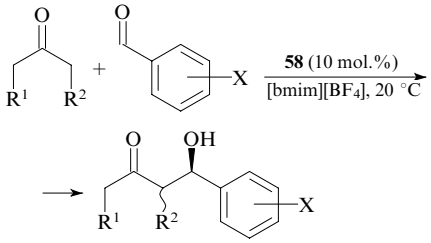
IL = [bmim][BF_4]; R^1 = Ar, Het, cymantrenyl; R^2 = H, OH; R^3 = Me, Et, cyclo-C_3H_5, $(CH_2)_2CH{=}CMe_2$; $R^2–R^3$ = $(CH_2)_n$ (n = 3, 4).

Asymmetric aldol reactions in the IL media can also be induced by derivatives of α-amino acids other than proline. An example of this type of catalyst is the salt of arginine with *p*-toluenesulfonic acid (PTSA) **57**. In the presence of an aqueous solution of catalyst **57** (10 mol.%), aldol reactions of aromatic aldehydes with cyclic ketones in the [bmpyr][OTf] medium give products in higher yields than in DMSO.[122] The catalytic system salt **57**–[bmpyr][OTf] was recovered and reused two times, the aldol yield decreasing by 10% in every subsequent run; however, after the third recovery, the conversion halved and the enantioselectivity decreased by 20%.



57

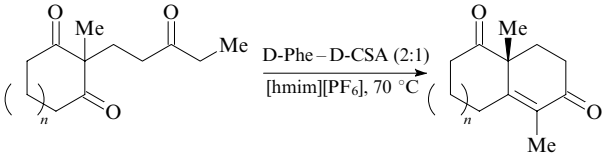
Recently, researchers from Singapore[123] found that the silyl ether of L-serine [L-$Bu^tPh_2SiOCH_2CH(NH_2)CO_2H$, **58**] catalyzes the asymmetric aldol reaction between ketones and aromatic aldehydes in the [bmim][BF_4] medium. The system ether **58**–[bmim][BF_4] withstood four recovery cycles with only a minor decrease in the enantioselectivity and the product yield.



[42%–86%, *dr* (*anti* : *syn*) = (52 : 48)–(88 : 12), (*anti*) 41%–92% *ee*]

R^1 = R^2 = H; $R^1–R^2$ = $(CH_2)_2$, $(CH_2)_3$; X = H, 3-NO_2, 4-NO_2, 4-Cl, 4-CN, 4-OMe, 3,4-benzo.

The intramolecular aldol reactions can also be carried out in IL. An example of these transformations is the synthesis of the Wieland–Miescher ketone analogues **59** from triketones induced by the catalytic system D-phenylalanine (D-Phe)–D-camphorsulfonic acid (D-CSA) (in 2 : 1 molar ratio). Product **59** was obtained in a [hmim][PF_6] solution in high yield (87%) and with reasonably high enantioselectivity (*ee* 86%).[124] In this case, too, the D-Phe–IL system can be used at least five times with retention of its activity and enantioselectivity of the reaction.



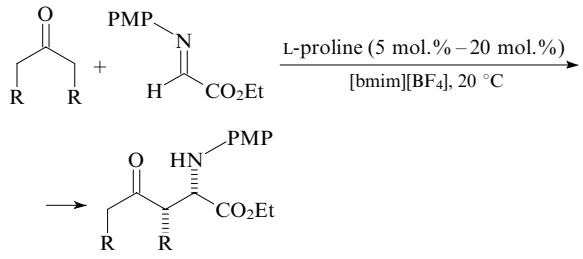
n = 0, 1.

59 (87%, 86% *ee*)

b. Enantioselective Mannich reactions

The proline-catalyzed asymmetric reactions of ketones with aldimines and three-component condensations involving a ketone, an aldehyde and an aniline derivative (the Mannich reactions) occur efficiently in IL media. Thus in the presence of proline (5 mol.%), *N*-PMP-protected ethyl α-iminoacetate reacts with acetone or cyclohexanone in [bmim][BF_4] at room temperature to afford chiral adducts **60** in high yields and enantioselectivities.[125] Unlike the products of aldol reactions, adducts **60** have predominantly *syn*-configuration.[126] The use of IL resulted in a 4–50-fold increase in the process rate compared with the same reac-

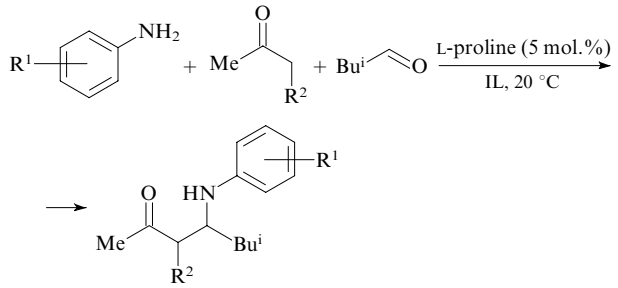
tions in organic solvents; the proline–IL system was reused (four runs) without loss in the *ee* values of products **60**.



60 [80% – 99%, *dr* (*syn* : *anti*) = > 19 : 1, (*syn*) 97% – 99% *ee*]

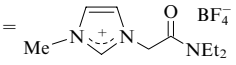
R = H, R – R = $(CH_2)_3$; PMP = 4-$MeOC_6H_4$.

The aldimine component of the Mannich reaction can be generated directly in the IL medium from aldehydes and amino compounds. In this case, good results were obtained by using IL containing amide groups that belonged to the class of task-specific ionic liquids.[32, 127] Under these conditions, proline-catalyzed (5 mol.%) three-component reaction of aniline derivatives with methyl ketones and isovaleric aldehyde gave Mannich adducts **61** in one experimental step in high yield and reasonable enantioselectivity (78% – 99% *ee*).[128] An exception is provided by reactions involving *ortho*-substituted arylamines whose enantioselectivity is much lower (28% – 33% *ee*). The reaction of butan-2-one is not diastereoselective under the proposed conditions. The possibility of recycling of this catalytic system was demonstrated.



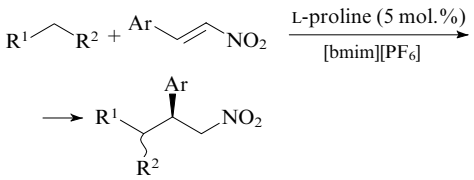
61 (72% – 96%, 28% – 99% *ee*)

R^1 = H, 2-Cl, 2-Me, 3-Cl, 3-CF_3, 4-Cl, 4-F, 4-Me; R^2 = H, Me;

IL = 

c. Enantioselective Michael reactions

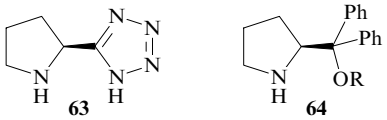
An asymmetric Michael reaction in the IL medium was first carried out by Toma and co-workers,[129] who added carbonyl and 1,3-dicarbonyl compounds to β-nitrostyrene and β-(nitrovinyl)thiophene in [bmim][PF_6] in the presence of proline (5 mol.%) and thus obtained the corresponding Michael adducts **62** in moderate to high yields and in some cases with rather high *syn*-diastereoselectivities. The reaction enantioselectivities were, however, rather low: the enantiomeric excess did not exceed 60%. The reactivity of carbon acids under the reaction conditions studied decreased in the sequence aldehydes > ketones > 1,3-diketones.



62 [11% – 93%, *dr* (*syn* : *anti*) = (3 : 2) – (25 : 1), *ee* (*syn*) = 3% – 60%]

R^1 = CHO: R^2 = Me, Et, Pr^i, Bn; R^1 = H, Me: R^2 = Ac, C(O)Bu^i, C(O)Bu^t; R^1 = CO_2R, R^2 = CN; R^1 = R^2 = Ac, Bz, CN; $R^1 – R^2$ = $C(O)(CH_2)_n$ (*n* = 3 – 5); Ar = Ph, 2-thienyl.

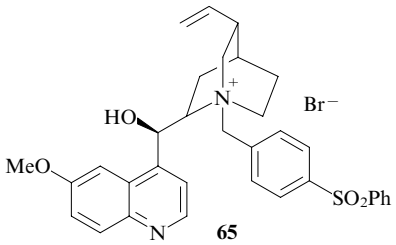
Subsequently this reaction was studied in the presence of various organocatalysts and IL. Apart from proline,[130] sulfonylated proline amide **56** [131] and pyrrolidine derivatives **63** and **64** were used as catalysts.[132] The *ee* values of the products were relatively low with rare exceptions. An effect of IL on the transition state is indicated by the fact that in some cases, the sign of optical rotation of the product can be changed by varying the IL anion.[132]



63 **64**

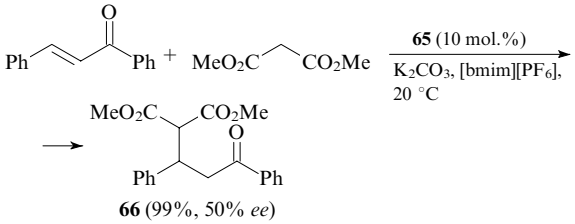
R = H, $SiMe_3$.

At least one example of asymmetric addition of carbon acids to α,β-unsaturated ketones in IL was published. Dimethyl malonate reacts with chalcone (benzylideneacetophenone) under the action of potassium carbonate in the [bmim][PF_6] medium in the presence of quinine salt **65**



65

as the chiral phase transfer catalyst to give adduct **66** in high yield;[133] IL can be recovered and reused two more times.

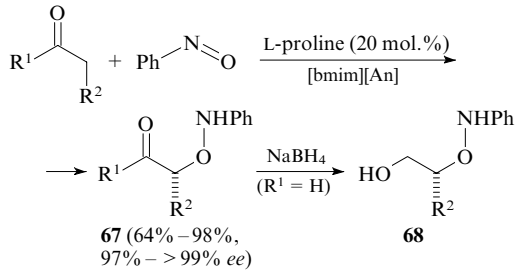


66 (99%, 50% *ee*)

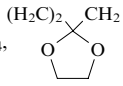
d. Miscellaneous enantioselective reactions

Aldehydes and ketones are involved in L-proline-catalyzed direct asymmetric α-aminooxylation with nitrosobenzene in the IL medium to give (2*R*)-2-aminooxyaldehydes or -ketones **67** with exceptionally high enantioselectivity (95% – 99% *ee*) and in yields that substantially exceed the yields attained in usual organic solvents.[134,135] In addition, IL considerably accelerate the process, and the catalyst can be quantitatively recovered and reused (5 – 6 times). By the reduction of α-aminooxyaldehydes **67** (R^1 = H) under the

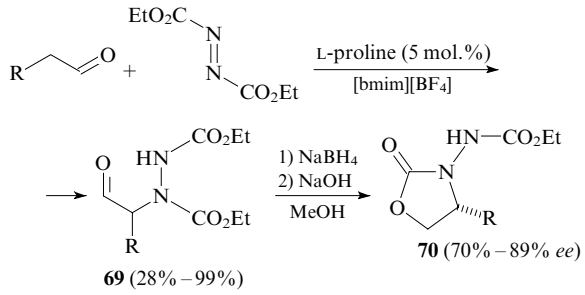
action of $NaBH_4$, chiral 1,2-diol derivatives **68**, valuable intermediates for asymmetric synthesis, were prepared.



R^1 = H: R^2 = Me, Et, Pr^i, Bu^n, Bn; R^1 = R^2 = Me;

$R^1-R^2 = (CH_2)_4$,  ; An = BF_4, PF_6.

Aldehydes react with diethyl azodicarboxylate in the presence of L-proline or L-thiazoline-2-carboxylic acid (5 mol.%) in [bmim][BF_4] faster than in organic solvents to give addition products **69** in moderate to high yields.[136] Compounds **69** were converted to configurationally stable heterocycles **70** with *ee* values of 70%–89%. The authors did not report on the IL recovery.



R = Me, Et, Pr^i, Bu^t, Bn.

III. Generation and transformations of 1,3-dipoles in ionic liquids

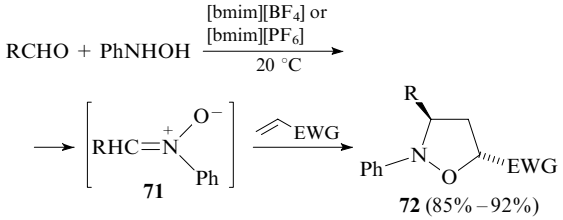
The 1,3-dipolar cycloaddition (1,3-DCA) of 1,3-dipoles to dipolarophiles is one of the most convenient and general methods for the synthesis of heterocyclic compounds of various classes, in particular, 1,2,3-triazole, tetrazole, imidazole, pyrrole, isoxazoline, isoxazolidine, imidazoline and pyrazolidine derivatives.[137–141] Many of the obtained compounds are used as medicinal agents and crop protection means.[142,143] It is evident that development of effective, simple and environmentally friendly methods for their synthesis using alternative types of solvents and catalysts, in particular those based on IL,[21,33–37] and resource-saving methods of reactant activation, for example, microwave irradiation,[144–146] is a topical task. The IL consisting of non-coordinated ions form an ideal ionic environment for the 1,3-dipolar intermediates formed in the reaction, which may lead to unprecedented increase in the rates and selectivites of these processes. This section of the review summarizes the data on 1,3-DCA reactions in IL media. According to the generally accepted terminology,[139,147] the information is divided into subsections describing reactions of allyl, propargyl-allenyl and mesionic type dipoles.

1. Reactions of allyl type 1,3-dipoles

Of dipoles of this type, nitrones, nitrile ylides, azomethine ylides and carbonyl ylides have been studied in 1,3-DCA reactions with various unsaturated compounds in IL.

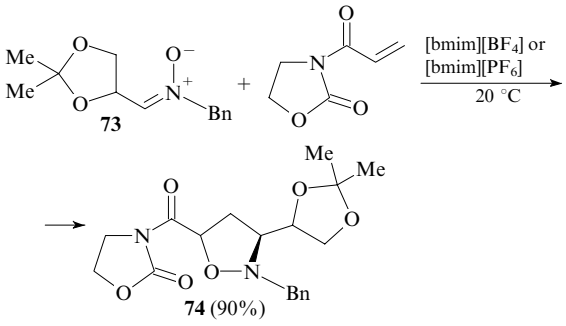
a. Reactions of nitrones with alkenes

Although nitrones, which are among the most reactive 1,3-dipoles, usually readily undergo 1,3-DCA electron-deficient alkenes giving rise to isoxazolidine derivatives,[148,149] the selectivity of these reactions and the product yields in common organic solvents are not always high.[150] In some cases, IL proved to be more suitable for these processes. Thus the reactions of *C*,*N*-diarylnitrones **71** generated *in situ* from aromatic aldehydes and *N*-phenylhydroxylamine with acrylonitrile, methyl acrylate and methyl vinyl ketone occur regio- and stereoselectively in [bmim][BF_4] and [bmim][PF_6] at 20 °C giving rise to isoxazolidines **72** in high yields, whereas in benzene these reactions require heating (80 °C) and afford mixtures of diastereomers (2 : 1). Moreover, IL can be recovered and reused in the reactions at least four times.[151]

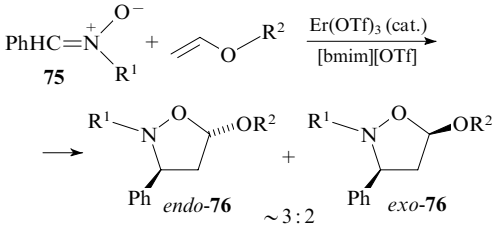


R = Ph, PhCH=CH, 2-furyl, 3(4)-ClC_6H_4, 3,4-$Cl_2C_6H_3$, 3-$NO_2C_6H_4$, 4-$MeOC_6H_4$; EWG = CN, CO_2Me, Ac.

In these IL, cyclocondensation of *N*-benzylnitrone **73** with 3-acryloyl-1,3-oxazolidin-2-one was also regio- and stereoselective and gave heterocyclic compound **74** in high yield.[152]



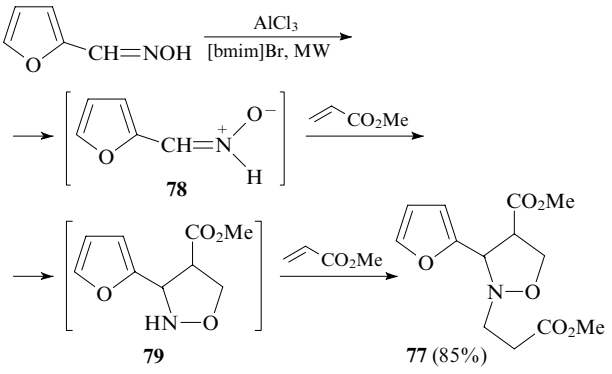
The cycloaddition of *N*-benzyl- and *N*-methyl-*C*-phenylnitrones **75** to vinyl ethers was substantially facilitated in the [bmim][OTf] medium; however, in this case, as in organic solvents, the addition of $Er(OTf)_3$ as a catalyst was needed. This gave a mixture of *endo*- and *exo*-isomers of



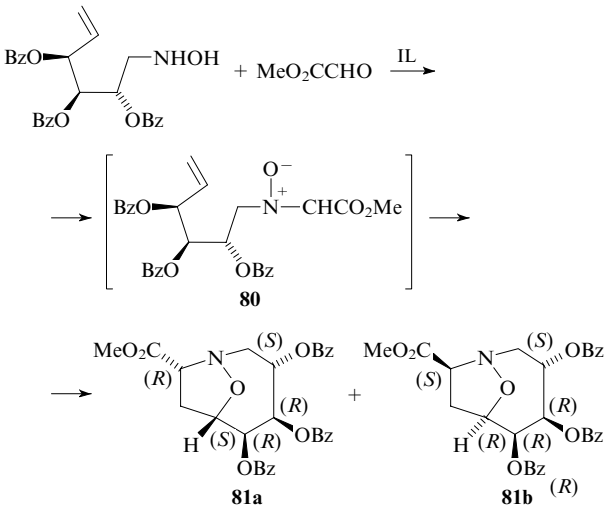
R^1 = Me, Bn; R^2 = Et, Bu^n, Bu^i, Bu^t.

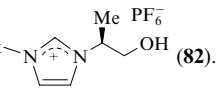
isoxazolidines **76** the ratio of which depended little on the reaction conditions.[153]

An unusual synthesis of 3-furylisoxazolidine **77** was accomplished in the [bmim]Br medium starting from furfural oxime and methyl acrylate in the presence of $AlCl_3$ under microwave irradiation conditions. The process apparently includes $AlCl_3$-catalyzed isomerization of the starting oxime to nitrone **78**, the Michael reaction of the latter with methyl acrylate and transformation of the resulting cycloadduct **79** to 3-furylisoxazolidine **77** with a second methyl acrylate molecule.[154]



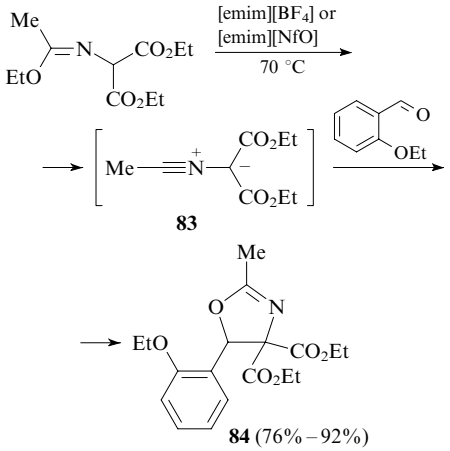
The intramolecular 1,3-DCA also readily occurs in the IL medium. Thus in [bmim][PF_6], the ω-unsaturated chiral nitrone **80** generated *in situ* from the corresponding hydroxylamine and methyl glyoxylate was converted to isomeric 9-oxa-1-azabicyclo[4.2.1]nonanes **81a**,**b** containing 5 asymmetric carbon atoms in 72% yield.[155,156] The reaction was stereoselective: the diastereomer ratio **81a** : **81b** was 8 : 1 (3 : 1 in MeOH). When chiral IL **82** was used as the solvent, owing to asymmetric induction, only compound **81a** was formed in 79% yield.



