

Regio-, stereo-, and enantioselective reactions of carbon acids catalyzed by recoverable organic catalysts bearing ionic liquid moieties*

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Abstract: Organic compounds bearing specific ionic liquid (IL) moieties, in particular, bulky organic cations and fluorinated organic or inorganic anions, catalyze many important reactions of carbon acids involving carbanions and enols as reactive species, such as aldol, Michael, and dichlorocyclopropanation reactions. Many of these catalysts are at least comparable to traditional phase-transfer catalysts (PTCs) with halide anions or organocatalysts based on amino acid derivatives. Furthermore, they enjoy the advantage of being readily recoverable and hence are available for multiple recycling in chemical reactions.

Keywords: aldol reactions; carbon acids; dichlorocyclopropanation reactions; enantioselective reactions; ionic liquids; Michael reactions; phase-transfer catalysts; recoverable organocatalysts.

INTRODUCTION

Environmental protection is the crucial challenge faced by humanity in the 21st century. Progressive environmental pollution has been induced by an accumulation of man-caused factors. Amongst them is the intensive development of chemical industry that increasingly aggravates industrial waste generation [1]. Massive wastage levels that may reach hundreds of tons per a product ton, are particularly evident in those multistep processes in low-tonnage chemistry that produce natural compounds, pharmaceuticals, and plant protectors. Environmental issues of chemistry underlie the chemical research area “green chemistry”, which has been vigorously advancing over the last decade [2]. A key objective of green chemistry is the design of efficient chemical processes to ensure complete transformation of starting molecules to the target products and multiple use of auxiliary compounds and materials, including solvents and catalysts. Future chemical processes should be based on selective catalytic methods and non-traditional reaction activation techniques.

A promising approach to addressing these issues is the application of salts of organic and inorganic acids with bulky organic bases, e.g., ionic liquids (ILs) in chemistry and chemical technologies [3]. The salts are stable, nonvolatile, and noninflammable, which impedes their ready migration into the environment. Given high polarity, they are able to dissolve a great variety of chemical compounds and

*Paper based on a presentation at the 2nd International Conference on Green Chemistry (ICGC-2), 14–20 September 2008, Moscow, Russia. Other presentations are published in this issue, pp. 1961–2129.

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are considered as practical alternatives to toxic and fire-hazardous organic solvents [4]. Furthermore, ILs are recoverable and can thus be recycled.

The use of ILs and their congeners as recoverable organic catalysts of chemical reactions offers extensive capabilities, which remain far from being fully explored. Organic catalysis (organocatalysis) has lately attracted increasing attention from researchers, partly because of its scope to offer alternatives to organometallic catalysis. It allows synthesis of complex organic molecules without recourse to costly and often toxic transition-metal complexes [5]. Metal-free organic compounds are applied *inter alia* as phase-transfer (PTC) [6] and acid–base catalysts [7] of carbon acid reactions with electrophiles, a major area of carbon–carbon bond formation in organic synthesis. Furthermore, they appear to be excellent catalysts for those reactions of CH acids that are mediated by generation of enamines or iminium ions [8]. Some of these reactions display high levels of stereo- and enantioselectivity that may approach those of comparable reactions in living systems.

Organocatalysts, however, are normally lost during product isolation. Methods for producing recoverable forms immobilized on polymers are multistep and labor-consuming, and present distinctive challenges associated with analytical control of the high-molecular-weight compounds that are formed in different steps [9]. Moreover, the performance of such catalysts is limited by a small area of catalytically active site(s) in the overall macromolecule.

