Monatshefte für Chemie 138, 1137–1144 (2007)
DOI 10.1007/s00706-007-0758-3
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

Invited Review

Sustainable Processes Employing Ionic Liquids for Secondary Alcohols Separation

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Received June 14, 2007; accepted (revised) June 25, 2007; published online October 17, 2007

Summary. Secondary chiral alcohols are very attractive intermediates in organic synthesis of pharmaceutical and the fine-chemical industries. The processes employing ionic liquids to obtain enantiomers of secondary alcohols have become sustainable. Furthermore, physico-chemical properties of ionic liquids opened new possibilities to design ''solvent free'' processes for the resolution of racemic secondary alcohols. This review is aimed to highlight some of the most important achievements in resolution of secondary alcohols.

Keywords. Chirality; Enantiomeric resolution; Enzymes; Ionic liquids; Supercritical fluids.

Introduction

Chirality is a feature making organic compounds very attractive in various fields. As an example, chiral secondary alcohols can be mentioned, which are very valuable auxiliaries in organic synthesis of pharmaceutical and the fine-chemical industries [1]. The awareness of the importance of chiral purity in the context of biological activity is increasing and stimulated a growing demand for efficient methods for the industrial synthesis of pure enantiomers. Chiral amines and acids can be resolved *via* diastereometric crystallization of their salts. However, alcohols do not form salts and this is not a method leading to resolution of the enantiomers of an alcohol.

Enzymes have a strong foothold in synthesis when it comes to resolution of racemates and besides they offer the advantages of chemical specificity and stereospecificity. The enzymatic catalysis is a useful tool to separate chiral alcohols with high efficiency.

The preparation of optically active alcohols by lipase-catalyzed acylation of racemic compounds in organic solvents has been already studied and is very well documented in literature [2–9]. Usually these processes are characterized by high E (enantiomeric ratio) values and *ee* (enantiomeric excess of recovered substrate or product fraction) close to 100% [10].†

Ionic liquids (ILs) are a large group of compounds but only small percentage of them have been deeply investigated. However, broad research is still performed in many directions starting from the method of synthesis of pure ionic liquids [11] and

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† When A is the concentration of the fast and B is the concentration of slow reacting enantiomer that compete for the same site on the enzyme and **A** reacts to produce **P** of concentration P and **B** reacts to give **Q** (concentration Q), then enantiomeric ratio can be described as $E = \frac{\ln[(1-c)(1-ee_s)]}{\ln[(1-c)(1+ee_s)]}$, where $c = 1 - \frac{A+B}{A_0+B_0}$ (c – conversion of racemic substrate) and $ee_s = \frac{B-A}{A+B}$ (ee_s – enantiomeric excess of recovered substrate fraction) or as $E = \frac{\ln[(1-c)(1+ee_p)]}{\ln[(1-c)(1-ee_p)]}$, where $ee_p = \frac{P-Q}{P+Q}$ (ee_p – enantiomeric excess of product fraction). Equations are taken from Ref. [10].

the properties of them and finishing on their applications in different areas of science [12]. The feasibility of employing ionic liquids as solvents in enzymatic processes improving the stability of enzyme and sometimes playing as an agent enhancing activity and enantioselectivity has been already reported in literature [13–32]. On the other hand, products of enzymatic reactions have been resolved by liquid extraction using organic solvents. The organic solvents were in fact used to remove the products of enzymatic catalysis and unreacted alcohols from the ionic liquid phase and subsequent separation has been performed in the traditional way. Nevertheless, employing organic solvents generates additional cost because of demands of recycling or disposal of large volumes of organic solvents. One of the innovations guided to diminish organic solvents emission, is using a combination of ionic liquid and supercritical carbon dioxide ($scCO_2$) [14–17].

In this review I present the results of enantioselective resolution of racemic secondary alcohols using reactions performed in ionic liquids.

Enzymatic Separation in Ionic Liquids

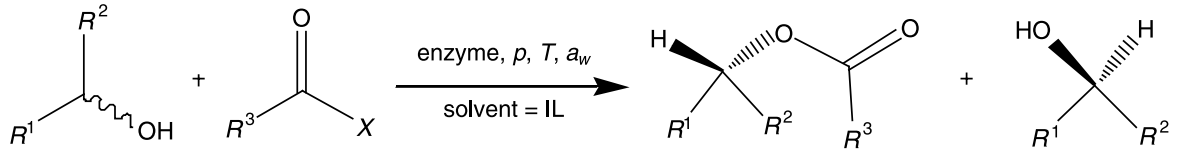
The separation of secondary alcohols *via* lipase-catalyzed esterification in ionic liquids has been presented in literature [13–17, 19–21, 28]. Esterification reaction performed in presence of ionic liquids is shown in Scheme 1.