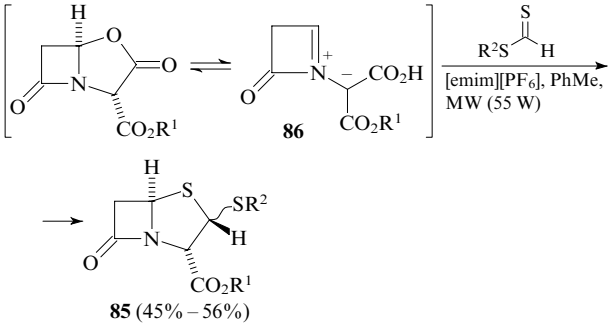
IL = [bmim][PF_6],  (**82**).

b. Reactions of nitrile ylides and azomethine ylides with dipolarophiles

The reaction of nitrile ylide **83** generated *in situ* from the corresponding imidate with *o*-ethoxybenzaldehyde, resulting in oxazoline **84**, was among the first examples of 1,3-DCA in IL.[157] Performing this reaction in the IL increased considerably the reaction rate and the yield of product **84** as compared with the reaction in conventional organic solvents.[158–160] The IL [emim][BF_4] and [emim][NfO] (NfO = n-$C_4F_9SO_3$) were most efficient. The reactions assisted by microwave irradiation were faster but the yield of cycloadduct **84** was lower.



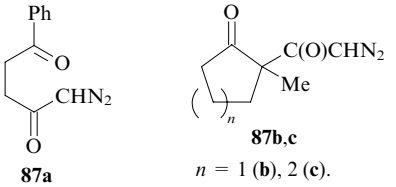
Compounds **85**, which are precursors of penems (antibacterial agents), were obtained as mixtures of *exo*- and *endo*-isomers in yields of 46% – 56% by cyclocondensation of azomethine ylides **86** prepared from the corresponding β-lactams with dithioformate in toluene in the presence of 10 mol.% of [emim][PF_6] as an additive with simultaneous microwave irradiation.[161] Under the studied conditions, the addition of IL did not result in a higher yield of the product; a similar result was obtained also without IL.

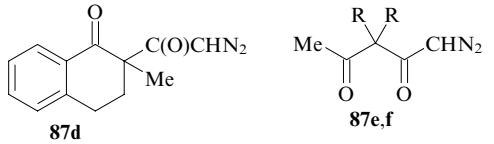


R^1 = 4-$NO_2C_6H_4CH_2$; R^2 = 4-$BrC_6H_4CH_2$, 2-naphthylmethyl.

c. Reactions of carbonyl ylides with alkenes

Tandem sequences of intramolecular cyclization and 1,3-DCA involving α-diazodiketones **87a** – **f** and dipolarophiles (*N*-arylmaleimide, dimethyl acetylenedicarboxylate, propargyl bromide, aromatic and heteroaromatic aldehydes, *etc.*) carried out in IL in the presence of Rh salts or copper acetylacetonate afforded bridged polycyclic systems of type **88**.

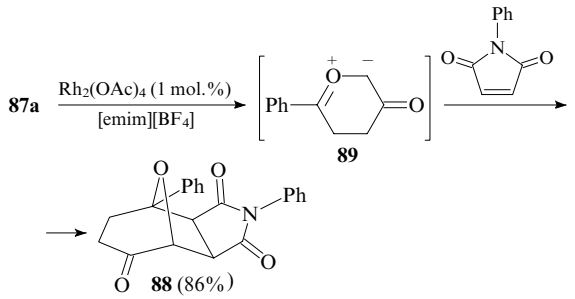




87d **87e,f**

R = Me (**e**), R – R = $(CH_2)_2$ (**f**).

The reactions include the formation of cyclic carbonyl ylides (for example, **89**) and their reactions with dipolarophiles. The yields and stereoselectivities of the reactions carried out in IL are higher than in organic solvents.[162] The most efficient system, [bmim][BF_4] – $Rh_2(OAc)_4$ (1 mol.%), can be recovered and reused at least five times without decrease in the product yield and selectivity.



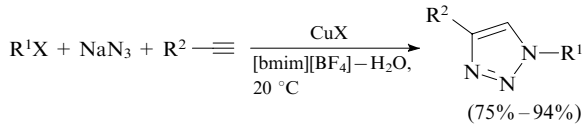
87a **89** **88** (86%)

2. Reactions of propargyl – allenyl 1,3-dipoles

The 1,3-DCA reactions of this type in IL media have been reported for azides and nitrile oxides with alkenes, alkynes and nitriles.

a. Reactions of azides with alkynes and nitriles

Cycloaddition of azides to alkynes (the Huisgen reaction) in conventional organic solvents leads to a mixture of 1,4- and 1,5-disubstituted 1,2,3-triazoles,[141] apparently due to the similar activation energies of these processes.[163, 164] However, in the presence of Cu^I salts in the IL – water system, 1,4-disubstituted 1,2,3-triazoles, representatives of a practically valuable class of compounds,[165] are selectively formed from aryl, benzyl or vinyl halides, sodium azide and terminal alkynes in good yields.[166]



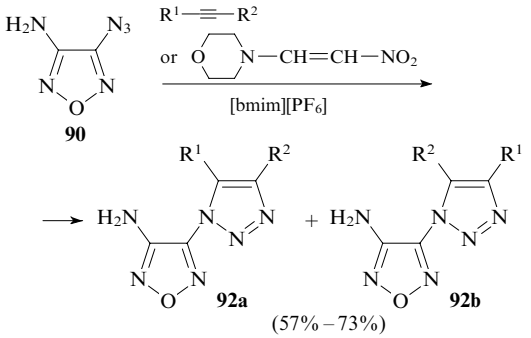
(75% – 94%)

R^1 = Bu^n, All, Bn, Ph; R^2 = Ph, Fc, cyclohexen-1-yl; X = Cl, Br, I.

Apparently, the regiodirection of the process is affected by the coordination between the IL anion and the Cu^+ cation. An important role of the catalyst coordination is consistent with publications [167, 168] in which the 1,3-DCA reaction in aqueous solutions of copper salts gave 1,4-disubstituted 1,2,3-triazoles and that catalyzed by the ruthenium complex (cyclo-C_5Me_5)RuCl(PPh_3)$_2$ yielded their 1,5-disubstituted isomers.[169]

The Cu^I salt-catalyzed 1,3-DCA in IL provided regioselective synthesis of 4-substituted and 1,4-disubstituted 1,2,3-triazole derivatives containing carbohydrate [170] and phosphonate [171] groups. In the latter case, the starting azidoalkyl phosphonates were generated *in situ* from bromoalkyl phosphonates and sodium azide in the IL medium. The reactions of organic azides with terminal alkynes can also proceed in the presence of Cu^0 nanoparticles obtained by the reduction of copper acetate with hydrazine hydrate directly in the IL ([bmim][BF_4] or [bmim][PF_6]).[172]

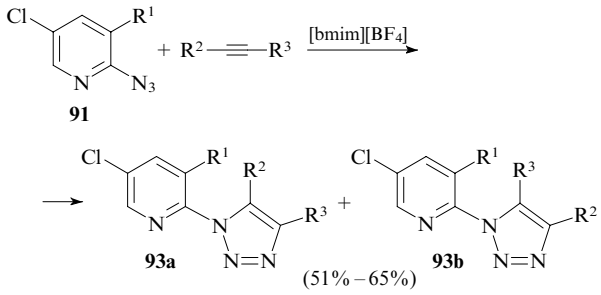
In some cases, the 1,3-DCA of azides to dipolarophiles in IL solutions can take place without a catalyst. Indeed, the cycloaddition of furazanyl azide **90** [173] and azidopyridine **91** [174] to alkynes, resulting in cycloaddition products **92** and **93** in relatively high yields, occurs in [bmim][PF_6] or [bmim][BF_4], at higher rate and with higher regioselectivity. 1-Morpholino-2-nitroethylene can also serve as the dipolarophile in the reaction with azides **90** in IL; in this case, triazoline derivatives are formed initially and are converted to the final reaction products upon elimination of morpholine.[173]



90 **92a** **92b** (57% – 73%)

92a : **92b** = 4.5 : 1 (2.5 : 1 in organic solvent)

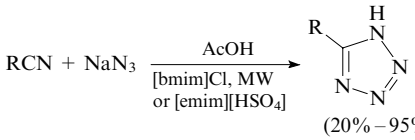
R^1 = R^2 = CH_2OH; R^1 = H: R^2 = CH_2OH, NO_2.



91 **93a** **93b** (51% – 65%)

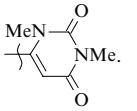
R^1 = Cl, F; R^2 = Bu^n, Ph; R^3 = H, I.

1,3-DCA between azides and nitriles resulting in tetrazole derivatives proceed efficiently in the IL medium.[175] For example, 5-R-tetrazoles were synthesized by the reaction of aryl, hetaryl or arylalkyl cyanides with sodium azide in molten 1,3-dialkylimidazolium salts.



(20% – 95%)

R = 4-XC_6H_4 (X = OMe, Br, NO_2, Me), MeCH=CH, PhCH=CH,

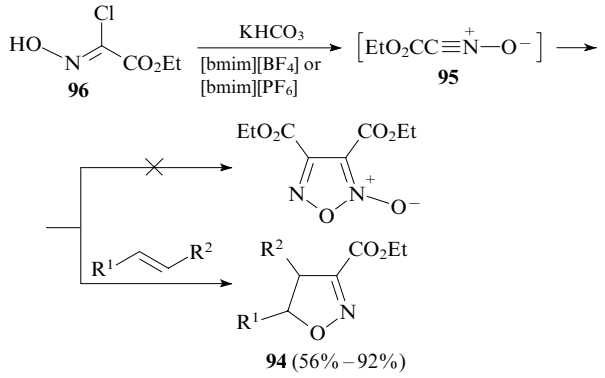
Pr, cyclo-C_6H_{11}, Bz, MeO_2CCH_2, 

The highest product yields were attained in the NaN_3 – [bmim]Cl – AcOH system under microwave irradiation. Recently it was found that in the presence of the IL with the hydrogensulfate anion ([emim][HSO_4]), the correspond-

ing tetrazoles are also formed without microwave irradiation.[176]

b. Reactions of nitrile oxides with alkenes

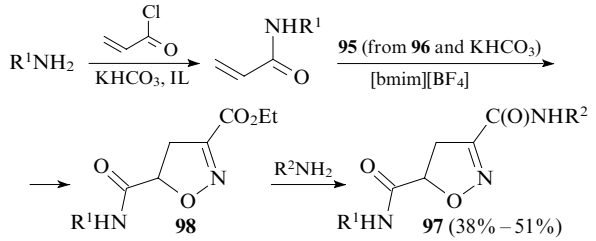
The possibility of accelerating the cycloaddition of nitrile oxides to alkenes in IL ([bmim][BF_4] or [bmim][PF_6]) was first demonstrated for the preparation of 3-ethoxycarbonylisoxazolines **94** from alkenes and ethoxycarbonylformonitrile oxide (**95**) generated *in situ* from chloride **96** and $KHCO_3$.[177] Under these conditions, no dimerization of nitrile oxide **95** to furoxan took place, which is observed in organic solvents.



94 (56%–92%)

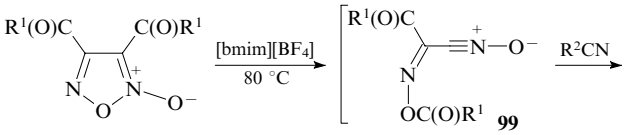
R^1 = H, Me, CO_2Et; R^2 = CO_2Me, CO_2Et, CN, $SiMe_3$, CH_2Cl; R^1-R^2 = $O(CH_2)_2$, $(CH_2)_4$.

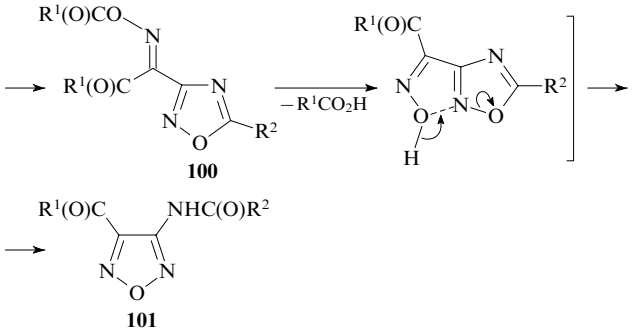
More recently the same authors performed one-pot synthesis of isoxazolinedicarboxamides **97** in the IL medium comprising acylation of amines with acryloyl chloride, cycloaddition of the resulting acrylamides to nitrile oxide **95** (generated from chloride **96** and $KHCO_3$) and introduction of the second amide group to isoxazoline **98**.[178] The IL recovered from the multistep process could be reused seeral times.



R^1, R^2 = Pr^i, Bn, cyclo-C_6H_{11}, Ph.

Nitrile oxides **99** generated *in situ* in [bmim][BF_4] by thermolysis of diacetyl- and dicyclopropylcarbonylfuroxans readily underwent 1,3-DCA with activated nitriles under these conditions to give cycloadducts **100**, which were converted, through an azole–azole rearrangement, to 3-acetyl(cyclopropylcarbonyl)-4-acylaminofurazans **101**, which are difficult to prepare otherwise, in yields of 34%–40%.[179]

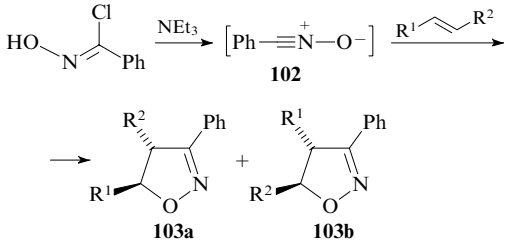




101

R^1 = Me, cyclo-C_3H_5; R^2 = CCl_3, CO_2Et.

A comparison of the rates and regioselectivities of 1,3-DCA reactions of benzonitrile oxide **102** generated *in situ* with alkenes to give cycloadducts **103** in IL and in organic solvents was reported.[180] It was found that the rates of both cycloaddition and nitrile oxide **102** cyclodimerization to diphenylfuroxan increase in the IL; in the case of sterically hindered cycloalkenes **103** (R^1 = Ph, R^2 = CO_2Et), the regioselectivity of 1,3-DCA is considerably higher in the IL [bmim]X [X = PF_6, NTf_2, $N(CN)_2$] (or in their melts) than in organic solvents (MeCN, ethyl acetate, THF). The **103a** : **103b** ratio is 1 : (10–15) in IL and 1 : (4–6) in organic solvents.

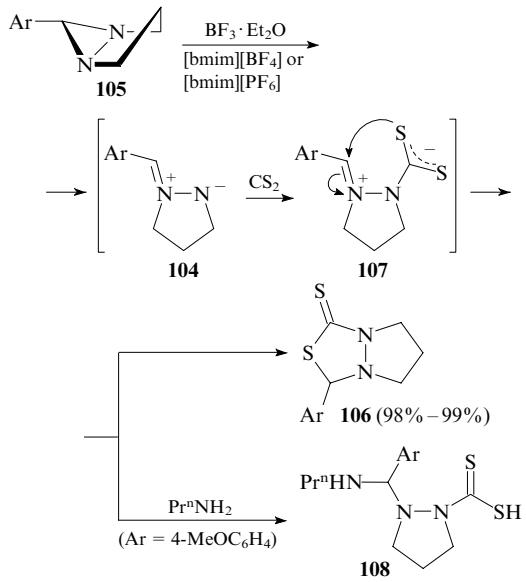


R^1 = Me, Et, Ph; R^2 = CO_2Et, CH_2OH.

3. 1,3-Dipoles of the mesoionic type: reactions of azomethine imines with dipolarophiles

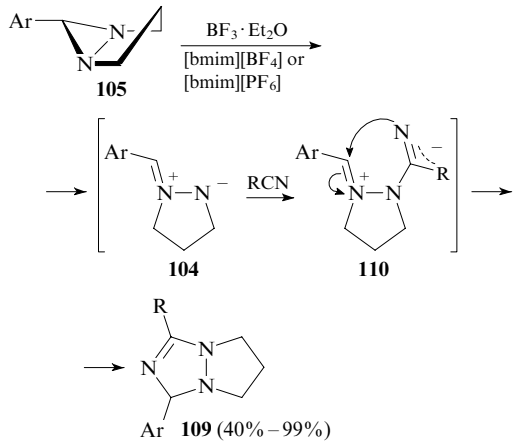
Reactions of this type in IL media are considered in a number of publications.[181–185] Azomethine imines **104** were generated *in situ* by heterolysis of the C–N bond in 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **105** under the action of $BF_3 \cdot Et_2O$ in IL. The diaziridine ring in compounds **105** is also opened in organic solvents (in xylene at 130–140 °C or in MeCN at 20 °C in the presence of $BF_3 \cdot Et_2O$);[186–190] however, in this case, only activated alkenes or alkynes react with the azomethine imines **104** formed according to the 1,3-DCA pattern. The use of IL considerably extended the synthetic potential of dipoles **104**, which were thus introduced in the reactions with CS_2, activated nitriles and some alkenes, which do not react with them in organic solvents.

The addition of CS_2 to azomethine imines **104** resulted in 3-aryldihydro-5*H*-pyrazolo[1,2-*c*][1,3,4]thiadiazole-1-thiones **106**.[181,182] These reactions involve the formation of rather stable 2-(arylidene)pyrazolidin-2-ium-1-carbodithioates **107** having a zwitterionic structure. Compound **107** (Ar = 4-$MeOC_6H_4$) was isolated, characterized by NMR spectra and microanalysis and converted to adduct **108** by the reaction with propylamine in IL.



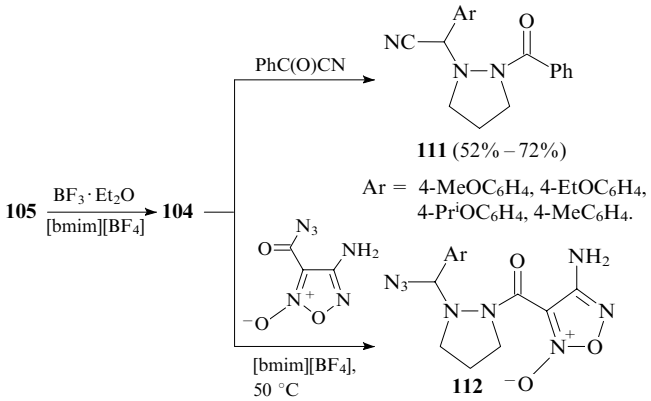
Ar = 4-XC_6H_4 (X = OMe, OEt, OPr^i, Me, Cl).

Azomethine imines **104** reacted with activated nitriles in [bmim][BF_4] or [bmim][PF_6] to give bicyclic compounds **109**.[182,183] In this case, too, zwitterions **110** similar to **107** were also formed; however, due to lower stability, they were only detected by spectroscopy and were converted rapidly and quantitatively to products **109**.



Ar = 4-XC_6H_4 (X = Me, OMe, OEt, OPr^i); R = CCl_3, CO_2Et.

The reaction of azomethine imines **104** with benzoyl cyanide in the IL did not result in bicyclic compounds. Instead, conjugated addition of the benzoyl and cyano groups to the opposite ends of the dipole took place to give (2-benzoylpyrazolidin-1-yl)(aryl)acetonitriles **111**. Similarly, the reaction of dipole **104** with 4-amino-3-furoxancarbonyl azide yielded compound **112**. The synthesis of adducts **111** and **112** provided additional chemical evidence for the formation of zwitterions **104** in IL.[182] Note that in acetonitrile, unlike IL, these reactions do not occur.

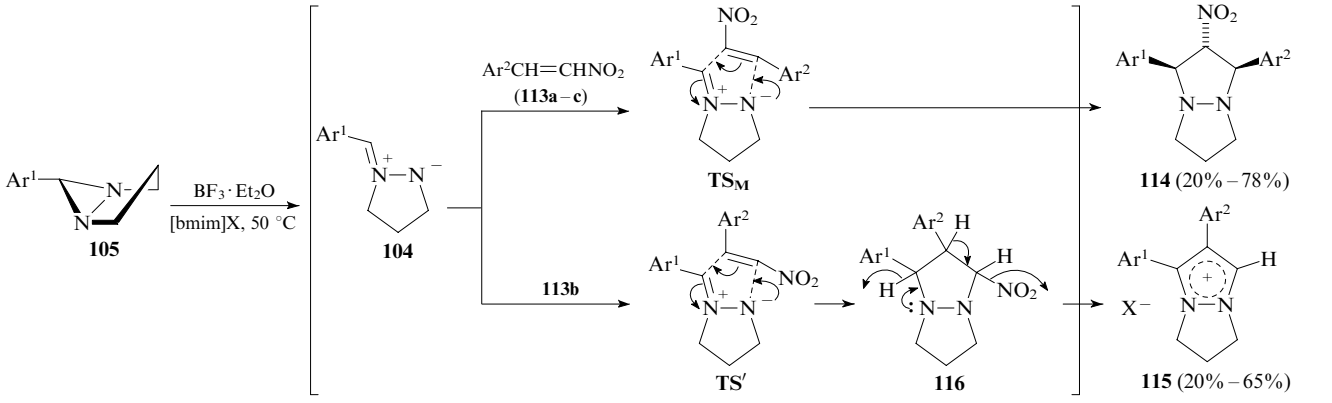


Ar = 4-$EtOC_6H_4$.