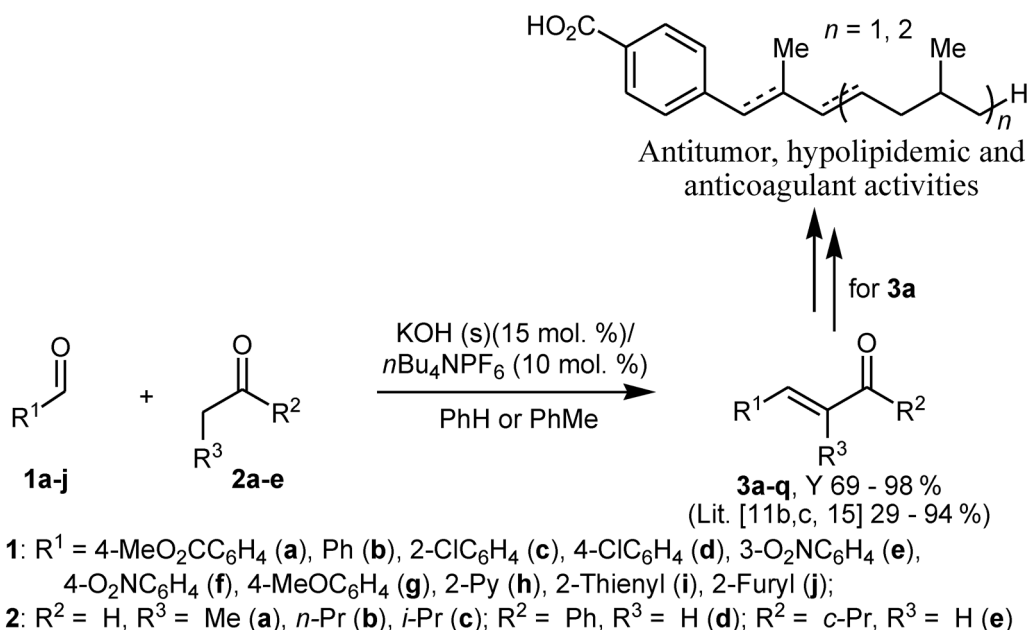
Herein we investigate another approach to the recovery of organocatalysts, based on the incorporation of specific IL moieties, viz., bulky organic cations and fluorinated organic or inorganic anions, into their structure. The compounds bearing these moieties generally display low solubility in organic and sometimes aqueous media and can therefore be easily separated from the reagents and products [10]. They acquire the catalytic activity from the ionic structure (e.g., PTC properties) or from incorporated specific functional groups.

RECOVERABLE PHASE-TRANSFER CATALYSTS WITH FLUORINATED ANIONS

First, we examined organic salts with perfluoroborate and -phosphate anions as PTCs in reactions of carbon acids that run through the steps where carbanions or products of their transformations, in particular, carbenes are generated, including aldol, Michael, and dichlorocyclopropanation reactions. These reactions can be performed under heterogeneous conditions in the presence of conventional PTCs with halide anions (Cl[−] or Br[−]) [11]. Yet, to the best of our knowledge, organic salts with fluorinated anions have not been applied as PTCs in these reactions so far.

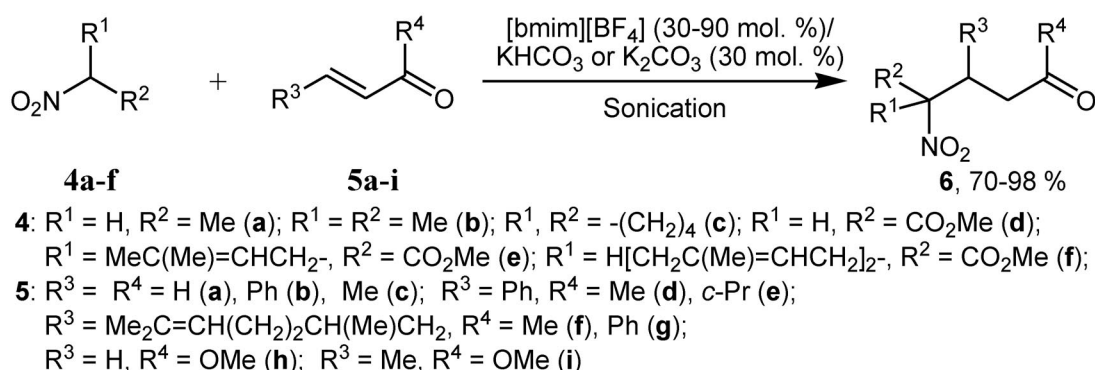
We selected an aldol reaction between 4-formylbenzoate **1** and propanal **2a** as a model. Its product **3** is a convenient building block for the synthesis of *para*-(*nor*-polyprenyl)benzoic acid derivatives possessing anticancer [12], hypolipidemic [13], and anticoagulant [14] activities. This reaction appeared to proceed in the heterogeneous system *n*Bu₄NPF₆ (10 mol %)/solid KOH (15 mol %)/PhH with extremely high yield (98 %) and selectivity (100 %) [15]. The yield and selectivity remained the same when toxic benzene was replaced by toluene. Substitution of the cation *n*Bu₄N⁺ for 1-butyl-3-methylimidazolium (bmim) or benzyltriethylammonium (BnNEt₃) cations and of the anion PF₆[−] for BF₄[−], Cl[−], or Br[−] anions resulted in 10–20 % decrease in the yield of **3a**. The use of other bases such as NaOH or LiOH instead of KOH was also accompanied by a decrease in the process efficiency.