Enzymatic separation reactions have been tested principally in imidazolium-based ionic liquids. Ionic liquids with *N*-butylpyridinium, 1,3-dimethylimidazolium [*mmim*], 1-ethyl-3-methylimidazolium [*emim*], 1-butyl-3-methylimidazolium [*bmim*], 1-hexyl-3-methylimidazolium [*hmim*], 1-methyl-3-octylimidazolium [*omim*], 1-nonyl-3-methylimidazolium [*nmim*] cations and hexafluorophosphate [PF_6], tetrafluoroborate [BF_4], bis(trifluoromethanesulfonyl)amide [N*Tf*$_2$], dicyanamide [$N(CN)_2$], ethyl sulfate [*Et*OSO_3], methyl sulfate [*Me*OSO_3], trifluoromethanesulfonate [CF_3SO_3], benzoate, and 2-(2-methoxyethoxy)ethylsulfate [*Me*O*Et*O*Et*OSO_3] anions have been broadly used. However, some tests with ammonium-based ionic liquids have been done as well [13, 22] (Table 1).

The separation of secondary alcohols has been performed in reaction with an acyl donor. As an acylating agent succinic anhydride [13, 21], vinyl acetate [14, 15, 19, 20, 30, 32], vinyl propionate [16, 28, 31], and vinyl laureate [15] have been tested (Table 2).

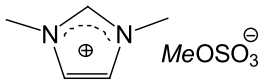
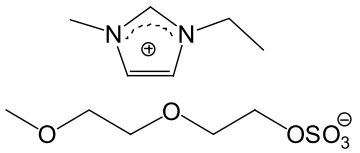
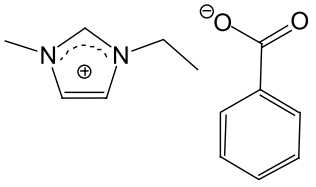
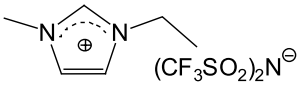
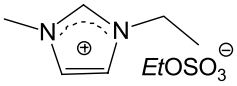
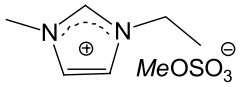
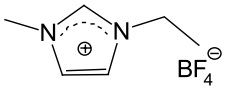
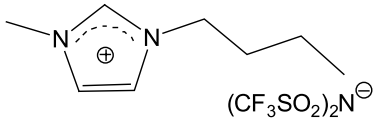
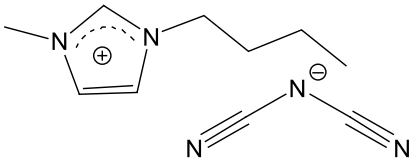
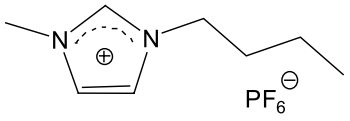
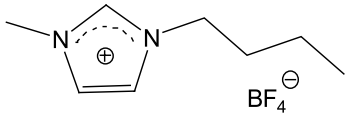
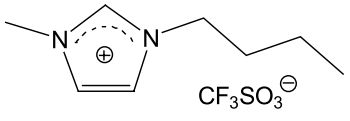
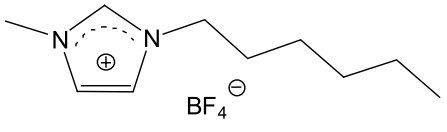
Esters as acyl donors have been used for reactions because this group of compounds leads to fast and very selective reactions what is very helpful to study potential outcomes. However, in literature some information about the applications of anhydrides in ionic liquids [13, 21] and/or organic solvents [9, 13] have been presented. Anhydrides [9] are superior to other acyl donors because an alcohol is not produced as a by-product of the reaction making the process irreversible. This feature is important because it increases the optical purity of demanded product. Besides, employing succinic anhydride offers interesting possibilities due to the fact that the semi-ester formed in the lipase-catalyzed reaction is soluble in aqueous phase while the unreacted compounds remain in the organic phase. This allows to apply the conventional separation methods for extraction of unreacted enantiomer [4].

The separation of secondary alcohols occurs in presence of specific catalyst such as enzymes. *Pseudomonas cepacia* (PCL) [13, 20, 21] and *Pseudomonas* sp. [19, 30, 32], *Candida antarcitica* (CAL B or Novozym 435) [13–16, 20, 28, 30, 31] and *Candida antarcitica* CAL B [19], *Candida rugosa* [19], *Thermomyces lanuginosa* [19], *Mucor miehei* [19], and *Alcaligenes* sp. [19] enzymes have been used to test their viability for this concept. The best results (high enantioselectivity, high enzyme stability and activity) have been achieved for *Pseudomonas cepacia* (PCL) and *Candida antarcitica* (CAL B). Besides, worth to mention is the



Scheme 1

Table 1. Ionic liquids (structures, names, and abbreviations)