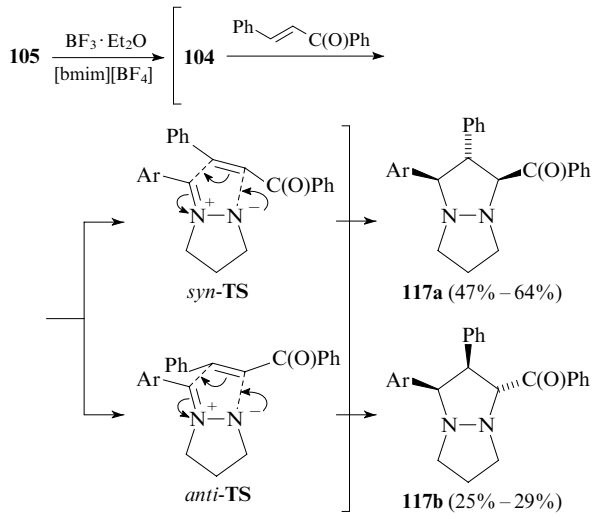
Azomethine imines **104** add β-nitrostyrenes **113a–c** in the IL [bmim][BF_4] or [bmim][PF_6] to afford 1,3-diaryl-2-nitrotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazoles **114**.[184] Upon the reaction involving compound **113b**, salts **115** containing the IL anion (BF_4^- or PF_6^-) were unexpectedly isolated apart from pyrazoles **114**. Apparently, they are formed *via* transition state **TS′** (isomeric to the Michael type transition state $\mathbf{TS_M}$), which is converted to intermediate **116**, the latter eliminating HNO_2 and the hydride ion (Scheme 4).

The [3 + 2]-cycloaddition of chalcone to azomethine imines **104**, which does not take place in organic solvents, was accomplished in the IL medium. This afforded diastereomeric products **117a** and **117b** with *trans–trans* and *cis–trans* arrangement of the substituents. In the authors' opinion, the products are formed *via* transition states *syn*-**TS** and *anti*-**TS** with the *syn*- and *anti*-positions of the C(O)Ph and $(CH_2)_3$ groups, respectively.[185]

Scheme 4



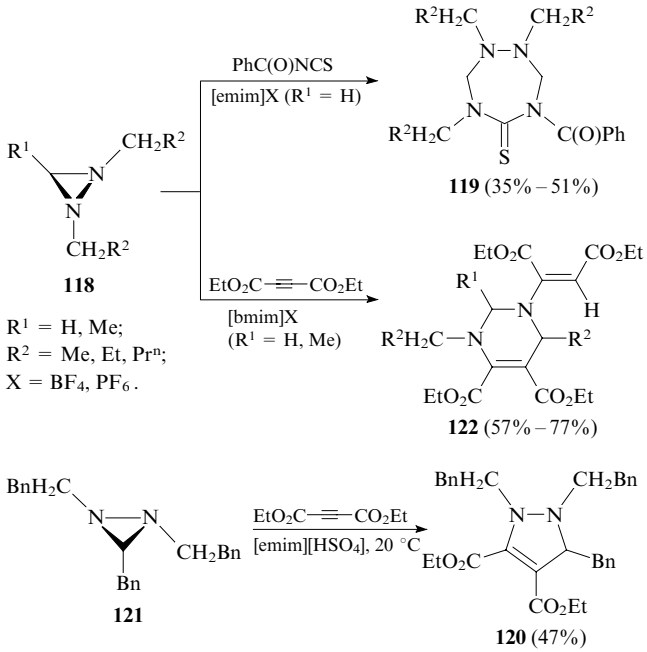
Ar^1 = 4-YC_6H_4 (Y = Me, OMe, OEt, OPr^i); Ar^2 = Ph (**a**), 3-$NO_2C_6H_4$ (**b**), 4-$MeOC_6H_4$ (**c**); X = BF_4, PF_6.



Ar = 4-XC_6H_4 (X = OMe, OEt, OPr^i).

The bicyclic compounds obtained in the [3 + 2] cycloaddition reactions of azomethine imines **104** to dipolarophiles belong to practically important classes some of which were patented for the use in medicine (anti-HIV agents,[191, 192] NO-synthase inhibitors,[193] antidiabetic agents[194]), in agriculture (herbicides, fungicides[195, 196]) and other areas (additives to lubricating oils,[197] semiconductors, sorbents,[198] and so on). In all cases, IL was recovered and reused (at least three times) in the reactions with the same efficiency. Note that the previously known methods for the synthesis of these heterocycles[199 – 201] include multistep procedures, and therefore, new methods for their preparation in IL are of interest for the development of efficient resource-saving chemical processes.

Recently, unexpected reactions of monocyclic diaziridines with dipolarophiles in IL were discovered. 1,2-Dialkyldiaziridines **118** react with benzyl isothiocyanate in [emim][BF_4] or [emim][PF_6] giving tetrazepanethiones **119**.[202] The mechanism of this reaction is not clear as yet; however, the molecule of the final product contains the C – N – N fragment, which theoretically could have been formed as a result of diaziridine ring opening at the C – N bond to give intermediates — analogues of azomethine imines **104**. The product of formal [3 + 2] cycloaddition **120** was obtained upon the reaction of 1,2-diphenethyl-3-benzyldiaziridine **121** with diethyl acetylenedicarboxylate in IL. However, diaziridines **118** with less bulky substituents react with this compound to give tetrahydropyrimidine derivatives **122** as a result of diaziridine ring opening at the N – N bond.[203] This reaction the mechanism of which is unknown as yet also takes place only in IL but not in conventional organic solvents.



IV. Ionic liquids and their congeners as organocatalysts of reactions involving carbon acids and 1,3-dipoles

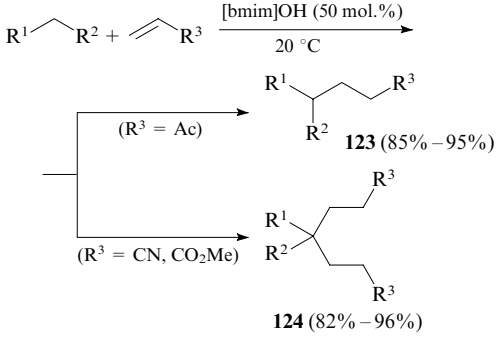
As shown in Sections II and III, some chemical reactions proceed in IL media without the addition of catalysts whose functions are performed by the IL. A clear-cut catalytic effect can often be attained in the presence of a small amount of IL (1 mol.% – 50 mol.%); in view of the possible catalyst recovery, this considerably increases the efficiency of these still expensive compounds. Usually IL function as base, acid or phase transfer catalysts (PTC); however, when they contain appropriate structural fragments, they also exhibit other types of catalytic activity.[31]

1. Ionic liquid-catalyzed reactions of carbon acids

This Section covers the reactions of active methylene compounds in the presence of IL containing the Lewis or Brønsted basic or acid sites, reactions in the presence of phase transfer catalysts based on IL and enantioselective reactions catalyzed by chiral IL.

a. Base catalysis of reactions of carbon acids

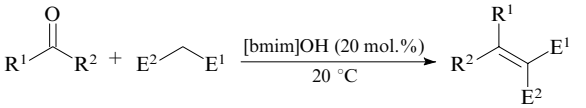
The Michael reaction. The available and inexpensive IL [bmim]OH proved to be an efficient catalyst of the Michael reaction between active methylene compounds and electron-deficient alkenes. In its presence (50 mol.%), the reactions proceed under neat conditions without addition of other catalysts or solvents giving Michael adducts **123** or **124** in high yields.[44, 204] The reactions are substrate-specific: diethyl malonates, ethyl acetoacetate and cycloalkanones react with vinyl ketones to give monoaddition products **123**, whereas linear 1,3-dicarbonyl compounds and methyl acrylate or acrylonitrile react under these conditions to give only bisadducts **124**, which are difficult to prepare in one step by other methods. The observed catalytic effect is consistent



R1, R2 = Me, Ac, Bz, CO_2Me, CO_2Et, NO_2, *etc.*;
R3 = Ac, CO_2Me, CN.

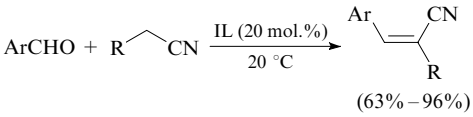
with the results of quantum chemical (DFT) calculations of the energy profile of the reaction of acetylacetone with methyl vinyl ketone without a catalyst or in the presence of [bmim]OH.[205]

The Knoevenagel condensation. The basic IL [bmim]OH effectively catalyzes the condensations of carbonyl compounds with carbon acids resulting in functionally substituted alkenes. These reactions are carried out most often in the reactant medium at room temperature. Under the conditions used, aliphatic and aromatic aldehydes and ketones are suitable for the reaction. Diethyl malonate, ethyl acetoacetate and cyanoacetate and malononitrile can serve as the active methylene component.[206] Unlike the traditional experimental procedures, [bmim]OH-catalyzed reactions allow one to obtain the condensation products of aliphatic aldehydes with diethyl malonate in high reproducible yields. The salicylaldehyde derivatives cyclize under these conditions to coumarin derivatives.



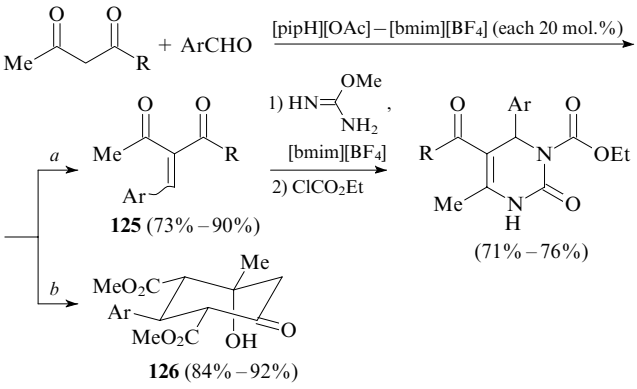
R^1, R^2 = H, Alk, Ar; R^1-R^2 = cyclo-Alk; E^1, E^2 = CN, Ac, CO_2Me, CO_2Et, CO_2H.

The Knoevenagel condensation can also be induced by less basic IL. For example, the reactions of aldehydes with malononitrile or ethyl cyanoacetate in a reactant mixture are substantially accelerated in the presence of 1,1,3,3-tetramethylguanidinium lactate ([TMGH][Lac])[207] or 2-hydroxyethylammonium acetate.[208, 209] The required amount of IL does not exceed 20 mol.%. Owing to the poor solubility in organic solvents, the catalysts are readily separated from the products and can be recycled many times.



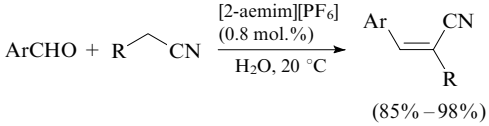
Ar = Ph, C_6H_4X (X = 3-NO_2, 4-NO_2, 4-Cl, 4-OMe, 4-OH), 2-furyl, *etc.*; R = CN, CO_2Et; IL = [TMGH][Lac] or [$HO(CH_2)_2NH_3$][OAc].

The [bmim][BF_4]–piperidinium acetate ([pipH][OAc]) system (1 : 1) efficiently catalyzes the condensation of aromatic aldehydes with β-diketones or β-keto esters under neat conditions. Depending on the aldehyde structure, enones **125** or cyclohexanone derivatives **126** are formed.[210] The components of the catalytic system complement each other: [pipH][OAc] serves as a soft base and [bmim][BF_4] stabilizes the CH acid anion, for example, by hydrogen bonding with the active hydrogen atom in position 2 of the imidazolium cation. Compounds **125** were further converted to dihydropyrimidine derivatives by treatment with *O*-methylisourea in IL.



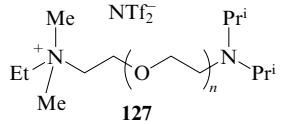
(*a*) Ar = C_6H_4X (X = H, 2-Cl); R = Me, OMe;
(*b*) Ar = C_6H_4X (X = 4-Cl, 4-F, 4-CO_2Me, 4-NO_2, 3-NO_2), 2-thienyl; R = OMe.

1-(2-Aminoethyl)-3-methylimidazolium hexafluorophosphate modified by an amino group ([2-aemim][PF_6]) proved to be an active organocatalyst for the Knoevenagel condensation in aqueous medium.[211] In the presence of 0.8 mol.% of this catalyst, a broad range of adducts were obtained in high yields. The aqueous solution of the catalyst remaining after separation of the water-insoluble products retained the catalytic properties in six subsequent reaction cycles.



Ar = C_6H_4X (X = H, 3-NO_2, 4-Cl, 4-CN, 4-OH, 4-OMe, 4-NMe_2), 3,4-$(OCH_2O)C_6H_3$, 2-furyl; R = CN, CO_2Et.

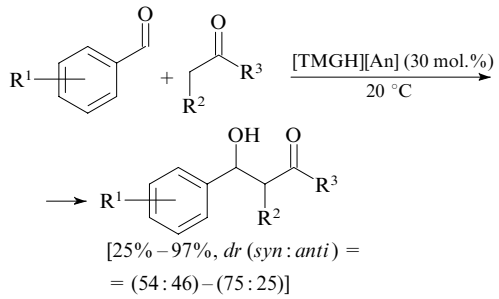
The condensation of carbonyl compounds with malononitrile or ethyl cyanoacetate proceeds efficiently in the presence of tetraalkylammonium salts **127** containing sterically hindered amino groups in the cationic fragment (Hünig's bases).[212] The reactions can be carried out in the reactant medium under homogeneous conditions or on treatment with 'heterogenized', silica gel-supported IL. The activity of catalysts **127** increases with increase in the chain length between the nitrogen atoms. Homogeneous catalysts are more active; however, immobilization on SiO_2 facilitates the catalyst regeneration.



127

n = 0–2.

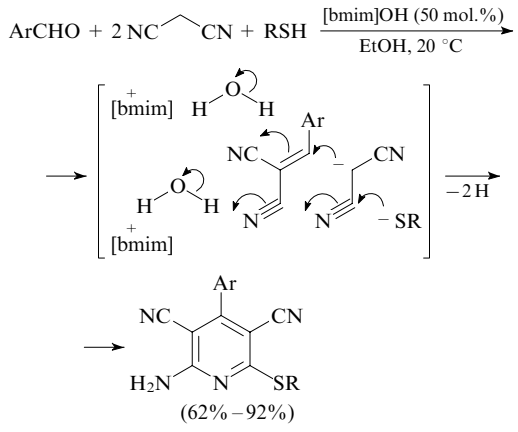
Aldol reactions. TMG lactate[213] and acetate[214] having basic properties were used as recoverable catalysts in aldol reactions between aldehydes and ketones resulting in β-hydroxy ketones. The reactions in the reactant medium proceeded with high chemo- and regioselectivities; however, the diastereoselectivity was usually moderate. As in the processes considered above, IL were reused several times without considerable decrease in their catalytic activity.



R^1 = 2-NO_2, 3-NO_2, 4-NO_2, 4-CHO; R^2 = Me: R^3 = H, Me, Et; R^2-R^3 = $(CH_2)_3$, $(CH_2)_4$; An is lactate or OAc.

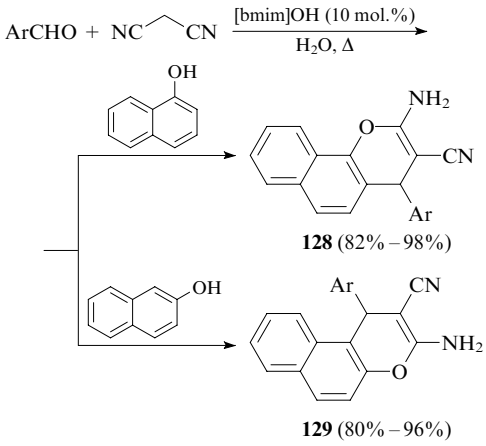
The aldol reaction between aldehydes and ketones induced by a stronger base (choline hydroxide) was accompanied by dehydration of the resulting aldols and yielded the corresponding crotonization products.[215] Crotonic condensation also took place when this reaction was catalyzed by choline immobilized on MgO.

Domino reactions. Basic IL efficiently catalyze some multicomponent reactions of carbon acids. The best studied catalyst is [bmim]OH. This catalyst (50 mol.%) induces selective three-component condensation of aldehydes with malononitrile and thiophenols, giving highly substituted pyridines in high yields in one experimental step.[216] This reaction can be carried out for aromatic aldehydes with electron-donating or -withdrawing substituents in the aromatic nucleus and thiophene-2-carbaldehyde. This domino reaction, evidently, includes the condensation of aldehyde with malononitrile, successive addition of a second malononitrile molecule and thiolate anion to the resulting adduct, heterocyclization and oxidation (by O_2). The ionic liquid acts in this process as a soft base, which ensures deprortonation of the carbon acid and thiol but, unlike stronger bases [DABCO (1,4-diazabicyclo[2.2.2]octane) or NEt_3], does not induce side reactions, in particular, the formation of enaminonitrile. When the basic IL [bmim]OH is replaced by neutral IL ([bmim]Br or ([bmim][BF_4]), the reaction stops after the formation of the Knoevenagel adduct.



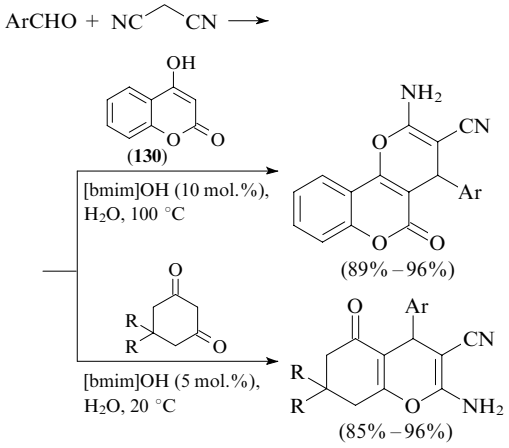
Ar = Ar or 2-thienyl; R = Ar or Bn.

In the presence of [bmim]OH, selective three-component condensations of aromatic aldehydes with malononitrile and α- or β-naphthols in water take place, resulting in the corresponding 2-amino-4*H*-chromenes **128** and **129** in high yields.[217] Advantages of this method include the experimental simplicity and the possibility to prepare products containing different substituents in the heterocyclic nucleus.



Ar = Ph, C_6H_4X (X = 2-Cl, 4-Cl, 4-F, 3-NO_2, 4-NO_2, 4-OH, 4-OMe, 4-Me), 2-furyl.

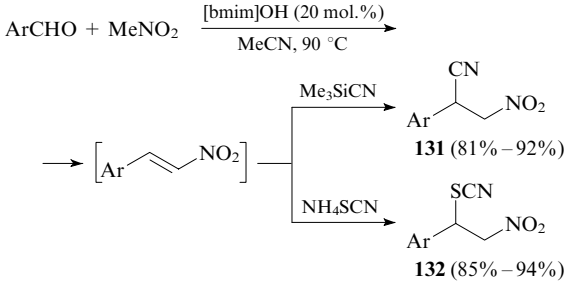
The replacement of naphthol in the reaction considered above by 4-hydroxycoumarin (**130**) or 1,3-cyclohexanedione derivatives made it possible to synthesize the corresponding polynuclear heterocycles in one step from simple and readily accessible precursors.[218] 1,3-Diketones reacted at much lower temperature than 4-hydroxycoumarin.



(1)

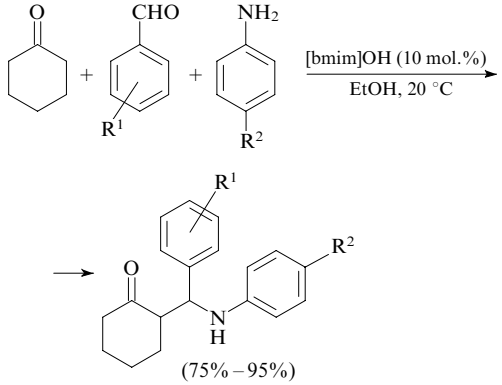
Ar = C_6H_4X (X = H, 2-Cl, 4-Cl, 2-NO_2, 3-NO_2, 4-NO_2, 4-F, 4-Me, 4-OH, 4-OMe, 4-NMe_2), 2,4-$Cl_2C_6H_3$, 2-furyl; R = H, Me.