The catalytic systems *n*Bu₄NPF₆/KOH/PhH and *n*Bu₄NPF₆/KOH/PhMe, which have manifested the best performance in the model reaction, were then examined in cross-aldol reactions with diverse carbonyl compounds. Benzaldehyde derivatives **1b–g** bearing both electron-donating and -withdrawing groups in the aromatic ring as well as aldehydes of the pyridine **1h**, thiophene **1i**, and furan **1j** series were used as electrophiles. Propanal **2a**, pentanal **2b**, 3-methylbutanal **2c**, acetophenone **2d**, and acetylcyclopropane **2e** were studied as the cross-components. In all the cases, the corresponding products **3a–q** were obtained in yields comparable to or higher than those reported in the literature [11b,c,16] (Scheme 1).



Scheme 1

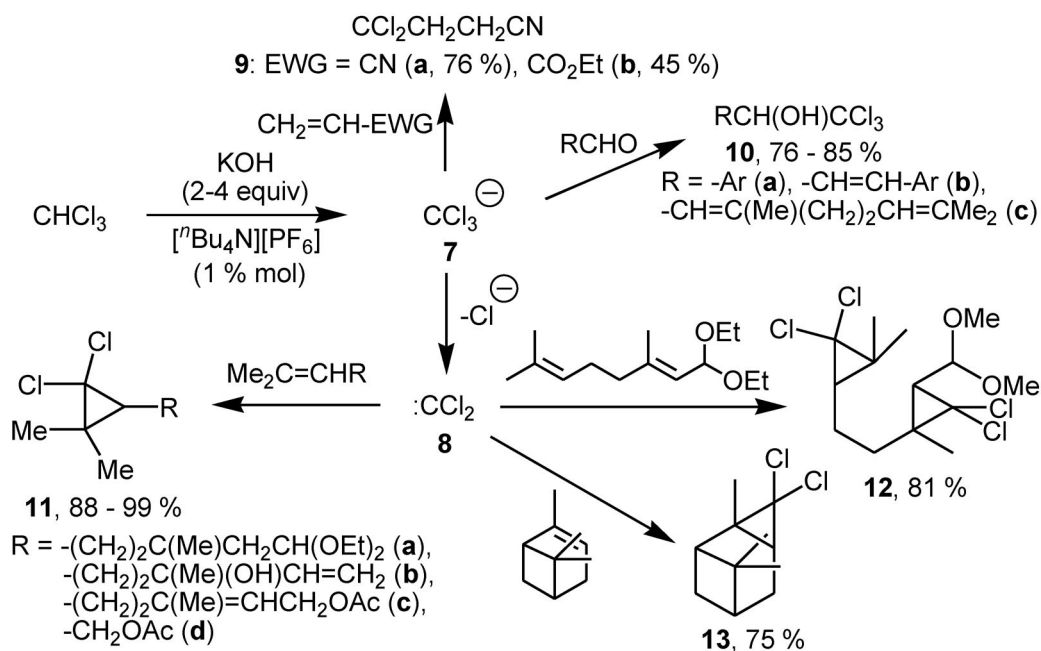
1-Butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF₄]) proved to be an efficient PTC for reactions of nitroalkanes **4a-c** and α -nitroesters **4d-f** with electron-deficient alkenes, in particular, acrolein **5a**, α,β -unsaturated ketones **5b-g**, and esters **5h,i** (Scheme 2) [17,18]. The reactions were carried out in organic solvent-free heterogeneous catalytic systems [bmim][BF₄] (30–90 mol %)/KHCO₃ (or K₂CO₃) (30 mol %) where the organic phase consisted of the reagents and the products and had a limited solubility in the IL. Possibly, in these systems IL played the role of both the PTC and the solvent liquefying the reaction mixture under the studied conditions and facilitating its efficient mixing. It is advisable to use finely ground solid base and apply sonication, which further increases the solid base dispersion and intensifies mass transfer.