Indian chemists developed a convenient method for the synthesis of β-nitrocarbonitriles **131** and β-nitrothiocyanates **132** by [bmim]OH-catalyzed three-component condensation of aromatic aldehydes, nitromethane and trimethylsilyl cyanide or ammonium thiocyanate in acetonitrile.[219] The reaction, obviously, includes the formation of



β-nitrostyrene derivatives from aldehyde and nitromethane and addition of the corresponding C- or S-nucleophile to them, both steps being accelerated in the presence of IL.

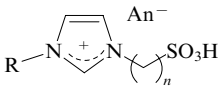
A variety of β-amino ketones were prepared in high yields by three-component Mannich condensation of cyclohexanone with aromatic aldehydes and aniline derivatives in the presence of [bmim]OH.[220] The catalyst was readily regenerated and remained active in at least five subsequent runs.



R^1 = H, 4-Cl, 4-OMe, 3-NO_2, 4-NO_2; R^2 = H, Cl, Br, Me.

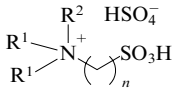
b. Acid catalysis of reactions of carbon acids

Many reactions of carbon acids proceed in the presence of IL containing the Brønsted or Lewis acid sites. Unlike the catalysts having basic properties, the function of acid catalysts is to activate the electrophilic component, for example, hydroxy- or carbonyl compound, rather than to deprotonate the carbon acid. These reactions are often carried out in the reactant media; however, examples of carbon acid reactions in aqueous solutions or neutral IL are also known. Some IL suitable as the Brønsted-type acid catalysts are presented below (compounds **133**–**136**). Another example of these catalysts is [Hmim][TFA].



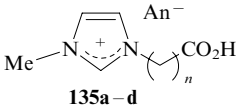
133a–d

133	R	*n*	An
a	Bu^n	3	OTf
b	Bu^n	4	HSO_4
c	Me	4	HSO_4
d	Me	4	OTs



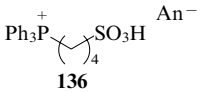
134a–c

134	R^1	R^2	*n*
a	Me	Me	3
b	Et	Et	4
c	Me	$n\text{-}C_{12}H_{25}$	4



135a–d

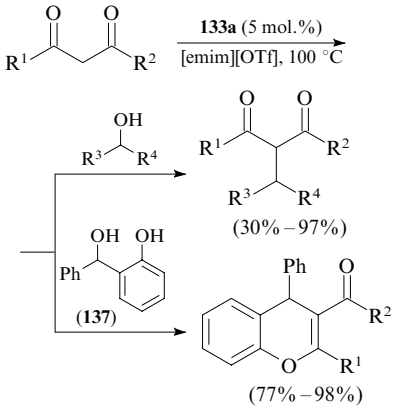
132	*n*	An
a	1	HSO_4
b	1	H_2PO_4
c	2	HSO_4
d	2	H_2PO_4



136

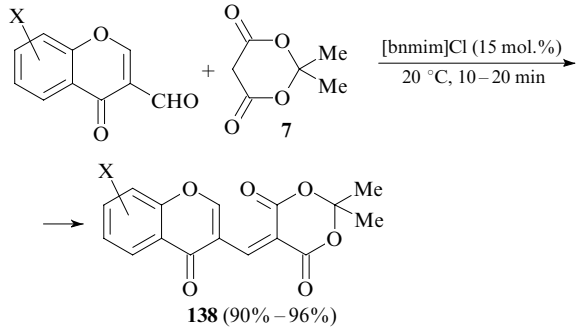
An = PTSA, TFA.

Alkylation reactions. Japanese chemists found that the Brønsted acid **133a** catalyzes direct benzylation, allylation and propargylation reactions of 1,3-dicarbonyl compounds with the corresponding alcohols in [emim][OTf].[221] The alkylation products are formed in moderate to high yields. The reactions do not require organic solvents; in addition, they are not accompanied by the formation of by-products typical of alkylation reactions, such as inorganic salts. The alkylation of β-diketones with diol **137** produced functionalized 4*H*-chromenes as a result of one-pot process comprising benzylation, cyclization and dehydration reactions. The acid ionic catalyst–IL system is readily recovered owing to poor solubility in the organic solvents used for product isolation and remains active in at least three reaction cycles.



R^1 = R^2 = Me, Ph; R^2 = OEt: R^1 = Me, Et;
R^4 = Me: R^3 = Ph, MeCH=CH;
R^4 = Ph: R^3 = Ph, PhCH=CH, PhC≡C.

The Knoevenagel condensation. 1-Benzyl-3-methylimidazolium chloride ([bnmim]Cl), which behaves as a weak acid, proved to be an effective catalyst of the Knoevenagel reaction between 4-oxo-4*H*-benzopyran-3-carbaldehyde derivatives and Meldrum's acid (**7**) resulting in products **138**.[222] Advantages of the method include experimental simplicity, mild conditions and high yields of products. In addition, IL does not pass to the organic phase during extraction of the products and can be again introduced in the reaction, although this requires evaporation of the wash water containing the catalyst.

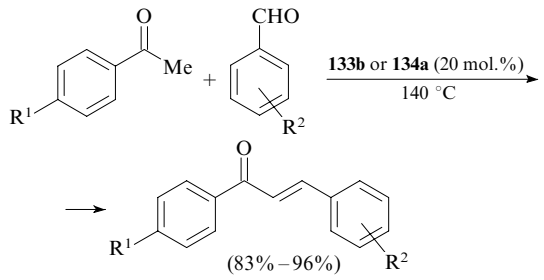


138 (90%–96%)

X = 6-Me, 7-Cl, 7-Br, 7-F, 5,7-Cl_2, 6,7-Cl_2.

Aldol condensation. The Claisen–Schmidt condensation of acetophenone derivatives with aromatic aldehydes efficiently proceeds in the reactant medium in the presence of hydrogen sulfates **133b** and **134a** whose cations are modified by the SO_3H groups; this gives the corresponding chalcones.[223, 224] The products are separated from the catalysts by decantation. After water released upon condensation has been removed from the mother liquor, salts **133b** or **134a**

can be reused (at least six times) and the product yields remain high.



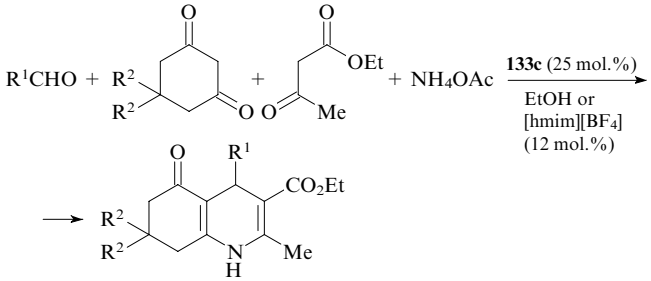
R^1 = H, OMe, NO_2; R^2 = H, 2-Cl, 2-OMe, 3-Cl, 3-OMe, 4-Cl, 4-OMe.

Multicomponent reactions. Alkylamonium and alkylimidazolium salts containing BF_4^-, PF_6^-, $AlCl_4^-$ and $Al_2Cl_7^-$ anions serve as soft acid catalysts in three-component reactions of β-dicarbonyl compounds, including fluorine-containing ones, with aldehydes and urea (thiourea) (the Biginelli reaction). In this case, the active form of the catalyst is apparently the corresponding hydrohalic acid (HF or HCl) liberated from the IL anions under the action of traces of water under the reaction conditions. The use of these IL (0.5 mol.%) made it possible to obtain (depending on the nature of the dicarbonyl compound and the catalyst) various tetra- (Ref. 225) and hexahydropyrimidine derivatives[226] (**139** and **140**, respectively), the classes of heterocycles in which antitumour agents[227, 228] and selective α_{1a}-adrenergic receptor antagonists[229] have been found. The yields of products **139** and especially **140** considerably exceed the yields attained previously. The catalyst recovery is facilitated by performing the reaction with 'heterogenized' IL supported on a polymer.[230] When 1-butyl-3-methylimidazolium saccharinate (**141**) (0.5 mol.%) was used as the catalyst, 1,4-dihydropyridine derivatives **142** (the Hantzsch products) were isolated together with 3,4-tetrahydropyrimidinones **139**.[231] Imidazolium salts **135a–d** containing the Brønsted acid groups in the IL cation and anion are more active catalysts for the Biginelli reaction; in the presence of these salts, the process temperature can be reduced from 100–120 to 70 °C (Scheme 5).[28]

The developed catalytic methods allow the Biginelli reaction to be carried out as efficiently as in IL;[232–234] however, the consumption of the ionic catalyst is much lower and, hence, the catalytic processes are preferred.

The three-component condensation of aromatic aldehydes with malononitrile and dimedone (or cyclohexane-1,3-dione) [reaction (1)] efficiently proceeds in water under the action of salt **134b** (10 mol.%).[235] The water-insoluble products (5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyrans) are readily separated from the reaction mixture, and their yield (86%–94%) does not decrease even after the catalyst has been used 10 times.

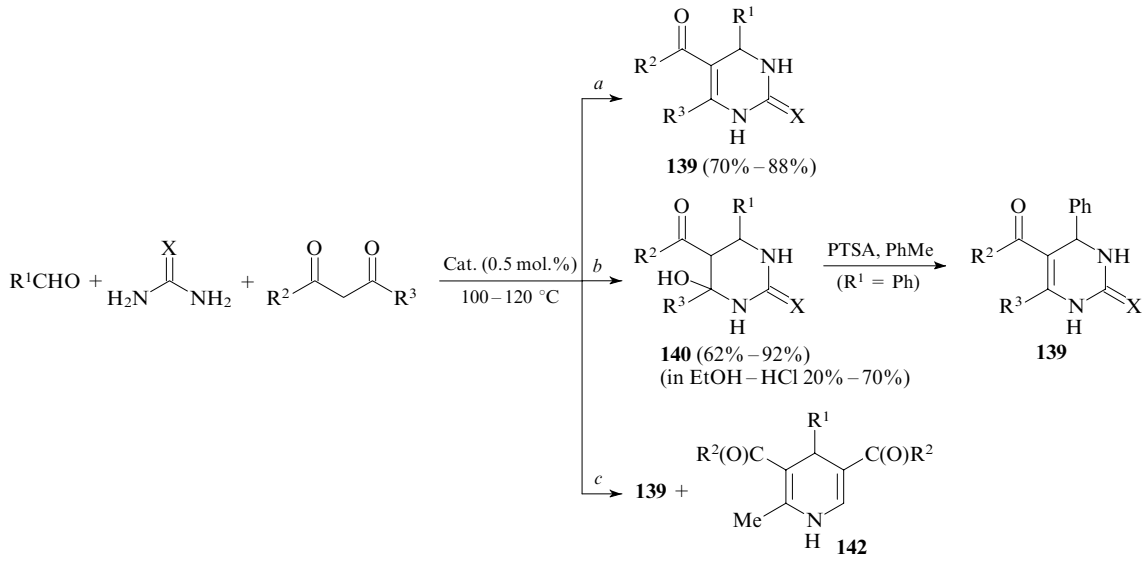
Acidic IL **133c** proved to be active catalyst of the four-component Hantzsch reaction between aldehydes, ethyl acetoacetate, cyclic 1,3-diketone and ammonium acetate in alcohol media resulting in hexahydroquinoline derivatives **143**.[236] After completion of the reaction, the catalyst was filtered off, washed with diethyl ether, dried *in vacuo* and recycled. The reaction can also be carried out under neat conditions with the commercially available IL [hmim][BF_4] as a catalyst (12 mol.%).[237] The reaction is completed in



143 (75%–96%)

R^1 = C_6H_4X (X = H, 2-Cl, 3-NO_2, 4-NO_2, 4-Cl, 4-Me, 4-OMe), 2-furyl, 3-thienyl, Et, Pr^n; R^2 = H, Me.

Scheme 5



(*a*) catalysts [bmim]An (An = BF_4, PF_6, $AlCl_4$, Al_2Cl_7), [Me_3NH]An (An = BF_4, PF_6), [Bu^n_4N][PF_6], [$BnMe_3N$]An (An = $AlCl_4$, Al_2Cl_7); R^1 = Ph, YC_6H_4 (Y = 3-NO_2, 4-Cl, 4-F), 2-thienyl; R^2 = Me: R^3 = Me, OMe; R^2–R^3 = $CH_2CMe_2CH_2$; X = O, S;

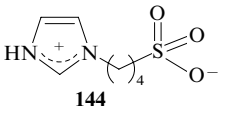
(*b*) catalyst [bmim][BF_4]; R^1 = Ph, 4-FC_6H_4, 3-thienyl; R^2 = OEt, R^3 = CF_3; R^2 = Ph, R^3 = CF_2CHF_2; X = O, S;

(*c*) catalyst **141**; R^1 = Ph, 4-YC_6H_4 (Y = F, Cl, MeO, NO_2, OH, NMe_2), 2-YC_6H_4 (Y = F, Cl, MeO), 2-furyl; R^2 = OEt, Me; R^3 = Me; X = O.

5–25 min depending on the aldehyde structure and the product yields exceed the yields attained under classical conditions.

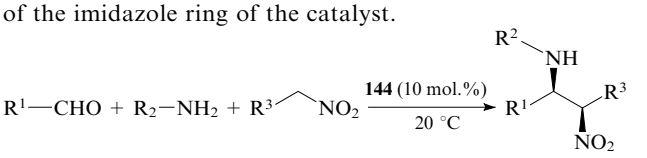
The three-component Mannich reaction between aromatic aldehydes, amines and ketones [reaction (2)] readily proceeds in the presence of salt **134c** (10 mol.%). This reaction is carried out in polar solvents, including EtOH [29] or in water.[238,239] The solution of catalyst **134c** in the corresponding solvent remaining after filtering off the products can be reused in the reaction six times without decrease in the activity. The Mannich reaction can also occur in melts of some acidic IL, for example, [Hmim][TFA] (Ref. 240) or salts **133d** and **136** containing the SO_3H group in the cation;[241] however, in these cases, the consumption of the IL is much higher than in those reactions where it is used as the catalyst.

Zwitterionic imidazolium sulfonate **144**

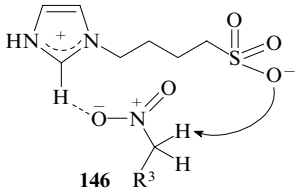


144

catalyzes three-component Mannich reactions involving nitroalkanes.[242] In the presence of this compound (10 mol.%), these reactions occur without a solvent to give mainly the *syn*-diastereomers of β-nitroamines **145** in high yields. The high *syn*-diastereoselectivity of the reaction was attributed to the formation of associate (**146**) of the carbon acid with the catalyst through hydrogen bonding between the nitro group oxygen and the active proton in position 2 of the imidazole ring of the catalyst.



145 [77%–92%, *dr* (*syn* : *anti*) = (74 : 26)–(98 : 2)]

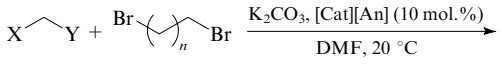


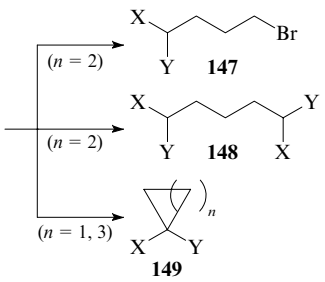
146

R^1 = 4-XC_6H_4 (X = H, Me, OMe, F, Br, NO_2), 3,4-$(OCH_2O)C_6H_3$;
R^2 = C_6H_4X (X = H, 3-Cl, 4-Me, 4-OMe, 4-F, 4-Cl, 4-NO_2, 4-CO_2Et);
R^3 = Me, Et.

c. Phase transfer catalysis of the reactions of carbon acids

Effective phase transfer catalysts of the reactions involving the step of formation of carbanions were found among the 1,3-dialkylimidazolium and tetraalkylammonium salts with tetrafluoroborate and hexafluorophosphate anions. In their presence (10 mol.%), alkylation of 1,3-dicarbonyl compounds and cyanoacetates with dibromoalkanes promoted by solid bases afford either monoalkylated products **147** or linear or cyclic dialkylated products (**148** and **149**, respectively), depending on the alkyl chain length of the dibromoalkane and component ratio, in good yield (56%–96%).[243] Unfortunately, the use of DMF as the solvent precludes the recovery of PTC.

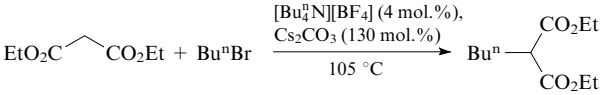




147 **148** **149**

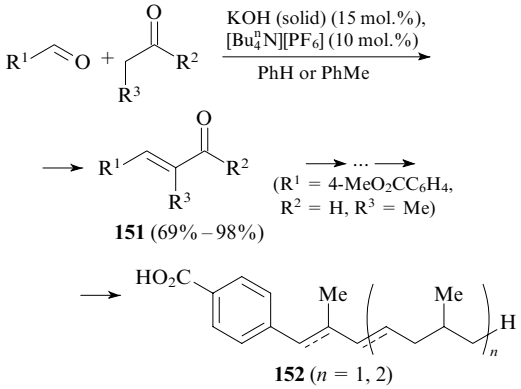
X, Y = Ac, CO_2Me, CO_2Et, CN; Cat (bbim is 1,3-dibutylimidazolium), Bu^n_4N; An = BF_4, PF_6, Br, I.

The recovery problem was solved by applying more hydrophobic PTC and performing the reactions under neat conditions or in nonpolar solvents. For example, the ionic liquids containing 1,3-dialkylimidazolium or tetraalkylammonium cations and BF_4^- or PF_6^- anions behaved as efficient PTC in the solid base-promoted alkylation of diethyl malonate with *n*-butyl bromide in the medium of reactants.[244] The highest yield of product **150** was attained in the presence of the $[Bu^n_4N][BF_4]$–Cs_2CO_3 catalytic system (in the molar ratio 4 : 130). The PTC poorly soluble in the organic phase was recovered and reused four times with the same efficiency.



150 (96%)

Aldol reactions between aromatic (heteroaromatic) aldehydes and various carbonyl compounds induced by the catalytic system $[Bu^n_4N][PF_6]$–KOH (solid)–PhH (PhMe) are exceptionally selective and give condensation products **151** in high yields.[245] In particular, compound **151** (R^1 = 4-$MeO_2CC_6H_4$, R^2 = H, R^3 = Me), a key intermediate in the synthesis of *para*-prenylbenzoic acid derivatives **152**, which possess antitumour, hypolipidemic and anticoagulant activities, were prepared in this way in 98% yield.[246,247]



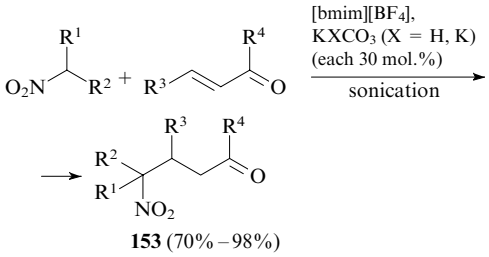
151 (69%–98%)

152 (*n* = 1, 2)

R^1 = Ph, C_6H_4X (X = 4-CO_2Me, 2-Cl, 4-Cl, 3-NO_2, 4-NO_2, 4-OMe), 2-pyridyl, 2-thienyl, 2-furyl; R^2 = H, Ph, cyclo-C_3H_5;
R^3 = H, Me, Pr^n, Pr^i.

The ionic liquid [bmim][BF_4] considerably accelerates the addition reactions of nitro alkanes and α-nitro esters to electron-deficient alkenes in the medium of reactants induced by a solid base.[248] For increasing the surface area

of the solid base (dispersion) and intensifying the mass transfer, the process should better be ultrasonically activated. The method has been successfully used for the synthesis of α-nitro derivatives of δ-oxocarboxylic and glutaric acids **153** containing isoprenoid groups, which are intermediates for the preparation of isoprenoid amino acids, in particular, analogues of known wound healing agents.[249]



153 (70%–98%)

R^2 = Me: R^1 = H, Me; R^2 = CO_2Me: R^1 = H, $H[CH_2C(Me)=CHCH_2]_n$ (n = 1, 2), CO_2Me; R^1-R^2 = $(CH_2)_4$;
R^3 = H, Me, Ph, $Me_2C=CH(CH_2)_2CH(Me)CH_2$;
R^4 = H, Me, Ph, cyclo-C_3H_5, OMe.

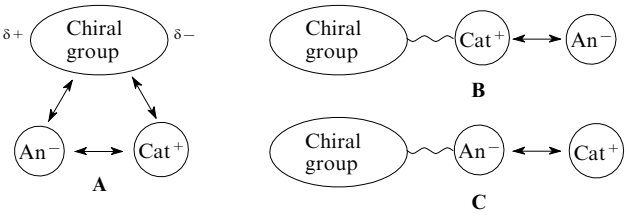
The use of the salt $[Bu^n_4N][PF_6]$ PTC (1 mol.%) substantially increased the selectivity and the product yields of heterogeneous reactions that include the steps of generation of the $^-CCl_3$ anion or dichlorocarbene ($:CCl_2$) from $CHCl_3$ under the action of a solid base. The reaction pathway depends on the reactant structure (Scheme 6). Electron-deficient alkenes and aldehydes react with the $^-CCl_3$ anion under these conditions to give the corresponding trichloromethyl derivatives **154** and **155**. In the absence of an electrophile, dichlorocarbene reacts with alkenes yielding 1,1-dichlorocyclopropane derivatives **156**–**158**.[250] A series of previously unknown or difficultly accessible isoprenoid and terpene derivatives were synthesized in this way.

A specific feature of the developed catalytic system that distinguishes them from traditional PTC based on halides is that the anion-exchange occurs resulting in regeneration of salts with fluorinated anions poorly soluble in the organic phase and in water.[250, 251] The regeneration procedure for the catalytic system is very simple. After removal of the organic phase (by decantation), new portions of the reactants are added to the remaining mixture of the solid base and the PTC and the reaction occurs again (up to 10 times) at the same rate and selectivity. The developed catalysts are simple and convenient to handle and, probably. they could find use in low-tonnage chemical processes.

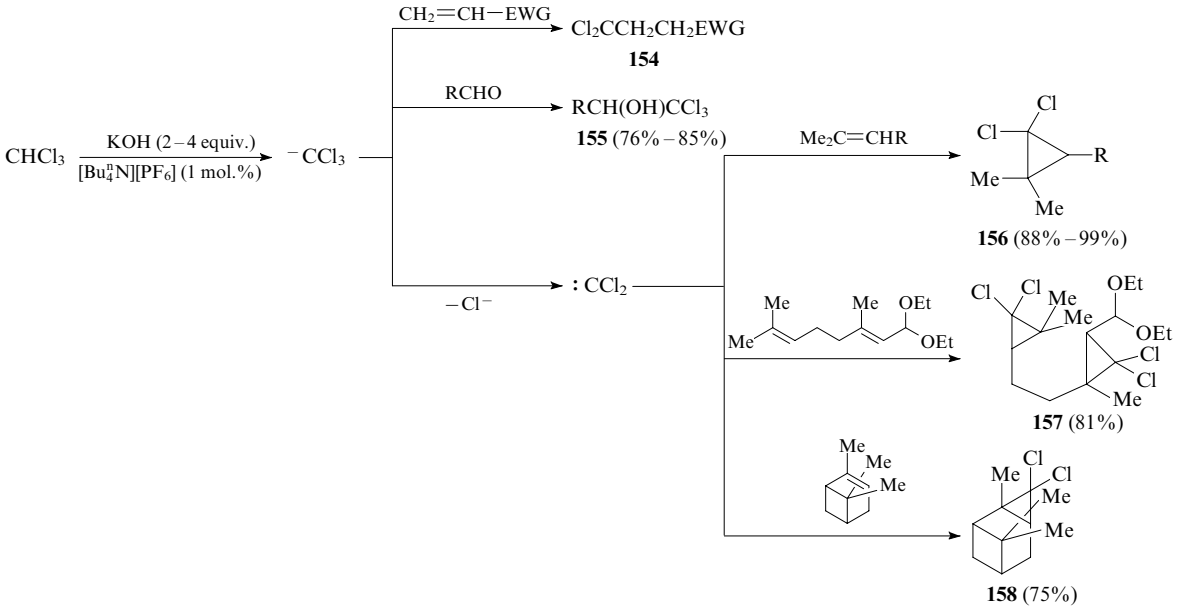
d. Organocatalysis of asymmetric reactions by carbon acids

Key results were attained in the use of chiral IL as organocatalysts in one of the most dynamic trends in modern organic chemistry, namely, the asymmetric organic catalysis.[101–107] Apart from the chiral fragments, the catalysts based on IL contain ionic groups, which decrease their solubility in the reaction medium and markedly facilitate the recovery.[252–254] In addition, by varying the IL cation and anion structures, it is possible to control the electronic and spatial structures and hydrophobic and lipophilic properties of the catalyst over a broad range, thus maximizing its efficiency in a particular reaction[255–258] (as has already been noted, the IL containing specific structural fragments needed for solving particular tasks are referred to as task-specific ionic liquids[31]).

In recent years, original approaches to the preparation of such catalysts have been proposed, in particular, based on combining a chiral group, for example, natural α-amino acid derivative with an ionic fragment through electrostatic interaction (**A**)[259–262] or incorporation of a chiral group into either cation or the anion of the IL by means of



Scheme 6



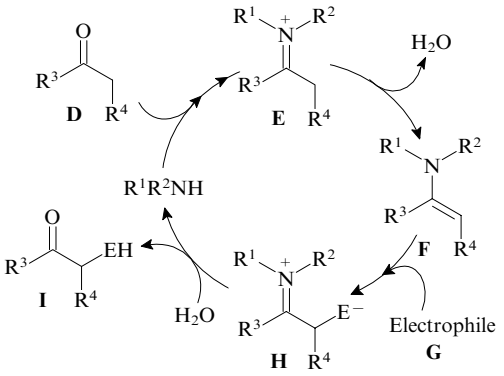
154: EWG = CN, CO_2Et; **155**: R = Ar, ArCH=CH, $Me_2C=CH(CH_2)_2C(Me)=CH$; **156**: R = $(EtO)_2CHCH_2CH(Me)(CH_2)_2$, $CH_2=CHC(Me)(OH)(CH_2)_2$, $AcOCH_2CH=C(Me)(CH_2)_2$.

covalent bonding (**B**, **C**) (double-point arrows designate the electrostatic interactions).[253]

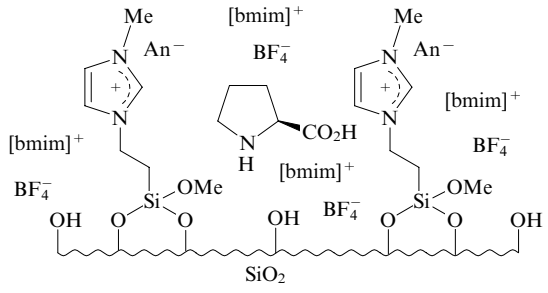
Recoverable organocatalysts of types **A** and especially **B** and **C** have found wide use in recent years in a number of asymmetric reactions, in particular, aldol reactions, the Michael and Mannich reactions, alkylation and some other.

Asymmetric aldol reactions. The catalytic cycle of the asymmetric aldol reaction in the presence of chiral amines includes the reaction of the catalyst R^1R^2NH with the donor ketone **D** to give iminium intermediate **E**, which is then converted to enamine **F**. The latter adds an electrophile (acceptor carbonyl compound) **G**, and the hydrolytic cleavage of adduct **H** gives aldol **I** and the recovered catalyst (Scheme 7).[263, 264] The key intermediate in this process is enamine **F**; therefore, this type of catalysis was called enamine catalysis.[101] It is clear that the presence of ionic groups in the catalysts **A**–**C** should influence the stability and the reactivity of the polarized enamine intermediates and thus the rate and selectivity of asymmetric reactions. Derivatives of α-amino acids or chiral amines usually serve as sources of chirality in the immobilized catalysts.

Scheme 7

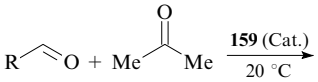


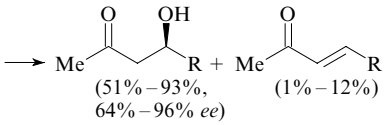
The first heterogeneous catalyst of type **A** is apparently system **159** obtained by Italian researchers, which comprises L-proline (30 mol.%) and IL, for example [bmim][BF_4], co-deposited on the silica gel surface modified by ionic groups.



159

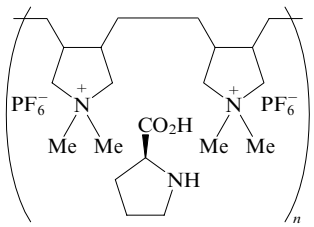
In the presence of this catalyst, aldehydes form aldols with acetone in reasonably good yields with satisfactory *ee* values. The catalyst can be reused; however, after the third recovery, the enantioselectivity of the reaction usually decreases.[260, 261] In addition, the reaction is complicated by the formation of enones as by-products.





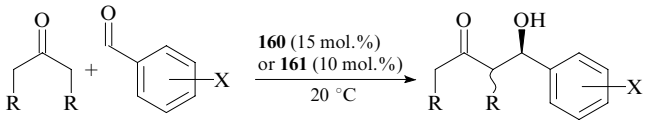
R = Pr^i, Ph, 4-$O_2NC_6H_4$, 4-BrC_6H_4.

The system L-proline–organic cationic polymer, in particular, poly(diallyldialkylammonium) hexafluorophosphate (**160**), proved to be a simple and effective catalyst.[259]



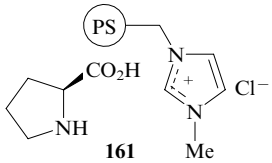
160

In the presence of catalyst **160** (15 mol.%), aldol reactions between aldehydes and ketones proceeded in good yields and with moderate to high enantioselectivity (62%–91% *ee*). Proline was not washed away from the ionic support surface to the organic phase and, hence, the catalyst could be used six times without decrease in the product yields and *ee*.



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

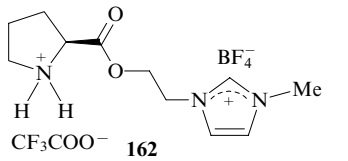
It is of interest that the stereochemistry of the reactions catalyzed by heterogeneous system **160** differed from the result obtained with proline catalysis: in the former case, the product [R–R = $(CH_2)_2$, X = 4-NO_2] was mainly the *syn*-diastereomer, while in the latter case, the *anti*-diastereomer predominated.[265] Similar results were obtained using system **161** containing L-proline and modified polystyrene (PS)



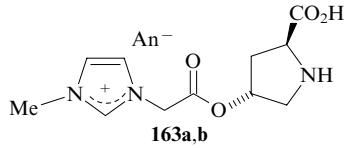
161

as the catalyst;[266] however, catalyst **160** was more preferable, as the polyelectrolyte is much cheaper than the modified polystyrene and contains more ionic groups per polymer unit weight.

The immobilized organocatalysts of types **B** and **C** are usually more stable than type **A** catalysts due to high energy of covalent bonds. In 2006, methods for the preparation of proline-containing chiral IL were proposed using an ester spacer attached to the proline carboxy group or to the 4-hydroxyproline hydroxy group.[267] Compounds **162**–**164** synthesized in this way exhibited various catalytic properties in the aldol reaction.

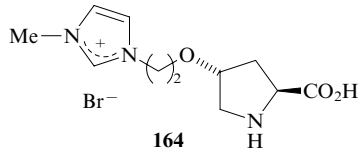


162



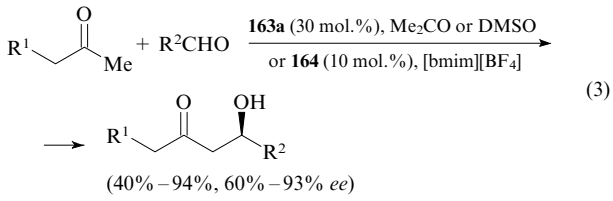
163a,**b**

An = BF_4 (**a**), NTf_2 (**b**).



164

Whereas in the presence of proline ester **162** the yield of the aldol product of reaction (3) (R^1 = H, R^2 = 4-NCC_6H_4) did not exceed 10% at 11% *ee*, in the case of 4-hydroxyproline **163** as the catalyst, the yield was 59% and *ee* was 72%.[267] An important role of the carboxy group proton in the asymmetric catalysis was subsequently taken into account in determining the strategy of synthesis of immobilized catalysts in the series of α-amino acid derivatives.

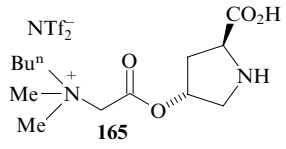


(3)

R^1 = H, Me; R^2 = Ph, C_6H_4X (X = 2-Cl, 2-Br, 2-NO_2, 4-Me, 4-CN, 4-Br, 4-NO_2, 4-AcNH, 4-CF_3), 2-naphthyl, cyclo-C_6H_{11}.

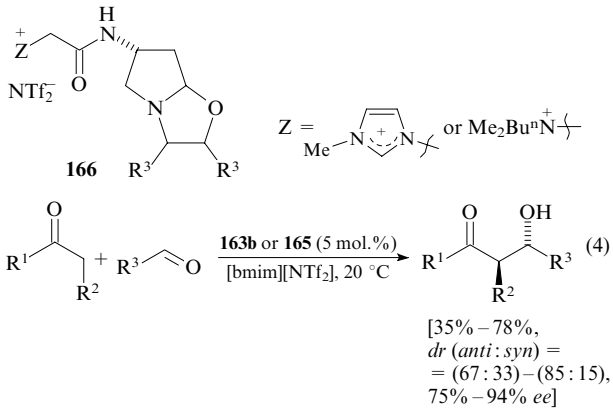
To facilitate the recovery of the ionic catalysts, commercially available IL were used as the reaction media (like dissolves like). In the **164**–[bmim][BF_4] system, aldol reactions between acetone and aromatic aldehydes afforded aldol (R^1 = H) in yields and *ee* values comparable with those obtained previously in organic solvents. The system composed of two IL was recovered and reused six times, the enantioselectivity of the reaction being retained.[268]

Lombardo *et al.*[269] synthesized 4-hydroxyproline derivatives **163b** and **165** modified by ionic groups and used them in the aldol reaction between aldehydes and ketones in [bmim][NTf_2].[269]



165

The use of these ionic catalysts in combination with IL made it possible to reduce the catalyst load to 5 mol.% and increase the rates and selectivities of reactions (4) compared to analogous reactions in organic solvents. However, the **165**–bmim[NTf_2] system lost activity after the recovery due to partial 'washing away' of the catalyst to the organic phase during extraction of the aldol product and/or transformation of the catalyst to oxazolidine **166** upon the reaction with the aldehyde.

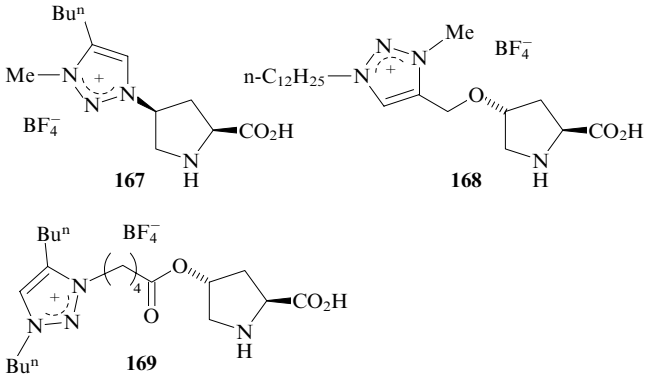


166

[35%–78%, *dr* (*anti*:*syn*) = = (67:33)–(85:15), 75%–94% *ee*]

R^1 = H: R^2 = H, OH; R^1–R^2 = $(CH_2)_3$, $OCMe_2O$;
R^3 = 4-XC_6H_4 (X = H, NO_2, Cl), 2-naphthyl.

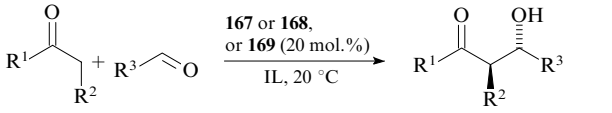
Attempts were undertaken to increase the efficiency and durability of proline-containing catalysts by changing their electronic and spatial structure and using alternative reaction media. Thus chiral IL **167**–**169** containing 1,2,3-triazolium cations connected to the proline fragment either directly or through an ester spacer were synthesized.[270]



167 **168**

169

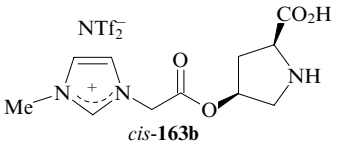
In the presence of these compounds, the asymmetric aldol reactions of acetone or cycloalkanones with aromatic aldehydes under neat conditions or in the IL medium afforded aldols with higher *anti*-diastereo- and enantioselectivities than the reactions catalyzed by non-immobilized proline, *i.e.*, synergistic effect of the ionic and proline groups is observed. The 4-substituent in the pyrrolidine ring (*cis* in compound **167** and *trans* in **168**, **169**) had little influence on the stereochemical outcome of the reactions; however, catalyst **167** was more stable upon the recovery retaining the activity over five cycles (the enantioselectivity decreased).



[35–78%, *dr* (*anti*:*syn*) = (67:33)–(85:15), 75%–94% *ee*]

R^1 = R^2 = H; R^1–R^2 = $(CH_2)_2$, $(CH_2)_3$;
R^3 = 4-XC_6H_4 (X = H, NO_2, Cl, Br, F, OMe);
IL = [bmim][BF_4], [GND]I.

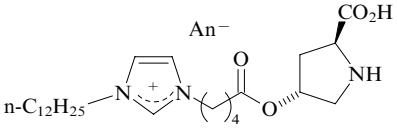
The catalytic activity of proline-containing chiral IL was increased by performing the aldol reactions in the presence of water, which, as a readily available and environmentally safe solvent, finds increasing use in organic synthesis.[271, 272] The turnover number (TON) of catalysts **163b** (Ref. 273) and *cis*-**163b** (Ref. 274)



cis-**163b**

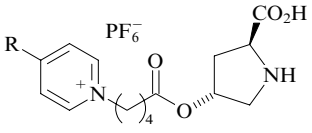
in the reaction between cyclohexanone and 4-nitrobenzaldehyde increased from 17 to 930 upon the addition to the reaction mixture (in excess ketone) of a slight (1–2 equiv.) amount of water, which probably suppressed the side formation of oxazolidine **166**.[275] Under these conditions, the catalyst *cis*-**163b** with *cis*-arrangement of the ionic and carboxy groups in the pyrrolidine ring was more active than the corresponding *trans*-isomer **163b**: 0.1 mol.% of the catalyst was sufficient for a single-shot reaction. Salt *cis*-**163b** could be recovered and used four times without decrease in the yield and *ee* of aldol products; however, the initial catalyst load was 2 mol.% and its amount seemed to decrease in each subsequent run due to 'washing out'.

We proposed an efficient method for adapting amino acid-based chiral IL to the aqueous medium by introducing long-chain alkyl groups into their molecules and performing reactions in reactants–water heterophase systems. Thus proline-containing imidazolium **170a**[276] and pyridinium **171a**[277] salts



170a,**b**

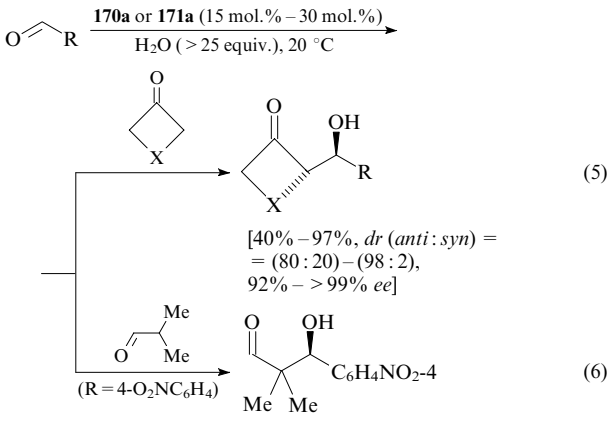
An = PF_6 (**a**), BF_4 (**b**).



171a,**b**

R = $CHBu^n_2$ (**a**), H (**b**).