Scheme 2

This procedure was employed for the synthesis of δ -oxocarboxylic and glutaric acid α -nitro derivatives **6** bearing prenyl moieties which are intermediates for producing isoprenoid amino acids, in particular, analogs of wound-healing medications [19].

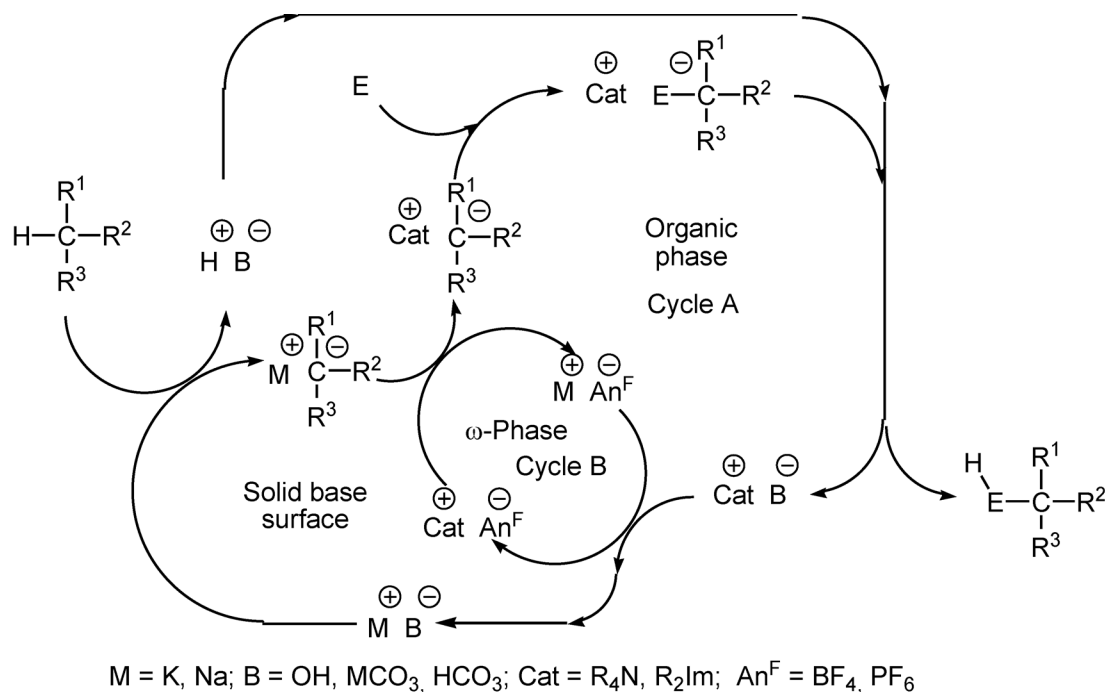
Tetrabutylammonium hexafluorophosphate ($n\text{Bu}_4\text{NPF}_6$) used as a PTC allowed increasing selectivity and product yield, as compared to the existing procedures, in heterogeneous reactions that run through the steps where CCl_3^- anion **7** or dichlorocarbene **8** are generated from CHCl_3 under the action of solid base. The reaction pathway depended on the reagent structure. Electron-deficient alkenes and aldehydes reacted with the CCl_3^- anion, affording the corresponding trichloromethyl derivatives **9** and **10**. In the absence of an electrophile, the anion **7** decomposed to Cl^- and dichlorocarbene **8**, which reacted with alkenes yielding 1,1-dichlorocyclopropane derivatives **11–13** [20] (Scheme 3). The hitherto unknown isopropenoid and terpene derivatives that can be used for the synthesis of insect juvenile hormone analogs and environment-friendly chemical plant protectors were obtained using the developed procedure.