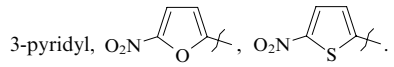
proved to be stable and selective catalysts of aldol reactions (5), (6) in the presence of a large excess of water (⩾25 equiv.).



(5)

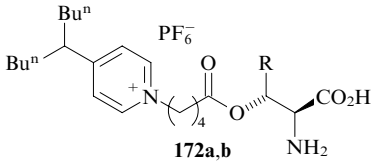
(6)

X = $(CH_2)_3$, $(CH_2)_2$, CH_2OCH_2, CH_2SCH_2, $CH_2N(Cbz)CH_2$;
R = Ph, 4-$O_2NC_6H_4$, 4-NCC_6H_4, 4-$MeO_2CC_6H_4$, 4-$MeOC_6H_4$,



3-pyridyl.

Under the action of these catalysts (15% – 30 mol.%), aldol products were formed under simple experimental conditions in high yields and with exceptionally high *anti*-diastereo- (*dr* up to 98 : 2) and enantioselectivities (*ee* up to 99%). In the reactions catalyzed by **170a** and **171a**, cyclic ketones and branched aliphatic aldehydes serve as nucleophiles, and aromatic and heteroaromatic aldehydes are electrophiles.[278] The reactions also occurred in the presence of lipophilic chiral IL **172a**,**b**

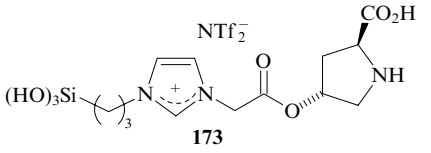


172a,**b**

R = H (**a**), Me (**b**).

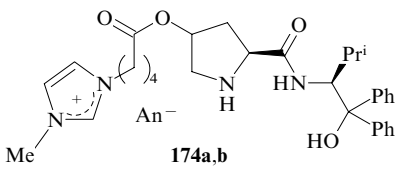
containing serine and threonine fragments; however, the conversion (84% – 89%), diastereoselectivity [*anti* : *syn* = (87 : 13) – (90 : 10)] and enantioselectivity (91% – 97% *ee*) were somewhat lower in this case.[277] The catalysts were easily recovered and retained the catalytic properties in 5–8 reaction cycles.

It is of interest that IL **170b** and **171b** with similar structures but without long-chain alkyl groups or hydrophobic anion do not catalyze the aldol reaction in the presence of water. Apparently, 'amphiphobic' IL **170a**, **171a**, **172a**,**b** poorly soluble in both aqueous and organic phase (reactant phase) are located, under the reactions conditions, at the interface where the catalytic transformation takes place. The hydrophilic IL **170b** and **171b** pass, under these conditions, to the aqueous solution in which the amino acid fragment exists as the zwitterion unable to react with carbonyl compounds to give enamines needed for triggering the catalytic cycle (see Scheme 7). The amphiphilic compound **173** probably occupies the intermediate position being distributed between the organic and aqueous phases and, on the one hand, catalyzes the aldol reaction between cycloalkanones and aldehydes in the reactants–water two-phase system being located in the organic layer and, on the other hand, passes into water during the extraction of products and can be recovered.[279]



173

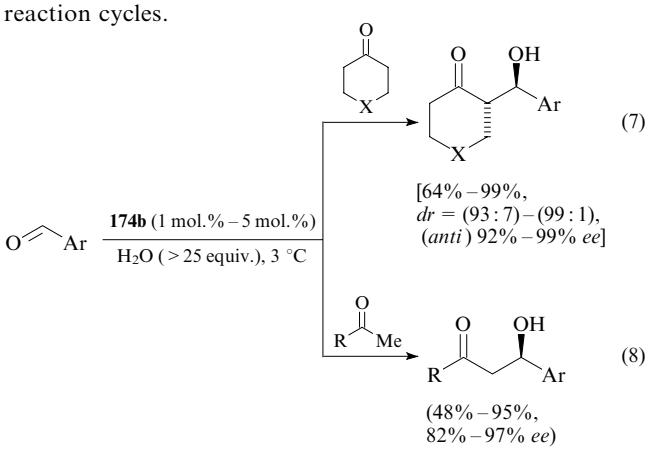
As noted in Section II, amino acid amides possess higher catalytic activity in the asymmetric aldol reaction than the proper amino acids. We synthesized chiral amides **174a**,**b** containing proline and α,α-diphenyl-(*S*)-valinol fragments and studied them in aldol reactions[280] with the assumption that these catalysts, which determine the transition state geometry through the formation of several hydrogen bonds,



174a,**b**

An = Br (**a**), PF_6 (**b**).

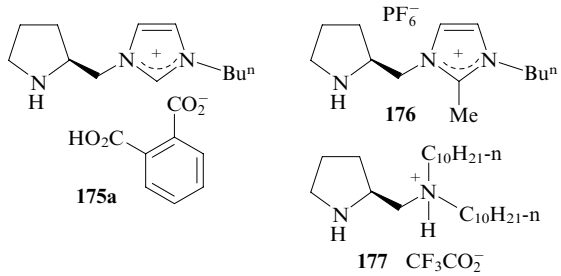
can combine high enantioselectivity with recoverability. In the given case, both compounds efficiently catalyzed the reactions in the presence of water, apparently, due to the fact that the amide group does not dissociate into ions in an aqueous medium. Nevertheless, the practically water-insoluble hexafluorophosphate **174b** was more active than hydrophilic bromide **174a**: in some cases, the required amount of the former was 1 mol.% (for **174a**, this was at least 5 mol.%). In the presence of salt **174b** under heterogeneous conditions, both cyclic and linear ketones and various aldehydes reacted to give aldols with high regio- [reaction (8)], *anti*-diastereo- [reaction (7)] and enantioselectivities. The reactions can easily be scaled and hexafluorophosphate **174b** retained the activity and selectivity in four reaction cycles.



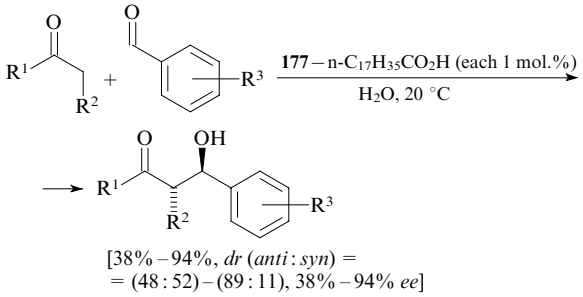
X = CH_2, O, S; R = Pr^n, n-C_6H_{13}, cyclo-C_3H_5, Bn;
Ar = C_6H_4X (X = 2-NO_2, 3-OPh, 4-NO_2, 4-CN, 4-CO_2Me, 4-F), C_6F_5, 2-naphthyl.

Note that as regards the selectivity, compounds **170a**, **171a** and **174b** approach aldolases, which catalyze the biosynthesis of carbohydrates in living systems under heterogeneous conditions in an aqueous medium.[281–283] In essence, the proposed approach opens up the way to the design of exceptionally effective and substrate-specific artificial IL analogues of natural enzymes, which could find use in asymmetric synthesis and biocatalysis.

In addition to proline derivatives, chiral IL **175a**, **176** and **177** containing a pyrrolidine fragment were synthesized and studied in asymmetric aldol reactions. It was found that in the presence of compounds **175a**[284] and **176**,[285] these reactions have rather low diastereoselectivity ($dr \leqslant 3:1$) and enantioselectivity ($ee < 65\%$) under the studied conditions (in the reactant medium[284] or in water[285]).



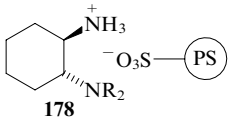
As in the case of amino acid catalysts, the activity and the selectivity of pyrrolidine-based chiral IL was increased by introduction of long-chain alkyl groups into their molecules and by performing reactions in the presence of water. Thus under the action of trifluoroacetate **177**, acetone and cycloalkanones reacted with aromatic aldehydes in water yielding aldols the diastereomeric and enantiomeric purities of which were only slightly inferior to the values attained in the presence of efficient proline-containing catalysts.[286]



R^1 = Me, R^2 = H; $R^1 - R^2$ = $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$;
R^3 = H, 2-NO_2, 3-NO_2, 4-NO_2, 4-CN, 4-Br, 4-CO_2Me, 4-Cl.

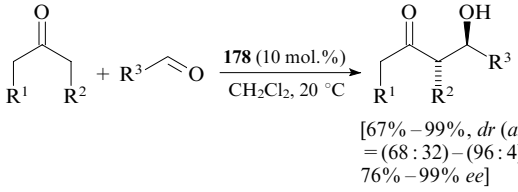
The key role was played by the degree of dispersion of the aqueous emulsion. For the formation of particles of the required size (< 1 μm), stearic acid was added to the system as an emulsifying agent. An advantage of this method is low catalyst load (1 mol.%); however, no data on the catalyst recovery were reported.

The asymmetric aldol reactions proceed fairly efficiently in the presence of chiral diammonium salts **178** with sulfated polystyrene as the anion.



R = Me, Pr^n.

Heterogeneous catalysts **178** can easily be recovered (by filtration) and used in the reaction at least six times with the same enantioselectivity and only a slight decrease in the yield of the aldol products.[262]

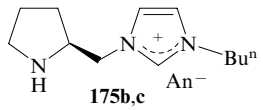


R^1 = H: R^2 = H, Pr^i; $R^1 - R^2$ = $(CH_2)_2$, $(CH_2)_3$;
R^3 = C_6H_4X (X = H, 2-NO_2, 3-NO_2, 4-NO_2, 2-Cl, 4-Cl, 4-CN, 3-Br, 4-CF_3), 1-naphthyl.

Asymmetric Michael reactions. Most of the examples of asymmetric Michael reactions in the presence of chiral IL are related to the addition reactions of carbonyl compounds to α-nitro alkenes. The catalytic cycle of these reactions includes the enamine activation of the carbonyl component and is similar to the cycle of aldol reaction shown in Scheme 7 with the only difference that the role of electrophile **G** belongs to nitro alkene rather than the acceptor aldehyde. Due to this seemingly insignificant distinction, amino acid catalysts of aldol reactions are usually inactive in the Michael reactions, whereas pyrrolidine type catalysts, which have low selectivity in aldol reactions, are extremely efficient in the nucleophilic addition to α-nitro alkenes.

The application of chiral IL as organocatalysts of asymmetric Michael reactions was pioneered by Chinese chemists. In 2006, they synthesized IL **175b**,**c** containing a

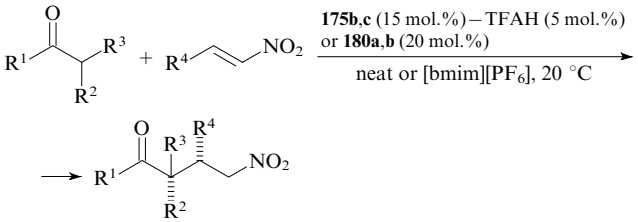
chiral pyrrolidine fragment in the α-position to the alkylimidazolium cation



175b,c

An = Br (**b**), BF_4 (**c**).

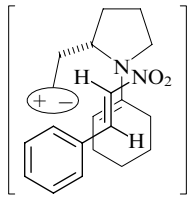
and found that these compounds (15 mol.%) combined with trifluoroacetic acid (TFAH) (5 mol.%) are very efficient as catalysts of the Michael reaction involving a broad range of donors (ketones and aldehydes) and acceptors (α-nitro alkenes) to give Michael adducts **179** in high yields (up to 99%) and with high enantioselectivity (up to 99% *ee*) and *syn*-diastereoselectivity (*syn* : *anti* up to 99 : 1).[287]



179 [51% – 99%, *dr* (*syn* : *anti*) = = (63 : 37) – (99 : 1), 43% – 99% *ee*]

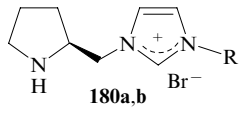
R^3 = H: $R^1 - R^2$ = $(CH_2)_3$, $(CH_2)_4$; R^1 = Me, R^2 = R^3 = H;
R^1 = R^3 = H, R^2 = Pr^i; R^1 = H, R^2 = R^3 = Me;
R^4 = C_6H_4X (X = H, 2-Cl, 3-NO_2, 4-Cl, 4-Me, 4-OMe, 4-CF_3), 2-naphthyl, 2-furyl.

The authors explained the obtained results in terms of formation of an acyclic synclinal transition state syncl-**TS** (shown for cyclohexanone) in which the ionic group selectively shields the *Si*-side of the enamine double bond, thus dictating the *Re* – *Re* direction of the nitroalkene attack.



syncl-**TS**

The reaction proceeds nearly as efficiently as in the [bmim][PF_6] medium (in this case, compounds **180a,b** served as the catalysts); there is no need for delivery of the acid co-catalyst (TFAH) to the system, this role being obviously played by IL.[288]

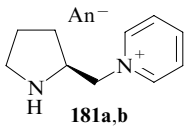


180a,b

R = Me (**a**), Et(**b**).

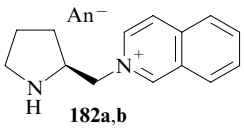
In both cases, the catalysts were recovered; from the reactant medium, they were precipitated with ether, while the **180** – IL system was recycled after extraction of the products without further purification. Four reaction cycles of catalysts **175b,c** (or **180a,b**) did not reduce the diastereo- and enantioselectivities of the reactions; however, the duration of the reaction increased due to gradual catalyst deactivation.

The change in the nature of the cationic fragment can affect the selectivity of reactions involving particular substrates; however, generally, the stereochemical outcome of the reactions remains high. Indeed, pyrrolidine derivatives containing pyridinium cations **181a,b**,[289] isoquinolinium **182a,b** [290] or 1,2,3-triazolium derivatives **183a,b** [291] proved to be efficient catalysts of asymmetric reactions of six-membered cyclic ketones with α-nitro alkenes; in these cases, the reactions can be carried out both in the reactant medium in the presence of TFAH (catalysts **181**, **183**) and in the IL medium (catalysts **182**).



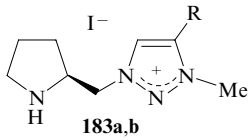
181a,b

An = Cl (**a**), BF_4 (**b**).

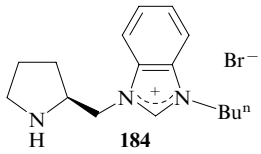


182a,b

An = Br (**a**), PF_6 (**b**).



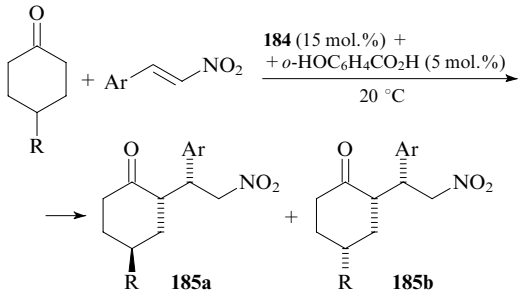
183a,b



184

R = Ph (**a**), Bu^n (**b**).

The use of pyrrolidine-containing IL made it possible to perform the first desymmetrization of prochiral ketones by the asymmetric Michael reaction. Ionic liquid **184** containing benzimidazolium cations proved to be the compound of choice. In the presence of **184** – salicylic acid system, 4-substituted cyclohexanones added to nitro alkenes to give mixtures of products **185a** and **185b** containing three asymmetric carbon atoms with isomer **185a** markedly predominating.[292] The very high enantiomeric excess of adducts **185a** (93% – 99% *ee*) was retained with the recovered catalyst; however, its activity decreased.



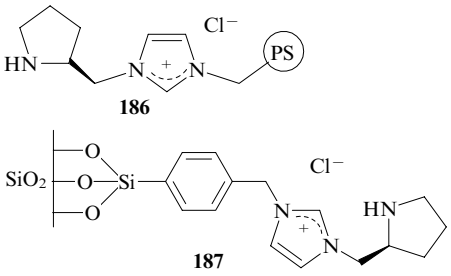
185a **185b**

[61% – 99%, **185a** : **185b** = (4 : 1) – (12 : 1), (**a**) 93% – 99% *ee*]

R = Me, Et, Bu^t, Ph, N_3, SAc; Ar = C_6H_4X (X = H, 2-Cl, 4-Cl, 4-Me, 4-Ph, 4-OMe, 2-NO_2, 3-NO_2, 4-NO_2), 1-naphthyl, *etc.*

To facilitate the catalyst recovery, the cationic group they contained (imidazolium cations) was attached to the polymeric matrix, for example, polystyrene or silica gel. The immobilized catalysts **186** [293] and **187** [294] obtained in these way were highly efficient in asymmetric reactions of β-nitrostyrene derivatives with various carbonyl compounds without a solvent, which gave Michael adducts **179** with diastereomeric excess and enantiomeric purity not inferior to those attained under the action of catalysts **175b,c** and **180a,b**.

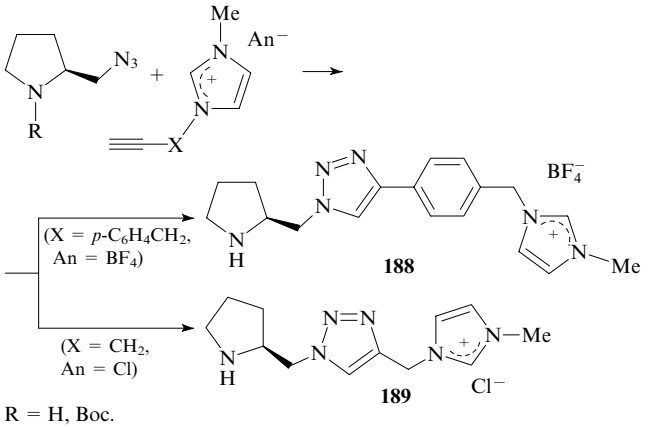
Heterogeneous catalysts **186** and **187** were readily separated from the products (by filtration), and they could be introduced in the Michael reactions at least six (for **187**) or eight times (for **186**) without decrease in the diastereo- and enantioselectivity.



186

187

In order to increase the efficiency and recover, ability of pyrrolidine-containing IL, the catalysts were modified by introducing various spacer groups between the pyrrolidine and cationic fragments. A common spacer is the 1,2,3-triazole fragment formed by 1,3-DCA reactions between (*S*)-2-azidomethylpyrrolidine and alkynes modified by the imidazolium cation. This process can be regarded as an example of 1,3-DCA involving IL as a reactant (see Section V of the review).

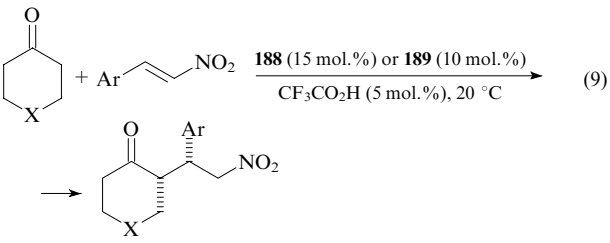


188

189

R = H, Boc.

Compounds **188**[295] and especially **189**[296] synthesized in this way in combination with TFAH proved to be efficient catalysts of the reactions of cyclic ketones with β-nitrostyrene derivatives in the reactant medium [reaction (9)]. In the presence of the developed catalytic systems, γ-nitro ketones **190** were formed with exceptionally high *syn*-diastereo- and enantioselectivity, and catalyst **189** retained the catalytic properties in eight reaction cycles.

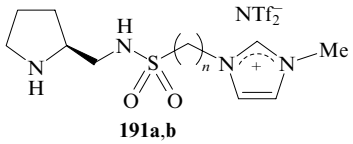


(9)

190 [85% – 95%, *dr* (*syn* : *anti*) = = (92 : 8) – (99 : 1), 91% – > 99% *ee*]

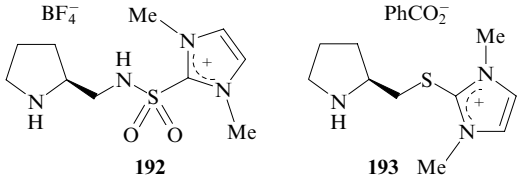
X = CH_2, O, S; Ar = C_6H_4Y (Y = H, 2-Cl, 2-Br, 3-NO_2, 4-Me, 4-OMe, 4-CF_3, 4-Cl, 4-F), 3,4-$(MeO)_2C_6H_3$, 3,4-$(OCH_2O)C_6H_3$, 2,4-$Cl_2C_6H_3$, 2-furyl, 1-naphthyl, 2-naphthyl.