Scheme 3

Reactions in the studied solid base–PTC systems are assumed to proceed according to Makosza's scheme [21a,b], which consists of the carbon acid deprotonation on the solid base surface followed by the carbanion interception with a PTC and its transfer into the organic phase, where further transformations take place (Scheme 4). They may also occur within the interfacial region (the so-called “ ω -phase” [21c,d]), followed by the extraction of products into the organic phase. The important role of the solid–liquid interfacial region is consistent with a strong influence exerted by the metal cation and the degree of dispersion of a solid base on the reaction efficacy. Indeed, the use of a “milder” deprotonating agent (NaOH instead of KOH) in the aldol reaction (Scheme 1) resulted in a slower reaction rate [15]. On the other hand, increasing solid base surface by means of sonication accelerated the studied reactions (Scheme 2) [17].

The designed systems are assumed to differ from traditional PTCs with halide anions by an additional catalytic cycle (Scheme 4, cycle B). The equilibrium between organic bases and poorly soluble



Scheme 4

in the organic phase salts with weakly solvating fluorinated (PF_6^- or BF_4^-) anions shifts to the latter, enabling recovery of fluorinated PTC. The feasibility of ion exchange was indirectly confirmed by the preparation of nBu_4NPF_6 from nBu_4NCl and KPF_6 under the reaction conditions [20].

The recycling procedure is extremely easy. Following removal of the organic phase, fresh portions of the reactants are added to the remaining base and IL mixture, and the process is re-performed with the same rate and selectivity. Normally, after 4–5 cycles, additional amount of the base should be only added to the system to compensate for its losses during isolation of the product and because of its gradual conversion to a conjugated acid. Unlike the catalysts with fluorinated anions, PTCs with the bromide anion having a much better solubility in the organic phase and water lose the catalytic properties during repeated runs because of removing with the products (Scheme 5).

Thus, we have proposed a new type of PTC with fluorinated anions distinguished by high performance and recoverability. The catalysts are available, convenient in handling, and are likely to find applications in low-tonnage chemical processes.

Organic phase

PTC

Solid Base

Reagents

Product

≥ 10 cycles

3a, aldol reaction

PTC (5 mol. %)	Yield of 3a , % (cycle) [15]					
Bu ₄ NPF ₆	98 (1)	97 (2)	98 (3)	88 (4)	98* (5)	96 (6)
Bu ₄ NBr	93 (1)	40 (2)	5 (3)	-	-	-

11a, Dichlorocyclopropanation reaction

PTC (1 mol. %)	Yield of 11a , % (cycle) [20]					
Bu ₄ NPF ₆	99 (1)	99 (2)	99 (3)	98 (4)	99 (5)	98 (6)
Bu ₄ NBr	96 (1)	84 (2)	67 (3)	15 (4)	-	-

*Solid KOH (15 mol %) is added.

Scheme 5

RECOVERABLE CHIRAL ORGANOCATALYSTS BEARING IONIC LIQUID MOIETIES

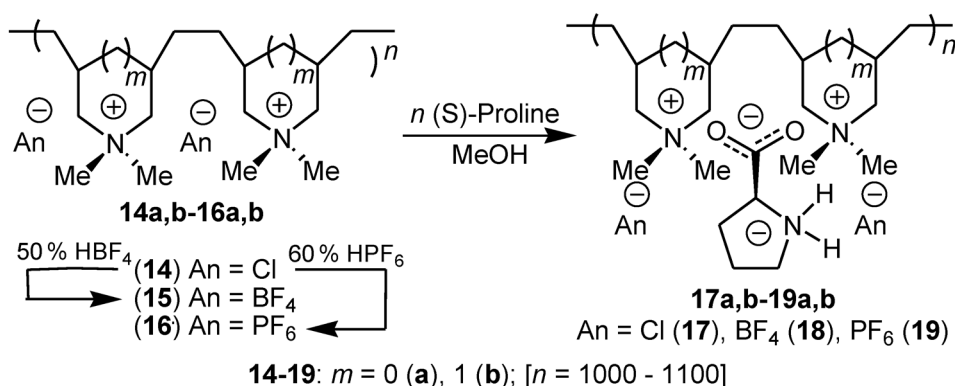
The IL catalytic potential is not limited to the PTC area. In the presence of catalytically active groups, such as amino groups, they are able to catalyze carbon acid reactions that proceed by other mechanisms, e.g., those involving enamines [5,8]. Functionalized chiral ILs may catalyze enantioselective reactions. A chiral inductor can be either immobilized on an ionic moiety by the electrostatic interactions (Scheme 6, **A**) or integrated with it into a common molecule by covalent bonds through a linker (Scheme 6, **B**).



Scheme 6

The former approach was implemented for designing organocatalysts supported on organic ionic polymers (polyelectrolytes), which may be considered as IL analogs [22]. We investigated poly(diallyldimethylammonium) **14a–16a** and poly(*N,N*-dimethylpiperidinium) **14b–16b** salts of different molecular mass (100 000–500 000 Da) containing Cl[−], BF₄[−], and PF₆[−] anions. Polymers **15** and **16** were prepared from commercially available 20 % aqueous solutions of hydrochlorides **14a,b** by anion exchange reactions with HBF₄ (50 % aqueous solution) and HPF₆ (60 % aqueous solution). These polymers are poorly soluble in water and precipitated from the reaction mixtures (Scheme 7).

The chiral inductor *S*-proline was supported on polyelectrolytes **14–16** by mixing a methanolic solution (suspension) of a polymer with a solution of the organocatalyst in the same solvent. To achieve better adsorption of (*S*)-proline, the amino acid/polymer ratio was chosen in such a way that each (*S*)-proline molecule would interact with two pyrrolidine moieties. Evaporation of the solvent under re-