Sulfamides **191a**,[297] **191b**[298] and **192**[299] developed by Headley and co-workers, which contain the (*S*)-pyrrolidine fragment and 1,3-dialkylimidazolium cation, were found to be promising organocatalysts for the asymmetric Michael reactions involving α-nitroalkenes.



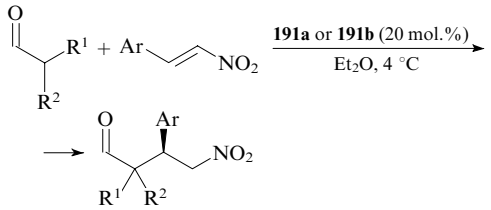
191a,**b**

n = 3 (**a**), 1 (**b**).



192 **193**

In the presence of catalysts **191a**,**b**, nitrostyrene derivatives add not only ketones but also α-substituted aliphatic aldehydes to give chiral adducts with reasonably high diastereo- and enantioselectivities. Catalyst **191b** is more active and suitable for performing the reaction of sterically hindered α,α-disubstituted aldehydes, although the enantiomeric excess of the products is not very high.

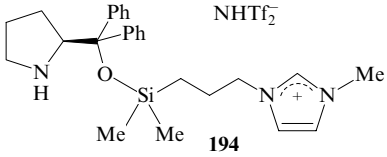


[29% – 98%, *dr* (*syn* : *anti*) = = (78 : 22) – (97 : 3), 33% – 90% *ee*]

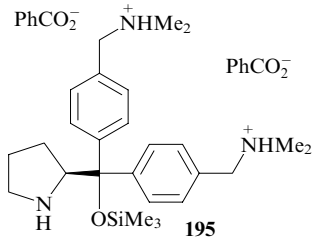
$R^1 - R^2 = (CH_2)_4$; R^1 = H, Me; R^2 = Me, Et, Pr^n, Pr^i, Bu^n; Ar = C_6H_4X (X = 4-Me, 4-MeO, 4-Br, 2-CF_3).

Sulfamide **192**[299] and IL **193** synthesized by Chinese chemists[300] in which the pyrrolidine and 1,3-dialkylimidazolium fragments are separated by the CH_2S group were successfully used to catalyze the Michael reactions involving cyclic ketones [reaction (9)]. The reactions were carried out in organic solvents, in particular, in Et_2O (catalyst **191a**), MeOH (**191b**), Pr^iOH (**192**) or poly(ethylene glycol) PEG-800 (**193**). Electrospray ionization mass spectrometry detected the 'host – guest' complexes between PEG-800 and organocatalyst **193**.[300] Compounds **191** – **193** were easily separated from the products and provided the enantioselectivity in 3 – 7 cycles.

Good results were obtained by applying chiral IL **194**[301] and **195**[302] containing α,α-diarylprolinol silyl ether fragments as organocatalysts for asymmetric Michael reactions.

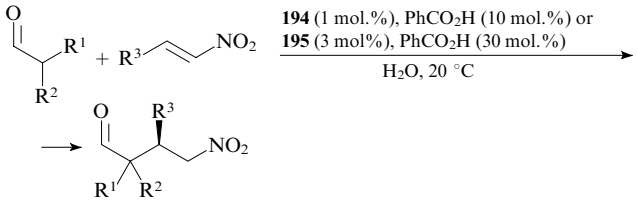


194



195

Unlike the above-considered catalysts, these compounds efficiently catalyzed the reactions of aliphatic aldehydes with nitro alkenes in water, high yields and stereochemical purity of the products being attained at low catalyst loads (1 mol.% – 3 mol.%) and a slight excess of the donor aldehyde (< 2 equiv. with respect to nitro alkene).



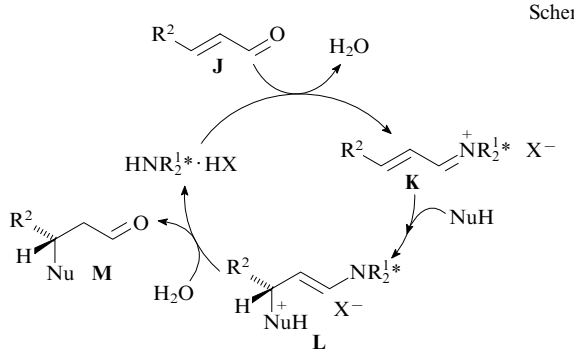
[65% – 99%, *dr* (*syn* : *anti*) = = (91 : 9) – (98 : 2), 76% – > 99.5% *ee*]

R^1 = H, Me; R^2 = Me, Et, Pr^n, Pr^i, Bu^n, n-C_5H_{11}, n-C_7H_{15}, Bn;
R^3 = C_6H_4X (X = H, 2-Cl, 2-Br, 2-CF_3, 4-Br, 4-OMe), 2-furyl, Bu^n, cyclo-C_6H_{11}.

The catalytic system IL **195** – water can be introduced in the reactions up to eight times without decrease in the diastereo- and enantioselectivities, although gradual catalyst deactivation was observed after the fourth cycle (increase in the reaction time). In the author's opinion, owing to the simple procedure and the scalability, this method may be useful not only in the laboratory but also in industry.

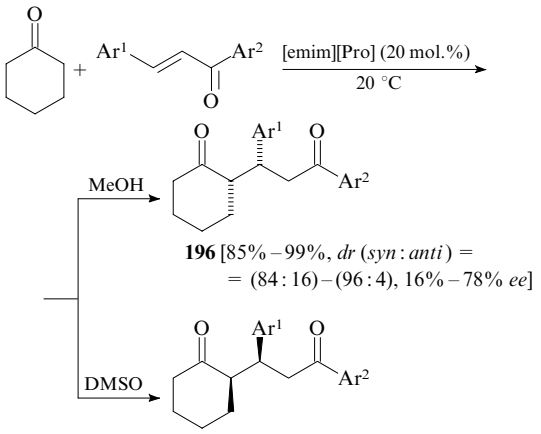
Yet another, much less studied type of asymmetric Michael reactions comprises the reactions of carbon acids with α,β-unsaturated carbonyl compounds in which the catalyst activates the acceptor component by the formation of the iminium cation with it. The catalytic cycle of these reactions is initiated by the 1,2-addition of the chiral amino compound to the carbonyl group of acceptor **J**, resulting in iminium cation **K**. The latter reacts with the nucleophile to give first intermediate **L** and then product **M** and the catalyst thus returns to the cycle (Scheme 8, the asterisk points to the chiral catalyst).[303, 304] The difficulty of developing recoverable catalysts of these processes is related to high reactivity of iminium cations **K**, which can undergo

Scheme 8



side transformations under the reaction conditions thus deactivating the catalyst.

The iminium type of catalysis is implemented (probably, simultaneously with the enamine activation of the donor ketone) in the reactions of cyclohexanone with chalcones in the presence of 1-ethyl-3-methylimidazolium prolinate (Pro) to give Michael adducts **196** in high yields and, in some cases, with reasonably high diastereo- and enantioselectivities.[305] Note that the enantiomeric structure of adducts **196** depends on the solvent used, adducts **196** being formed in methanol and *ent*-**196** being formed in DMSO. The possibility of catalyst recovery was not discussed in the publication.

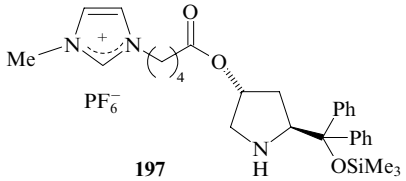


196 [85% – 99%, *dr* (*syn* : *anti*) = = (84 : 16) – (96 : 4), 16% – 78% *ee*]

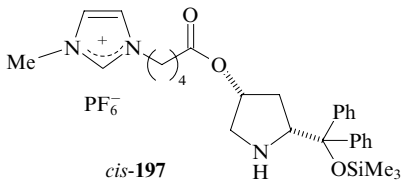
ent-**196** [80% – 90%, *dr* (*syn* : *anti*) = = (77 : 23) – (99 : 1), 23% – 94% *ee*]

Ar^1 = C_6H_4X (X = H, 2-Cl, 4-Me, 4-Cl, 4-Br);
Ar^2 = C_6H_4Y-4 (Y = H, Me, Cl, OMe, NH_2).

Recently, we prepared chiral IL **197** [306] containing an α,α-diphenyl-(*S*)-prolinol fragment, which is the first representative of recoverable organocatalysts of asymmetric Michael reactions of the iminium type (see Scheme 8).

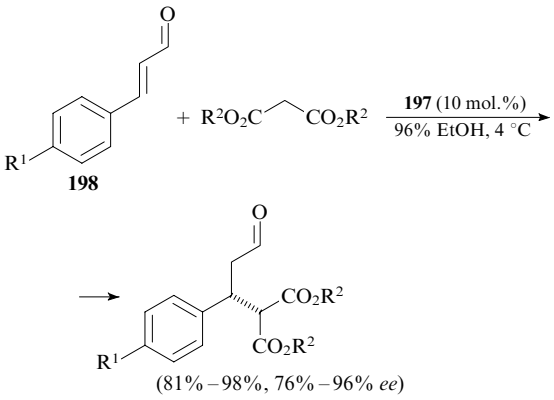


197



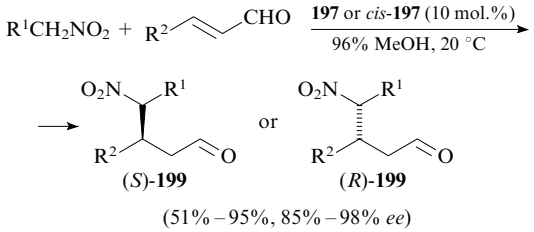
cis-**197**

In the presence of compound **197**, reactions of dialkyl malonates with cinnamaldehyde derivatives **198** took place under mild conditions to give the corresponding adducts in high yields (up to 98%) and with high enantioselectivity (up to 98% *ee*). In particular, using compound **197**, it was possible to considerably increase (as compared with the known method) the yield and the *ee* value of the adduct with R^1 = F, R^2 = Bn, which is the key intermediate for the preparation of promising antidepressant drug (–)-paroxetin.[307] Unlike the known prolinol type catalysts,[308 – 310] catalyst **197** can be used four times without decrease in its activity and the process enantioselectivity.



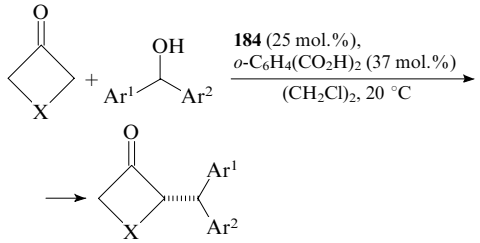
R^1 = H, Cl, F, NO_2, OMe; R^2 = Me, Et, Bn.

Chiral IL **197** and *cis*-**197** proved to be efficient catalysts of the asymmetric addition of nitro alkanes to α,β-enals.[311] They were used to synthesize (*S*)- and (*R*)-enantiomers of γ-nitro aldehydes **199** in high yield and with high enantiomeric purity; among these compounds, there are key intermediate for the preparation of the most active (*R*)-enantiomers of the pharmaceutical drugs phenibut, baclophen and rolipram, which are used to treat central nervous system disorders. Note that although compounds **197** and *cis*-**197** are not optical antipodes, enantiomers (*S*)-**199** and (*R*)-**199** have nearly equal magnitudes of *ee*, apparently, due to predominant effect of the C-5 atoms of the catalyst pyrrolidine rings having *S*- or *R*-configurations on the process stereochemistry. The catalysts can be used up to five times; the product yields and *ee* do not decrease, although the catalytic activity decreased after the third recovery.



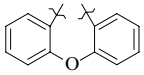
R^1 = H, Me; R^2 = 4-XC_6H_4 (X = H, Cl, Br, NO_2, OMe, F), 3-cyclo-C_5H_9-4-$MeOC_6H_3$, Fc, Me.

Miscellaneous asymmetric reactions. Apart from aldol reactions and the Michael reactions, chiral IL also catalyze some other asymmetric reactions of carbon acids. Chinese researchers found that in the presence of IL **184** containing a chiral pyrrolidine fragment, cyclic ketones react with diarylhydroxymethane derivatives to give α-alkylation products **200**.[312] In the authors' opinion, the reaction follows the enamine mechanism (see Scheme 7) in which electrophile **G** is represented by the diarylmethyl cation stabilized by aromatic substituents. The proposed approach proved to be a fairly efficient way of desymmetrization of 4-substituted cyclohexanones: the corresponding alkylation products **200** [X = $CH_2CH(R)CH_2$] were obtained in nearly quantitative yields (up to 99%) and with *dr* (*trans*:*cis* > 99:1) and *ee* (up to 87%) values that are very high for alkylation reactions. After the reaction, catalyst **184** was precipitated with diethyl ether and reused in the next cycle, which was characterized by the same diastereo- and enantioselectivity, as the previous one. Some decrease in the yield and *ee* values of products **200** was observed only in the fourth cycle; however, the diastereoselectivity remained high.



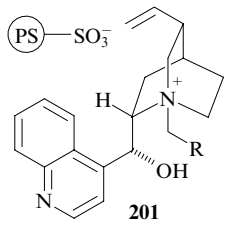
200 [43%–99%, *dr* (*trans*:*cis*) = = (2:1)–(>99:1), 18%–87% *ee*]

X = $(CH_2)_n$ (*n* = 1, 3), CH_2YCH_2 (Y = O, S, NMe, ), $CH_2CH(R)CH_2$ (R = Me, Et, Bu^t, *tert*-C_5H_{11}, Ph, 4-BrC_6H_4, N_3, OH, OAc, 4-$BrC_6H_4CO_2$).

Ar^1-Ar^2 = ; Ar^1 = Fc, Ar^2 = Ph;

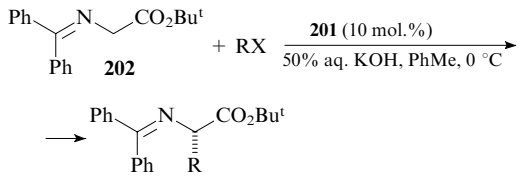
$Ar^1 = Ar^2 = C_6H_4NR^2$-4 [R = Me, Et; R–R = $(CH_2)_2O(CH_2)_2$].

Japanese chemists synthesized quininium salt **201** with sulfated polystyrene as the anion



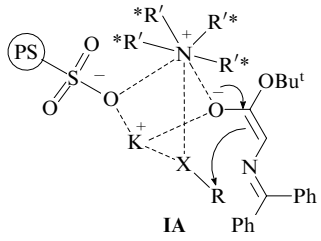
201 R is 9-anthryl

(practically at the same time this approach was used[262] to prepare catalyst **178**) and found that in the presence of this catalyst, *N*-(diphenylmethylidene)glycine ester **202** reacts with alkyl, allyl or benzyl halides to give the corresponding alkylation products in good yields (up to 95%) and with high enantioselectivity (up to 97% *ee*).[313]



R = Bn, 4-$MeC_6H_4CH_2$, 4-$BrC_6H_4CH_2$, $CH_2{=}CHCH_2$, Me; X = Br, I.

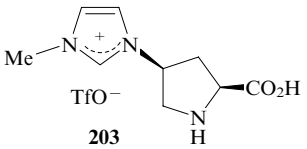
The high stereocontrol level was attributed to the formation of ion aggregates (**IA**) involving the enol form of glycinate **202**.



IA

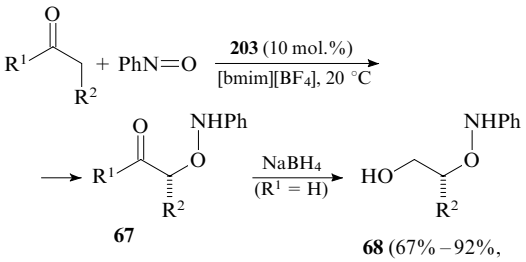
The heterogeneous catalyst **201** separated by filtration retained its activity and selectivity in the two subsequent reaction cycles.

It was found [314] that IL **203** containing directly linked proline and imidazolium fragments



203

catalyzes asymmetric aminoxylation of aldehydes and ketones with nitrosobenzene in the commercially available IL [bmim][BF_4]. Products **67** were isolated as the corresponding hydroxy derivatives **68** in high yield and almost 100% enantiomeric purity. After extraction of the products, the system IL **203** – [bmim][BF_4] catalyzed equally efficiently the reactions involving new portions of reactants and allowed at least seven reaction – recovery cycles. Note, however, that by conducting this reaction in the L-proline – [bmim][BF_4] system, one can attain almost the same selectivity and recoverability characteristics, without resorting to the synthesis of catalyst **203** (see Section II).[134, 135]

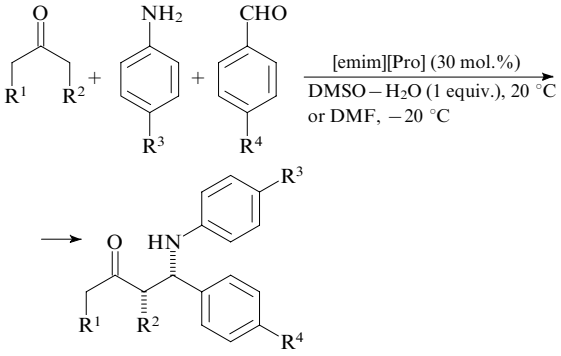


67

68 (67% – 92%, 99% – > 99% *ee*)

R^1 = H: R^2 = Me, Et, Pr^n, Pr^i, Bu^n, Bn;
$R^1 - R^2$ = $(CH_2)_4$, $CH_2CH_2OCH_2$.

Some three-component asymmetric reactions of CH acids occur in the presence of proline salts in which the amino acid serves as the anion or cation. The former version is implemented in the 1-ethyl-3-methylimidazolium prolinate-catalyzed (30 mol.%) Mannich reaction of carbonyl compounds with aniline derivatives and aromatic aldehydes. In moist DMSO or DMF, this reaction was highly regio-, stereo- and enantioselective to give coupling products **204**.[315] The proposed conditions that imply the use of

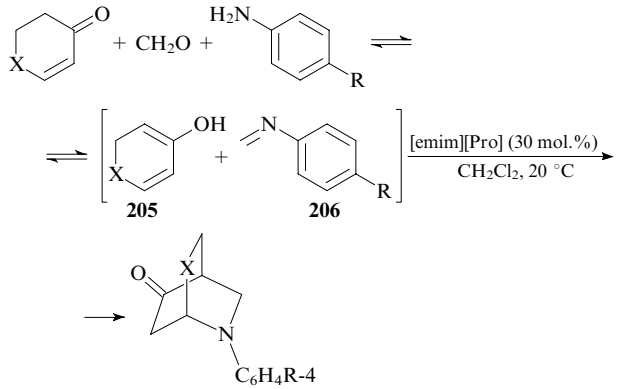


204 [48% – 99%, *dr* (*syn* : *anti*) = (54 : 46) – (> 99 : 1), (*syn*) 90% – > 99% *ee*]

R^1 = H, Me; R^2 = H, Me, OH; R^3 = H, OMe;
R^4 = H, NO_2, CN, Cl, F, Br, Me.

dipolar aprotic solvents do not allow, however, recovery of the IL after the reaction.

The IL [emim][Pro] was an efficient catalyst for the one-pot aza-Diels – Alder reaction between cyclic vinyl ketones, formaldehyde and aniline derivatives.[316] Dienols **205** generated *in situ* react with methyleneimines **206** to give bicyclic ketones **207** having high diastereomeric and enantiomeric purity. The catalyst can be introduced in the reaction six times, although the enantioselectivity somewhat decreases.

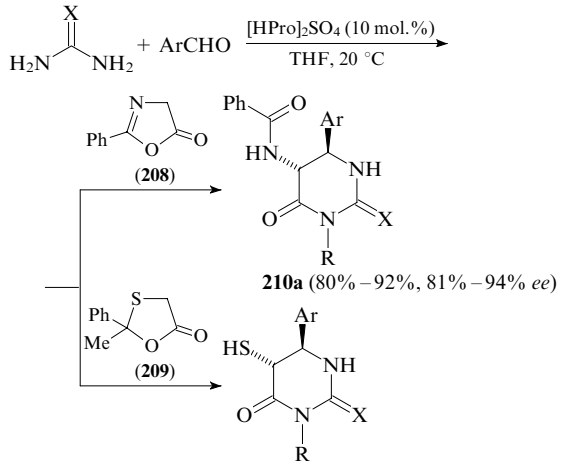


205 **206**

207 [40% – 93%, *endo* : *exo* = (84 : 16) – (> 99 : 1), (*endo*) 92% – 99% *ee*]

X = CH_2, $(CH_2)_2$, CMe_2; R = H, Cl, Br, F, OMe.

The acidic IL, prolinium sulfate ([HPro]$_2$$SO_4$), showed good performance in the asymmetric version of the three-component Biginelli reaction in which 2-phenyl-1,3-oxazol-5-one (**208**) or 2-methyl-2-phenyl-1,3-oxathiolan-5-one (**209**) serves as the active methylene component. The reaction gave the only diastereomers of hexahydropyrimidine derivatives **210** in high yields and with high *ee* values.[317]

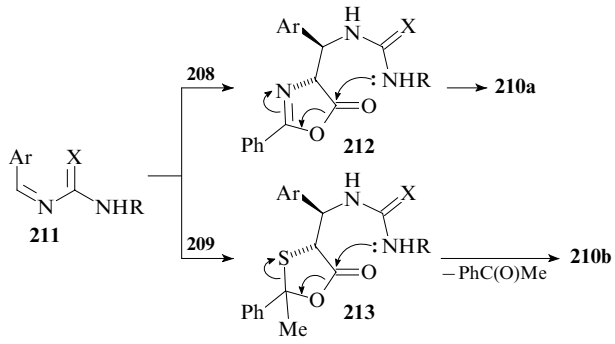


210a (80% – 92%, 81% – 94% *ee*)

210b (82% – 93%, 79% – 95% *ee*)

X = O, S; R = H, Et, Ph, 2-MeC_6H_4; Ar = Ph, 4-ClC_6H_4.

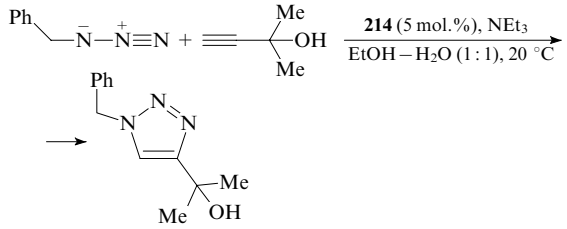
A reaction mechanism comprising the formation of coupling products **211** from aldehydes and urea (or thiourea) derivatives and their reaction with the carbon acid **208** or **209** was proposed; the authors were able to isolate intermediates **212** and **213**.



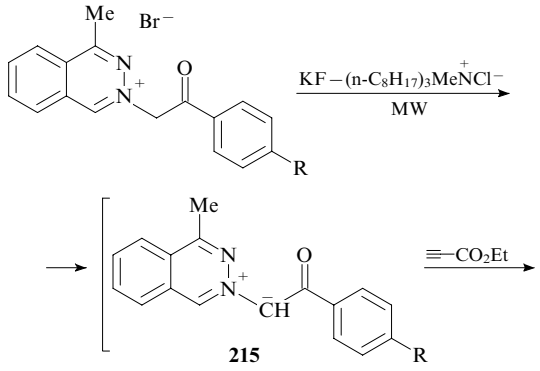
2. Catalysis of 1,3-dipole reactions by ionic liquids

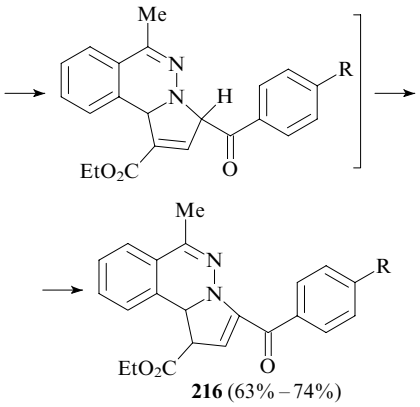
Ionic liquids exert clear-cut catalytic effect on some types of 1,3-dipolar cycloaddition reactions. As in the case of reactions of carbon acids, IL can themselves catalyze these processes. Alternatively, they are used in combination with other catalysts to increase their activity and facilitate their recovery.

For example, heterogeneous catalyst **214** for 1,3-DCA of organic azides to terminal acetylenes was prepared by CuBr immobilization on amorphous mercaptopropyl-silica gel containing the adsorbed IL [bmim][PF_6].[318] In the presence of this catalyst (5 mol.%), these reactions in aqueous ethanol at 20 °C were regioselective resulting in 1,2,3-triazoles in 73%–100% yields. The catalyst was recovered and reused six times.



Ionic liquids are widely used in 1,3-DCA reactions assisted by microwave irradiation.[21, 146, 319] The reaction of 1-methylphthalazine ylides **215** generated from the corresponding bromides with ethyl propiolate in the presence of heterogeneous catalytic system KF–(n-C_8H_{17})$_3$MeN$^+$Cl$^-$ (Aliquat 336) under microwave irradiation (50 W) furnished cycloadducts **216** in 63%–74% yields.[320] In this system, tetraalkylammonium chloride was likely to function simultaneously as a PTC and as a microwave conductor. This reaction does not take place on usual heating.

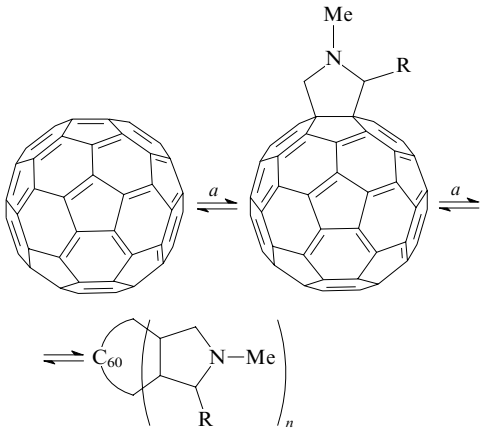


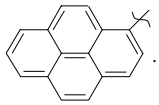


216 (63%–74%)

R = H, NO_2, Br, OMe.

Combining IL and microwave radiation catalyzes the functionalization of carbon nanostructures, *i.e.*, C_{60} fullerenes and nanotubes. In particular, fullerenes were involved in [3 + 2] cycloaddition to azomethine ylide generated from aldehydes and sarcosine in an IL–*o*-dichlorobenzene (1 : 3) mixture under microwave irradiation. This gave both mono- and polypyrrolidinofullerenes.

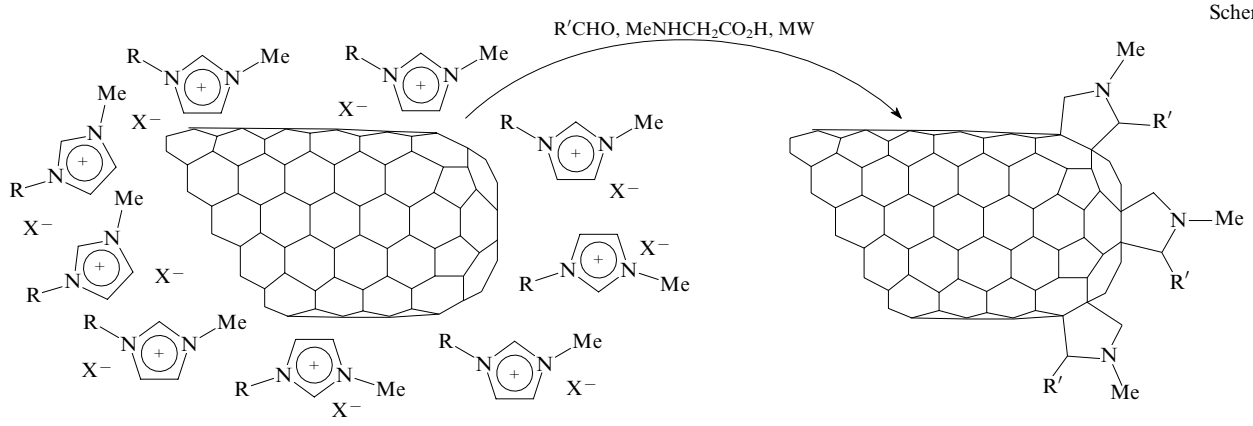


(*a*) RCHO, $MeNHCH_2CO_2H$, IL–1,2-$Cl_2C_6H_4$ (1 : 3);
IL = [bmim][BF_4], [bmim][PF_6], [omim][BF_4], [omim][OTf]
(omim is 1-octyl-3-methylimidazolium);
R = n-C_6H_{13}, 4-$MeOC_6H_4$, $CF_3(CF_2)_7CH_2CH_2$, .

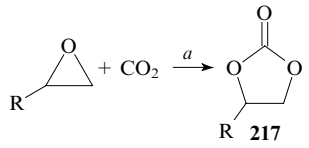
Nanotubes were functionalized under microwave irradiation of the gel obtained by applying the IL film on nanotubes (IL-containing bucky gels) (Scheme 9).[321]

The cycloaddition of CO_2 to propylene oxide giving rise to cyclic carbonate **217** in the presence of IL has been studied rather extensively.[322–325] Most often, 1,3-dialkylimidazolium and *N*-alkylpyridinium IL with the [BF_4] and [PF_6] anions are used for this purpose; in particular, high catalytic activity in this reaction was found for silica gel-supported dialkylimidazolium IL.[325] In some cases, Lewis acids are introduced in the catalyst to accelerate the reaction. For example, successful synthesis of cyclic carbonates **217** from epoxides and CO_2 was accomplished without a solvent in the presence of a mixture of [Bu^n_4N]Br and zinc benzenesulfonate octahydrate under microwave irradiation.[326]

Scheme 9

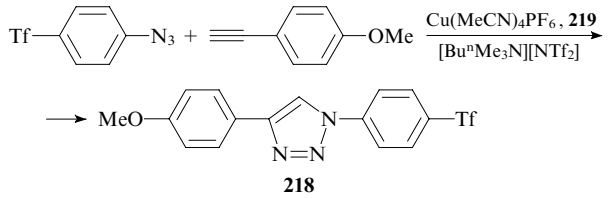


R = Bu^n, n-C_8H_{17}; R′ = n-C_6H_{13}, $CF_3(CF_2)_7CH_2CH_2$.

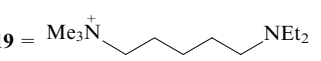


(*a*) Cat. = Bu^n_4NBr + $(PhSO_3)_2Zn \cdot 8H_2O$, MW; R = H, Bu^n, Cl, Ph.

1,2,3-Triazole **218** was prepared in a microreactor by 1,3-DCA of 1-N_3-4-$CF_3SO_2C_6H_4$ to 4-methoxyphenylacetylene in the IL $[Bu^nMe_3N][NTf_2]$ in the presence of $Cu(MeCN)_4PF_6$ (1 mol.%) and IL **219** used as the base.[327]



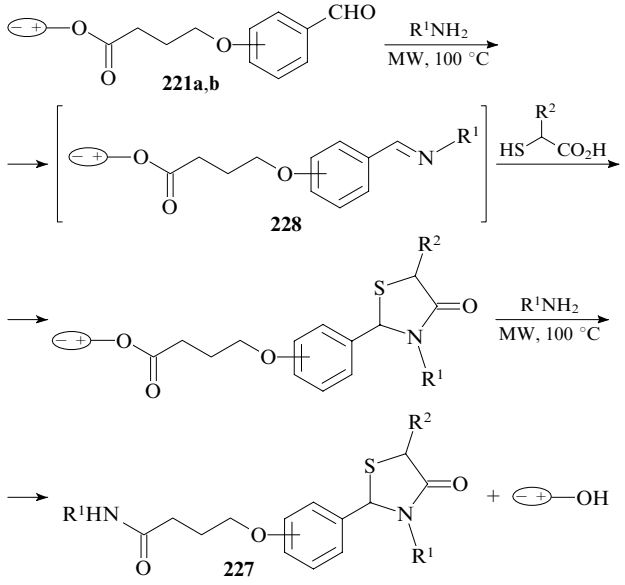
218

219 = 

V. Ionic liquids as reactants in the reactions involving carbon acids and 1,3-dipoles

Ionic liquids can be used not only as reaction media or catalysts but also as reactants.[31,32] The possibility of using these task-specific (tailor-made) IL in which one of the reactants is grafted to the IL was widely investigated by French researchers.[157,328–331] In particular, they performed the Knoevenagel reaction and 1,3-dipolar cycloaddition with participation of the IL containing grafted aldehyde and imine fragments, respectively (Scheme 10). In both cases, the initial IL **220** contained 2-hydroxyethyl ([hydremim]X) or polyethylene glycol ([PEGmim]X) fragments with the terminal OH group. These IL were used to esterify 4-(formylphenoxy)butyric acid in the presence of 1,3-dicyclohexylcarbodiimide (DCC) to give new IL **221a**. The latter were employed in the Knoevenagel reaction with CH acids thus producing adducts **222** or were made to react with primary amines to be converted to other IL **223** containing a C═N fragment, which transformed to isoxazoline derivatives **224**. After the reactions, the initial IL **220** were regenerated through transesterification (treatment with MeONa in MeOH) and reused, and the final products **225** and **226** contained a CO_2Me group.[328] This approach has advantages over the syntheses in organic solvents or in the IL medium, especially in the case of combinatorial synthesis, because by-products and remaining reactants can be separated by mere washing of adducts **222** and **224** to obtain high-purity final products without using chromatography. In addition, as opposed to the solid-phase synthesis, ionic intermediates can be analyzed by NMR, which allows monitoring of the whole process.

This strategy was utilized in the one-pot three-component synthesis of a library of 4-thiazolidinones **227**. As the starting compounds, IL **221a**,**b** or [PEGmim]X (**220**) were used, and imines **228** were made to condense, without isolation, with mercapto acids under microwave irradiation. Ionic liquids **221** were regenerated by treating the ionic products with aliphatic amines yielding amides **227**.[329]

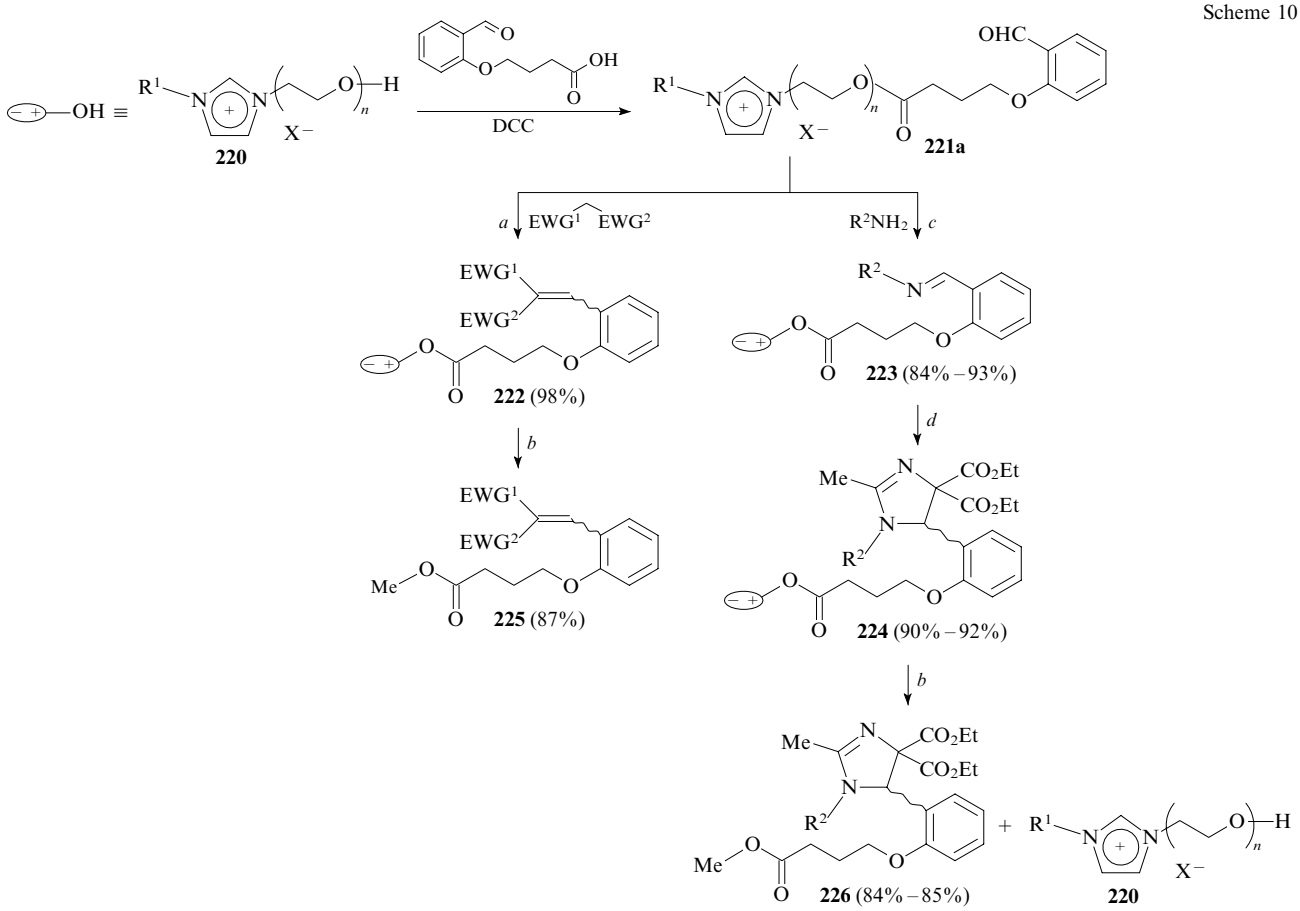


221a,**b** **228** **227**

R^1 = Pr^n, Pr^i, Bu^n, Bu^i, Bn, All, $CH_2CH(OMe)_2$;
R^2 = H, Me, CH_2CO_2H; isomers: *ortho* (**a**), *para* (**b**).

The strategy based on using IL as reactants has been called ionic liquid-phase organic synthesis. This was used to prepare 3,5-disubstituted 1,2,4-oxadiazoles,[330] 2-thioxotetrahydropyrimidin-4(1*H*)-ones,[331] to carry out the Diels–Alder, Heck and Stetter reactions[31,32] and, undoubtedly, offers good prospects for further development.

Scheme 10



$n = 1-3$; (*a*) piperidine (2%), MW, 80 °C; (*b*) MeONa (10%)–MeOH, 20 °C, 18 h; (*c*) MW, 80 °C, 20 min; (*d*) (Me)(EtO)C=NCH$(CO_2Et)_2$, 70 °C, 15 h; R^1 = Me, Et, Bu^n; R^2 = Pr^n, Pr^i, Bu^t; EWG^1, EWG^2 = CO_2Me, CO_2Et, CN.

VI. Conclusion

The information surveyed in this review attests to extensive possibilities opened up by the use of ionic liquids and their congeners as solvents, catalysts and reactants in fine organic synthesis. In the presence of IL, many practically valuable reactions involving active methylene compounds (carbon acids) and 1,3-dipoles proceed at higher rates and selectivities than under conventional conditions. Moreover, by varying the cation and anion structures for which several million combinations are possible, one can ensure the highest efficiency of the reactions. In the IL medium, it is possible to accomplish heterolytic transformations with participation of polar and zwitterionic intermediates that cannot occur in conventional organic solvents. The great potential of IL as organocatalysts of regio-, stereo- and enantioselective reactions of organic compounds playing key roles in medicinal and materials chemistry is far from being fully implemented. Some IL-catalyzed reactions are comparable in their efficiency and enantioselectivity with enzymatic reactions, which are sources of living matter in nature. Of exceptional significance is the environmental aspect of using IL, which allow one to avoid the use of toxic and flammable organic solvents produced from non-renewable raw materials (oil and gas) or catalysts containing heavy metals the presence of which in the product is in some cases inadmissible.

The works aimed at IL application in chemistry and chemical engineering are in progress in various countries (USA, UK, France, Italy, Japan, Canada, China, South Korea, *etc.*), in particular, in the laboratories of prominent chemical companies (Merck KGaA, BASF, DuPont, ExxonMobil, Cytec, Degussa, *etc.*).[7] It is obvious that introduction of IL in the operating processes of chemical industry, although is going to pay off, still requires huge investment and detailed evaluation of remote ecological and toxicological risks.[14] However, a number of innovation industrial processes using IL have already been commissioned, for example, so-called BASIL process (Biphasic Acid Scavenging utilizing Ionic Liquids) (BASF),[332] isobutene alkylation process (PetroChina)[333] and some other.[7] It is beyond doubt that in the near future one can expect the development of basically new, environmentally safe chemical processes for the industrial production of next generations of pharmaceutical drugs, crop protection agents, compounds with other useful properties involving the use of ionic liquids.

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