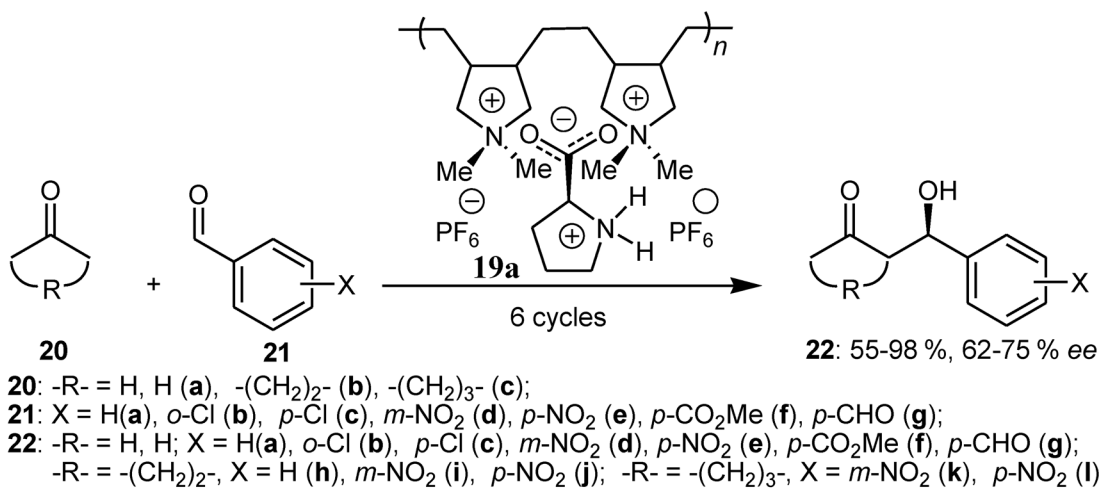


Scheme 7

duced pressure afforded corresponding supported catalysts **17–19** as colorless solids in quantitative yield (Scheme 7).

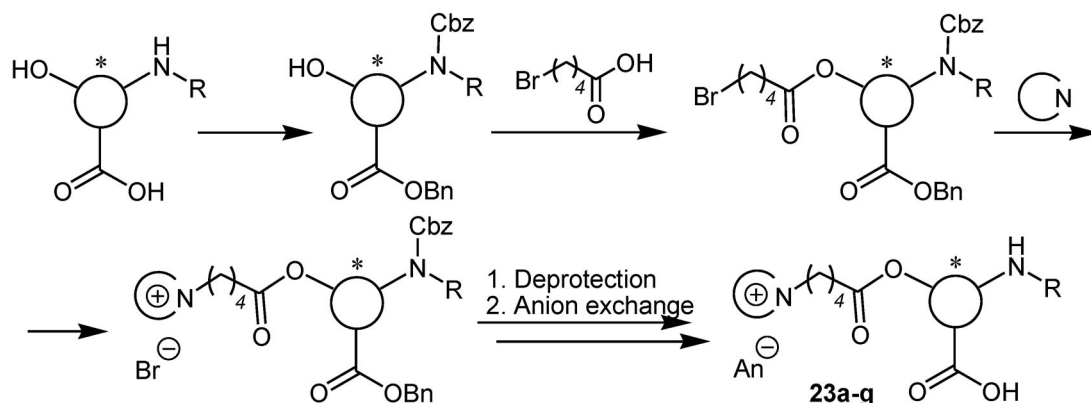
We compared the catalytic activities and recoverabilities of supported catalysts **17–19** (15 mol %) in the asymmetric aldol reaction between acetone **20a** and benzaldehyde **21a** in the acetone excess (30 equiv). In the first run, all studied catalysts provided (*S*)-aldol **22** in 54–55 % yield and 67–69 % ee. However, the outcome of the second run appeared different: recovered catalysts **17a,b** bearing chloride anions gave aldol **22** with as low as 25 % yield, whereas catalysts **18a,b** and **19a,b** with fluorinated anions yielded product **22a** in 54–55 % yield.

The application area of hexafluorophosphate **19a** (15 mol %) was examined in asymmetric aldol reactions between ketones **20a–c** and aldehydes **21a–g**. In all the cases, the respective aldols **22a–l** were obtained with 55–98 % yields and 62–75 % ee. The catalyst was readily recoverable: after the filtration and washing with a solvent, it could be reused at least 6 times with the same performance without any additional purification (Scheme 8).



Scheme 8

Aiming at development of recoverable forms of organocatalysts with the catalytically active sites covalently linked to ionic moiety (Scheme 6, Path B), we synthesized earlier unknown chiral ILs **23a–g** bearing moieties of α -amino acids, including of 4-hydroxyproline, serine, and threonine, along with hydrophilic and -phobic groups [23,24]. Chiral inductors were linked with imidazolium or pyridinium cations through a bifunctional linker—5-bromovaleric acid by a sequence of esterification and alkylation followed by N,O-deprotection and anion exchange (Scheme 9).

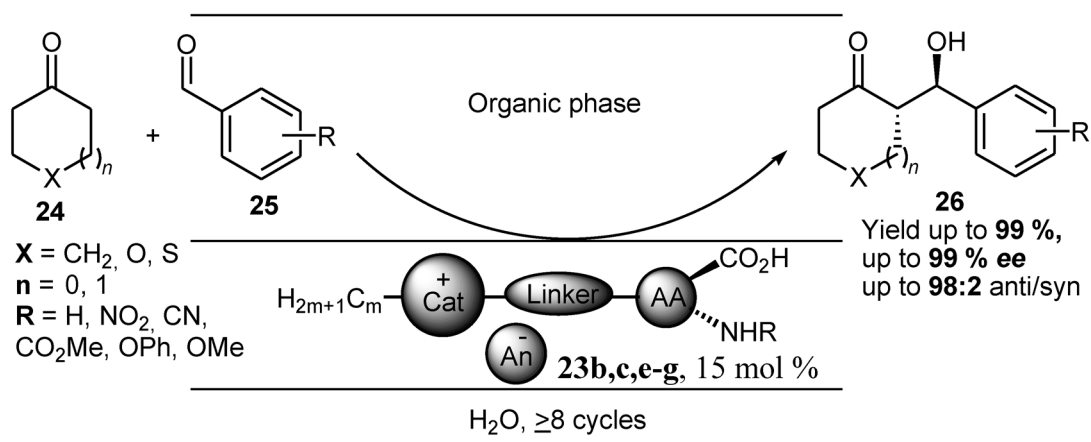


23	Chiral moiety	Cation moiety	An
a	<i>trans</i> -4-hydroxy- <i>S</i> -proline	3-(<i>n</i> -C ₁₂ H ₂₅)-imidazolium	BF ₄
b	—	—	PF ₆
c	—	—	NTf ₂
d	—	pyridinium	PF ₆
e	—	4-(<i>S</i> - <i>n</i> -C ₉ H ₁₉)-pyridinium	PF ₆
f	<i>S</i> -serine	—	PF ₆
g	<i>S</i> -threonine	—	PF ₆

Scheme 9

Compounds **23a–g** (15 mol %) were applied in asymmetric aldol reactions between non-modified ketones **24** and aldehydes **25** in the aqueous medium, i.e., under conditions that meet to a larger extent the green chemistry requirements. The reaction results appeared to be greatly dependent on the structure of a catalyst and the phase composition of a system. The reactions do not run under the action of water-soluble catalysts **23a** and **23d**. Water-soluble carbonyl compounds such as acetone and 2-butanone do not enter the reactions either. However, poorly water-soluble cycloalkanones **24** and aromatic aldehydes **25** react in the presence of amphiphilic catalysts **23b,c,e–g**, bearing hydrophobic anions (PF₆[−] or NTf₂[−]) and long-chained alkyl groups, to give the corresponding aldols **26** with exceptionally high yields and diastereo- and enantioselectivities. Of special note is that catalysts **23b,e–g** can be reused at least 8 times without any decrease in the reaction rate and selectivity [23,24] (Scheme 10).

Obviously, under these condition catalysts **23b,c,e–g** containing lipophilic alkyl groups along with the hydrophilic cation moiety are located on the water/organic interface where the catalytic reaction occurs. Water plays here the crucial role, which has not been elucidated so far, in providing efficient stereocontrol of the reaction. Under water-free conditions, diastereo- and enantioselectivity drops by 10–15 %. The devised systems may be evidently considered as organic models of natural enzymes aldolases which convert simplest carbonyl compounds to carbohydrates in living systems [25].



Scheme 10

CONCLUSIONS

Thus, a green chemistry area related to applications of ILs and their congeners as recoverable organic catalysts of chemical reactions, in particular of carbon acid reactions, has evolved. Efficient resource-saving methods for synthesizing compounds of various classes with high yield and stereo- and enantio-selectivities have been proposed. Practically important isoprenoids with wound-healing and anticancer properties, insect juvenile hormone analogs, and intermediates for producing enantiomerically pure pharmacologically active compounds have been prepared using the developed methods.

ACKNOWLEDGMENTS

The work was partially supported by the Russian Foundation of Basic Research (Grants 06-03-32603 and 09-03-00384) and the Russian Academy of Sciences.

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