	Structure	Name	Abbreviation	Ref.
1		1,3-dimethylimidazolium methyl sulfate	[*mmim*][*Me*OSO_3]	[19]
2		1-ethyl-3-methylimidazolium 2-(2-methoxyethoxy)ethyl sulfate	[*emim*]-[*Me*O*Et*O*Et*OSO_3]	[13]
3		1-ethyl-3-methylimidazolium benzoate	[*emim*][benzoate]	[19]
4		1-ethyl-3-methylimidazolium bis(trifluoromethanesulfonyl)amide	[*emim*][N*Tf*$_2$]	[16, 31]
5		1-ethyl-3-methylimidazolium ethyl sulfate	[*emim*][*Et*OSO_3]	[13]
6		1-ethyl-3-methylimidazolium methyl sulfate	[*emim*][*Me*OSO_3]	[13]
7		1-ethyl-3-methylimidazolium tetrafluoroborate	[*emim*][BF_4]	[20]
8		1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)amide	[*bmim*][N*Tf*$_2$]	[13–16, 19, 28, 31, 32]
9		1-butyl-3-methylimidazolium dicyanamide	[*bmim*][$N(CN)_2$]	[13]
10		1-butyl-3-methylimidazolium hexafluorophosphate	[*bmim*][PF_6]	[13, 15, 19–21, 30]
11		1-butyl-3-methylimidazolium tetrafluoroborate	[*bmim*][BF_4]	[13, 15, 19, 30]
12		1-butyl-3-methylimidazolium trifluoromethanesulfonate	[*bmim*][CF_3SO_3]	[19]
13		1-hexyl-3-methylimidazolium tetrafluoroborate	[*hmim*][BF_4]	[19]

(*continued*)

Table 1 (*continued*)

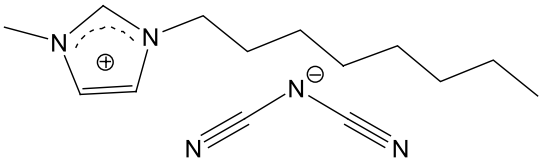
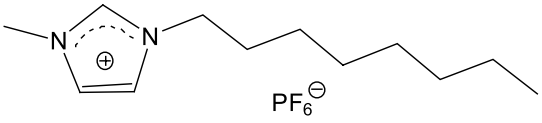
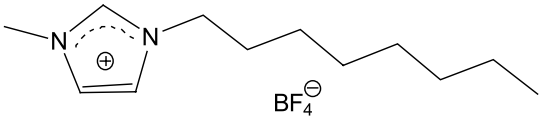
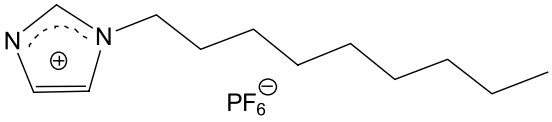
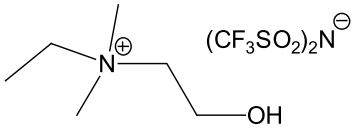
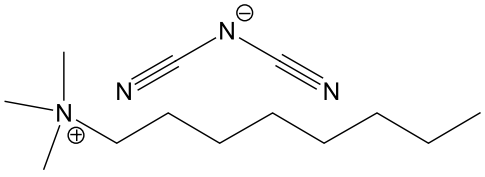
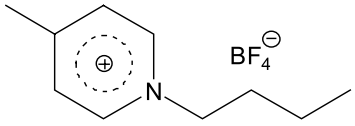
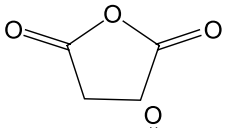
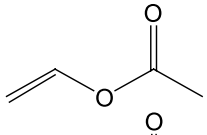
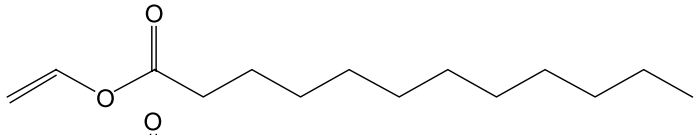
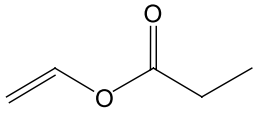
	Structure	Name	Abbreviation	Ref.
14		1-octyl-3-methylimidazolium dicyanamide	[*omim*][$N(CN)_2$]	[13]
15		1-octyl-3-methylimidazolium hexafluorophosphate	[*omim*][PF_6]	[13]
16		1-octyl-3-methylimidazolium tetrafluoroborate	[*omim*][BF_4]	[19]
17		1-methyl-3-nonylimidazolium hexafluorophosphate	[*nmim*][PF_6]	[19]
18		ethyl(2-hydroxyethyl)-dimethylammonium bis(trifluoromethylsulfonyl)amide	[C_2][N*Tf*$_2$]	[13]
19		octyltrimethylammonium dicyanamide	[*aliquat*][$N(CN)_2$]	[13]
20		*N*-butyl-4-methylpyridinum tetrafluoroborate	[*4-mbp*][BF_4]	[19]

Table 2. Acylating agents (structures and names)

	Structure	Name	Ref.
1		succinic anhydride	[13, 21]
2		vinyl acetate	[14, 15, 19, 20, 30, 32]
3		vinyl laureate	[15]
4		vinyl propionate	[16, 28, 31]

fact that ionic liquids increase the stability of enzyme as it is presented in literature [18, 30–32].

The optically pure secondary alcohols are compounds that meet industrial and pharmaceutical interest. Up to current moments secondary alcohols, such as 2-pentanol [28], 2-butanol [13], 2-octanol [13, 15], and secondary alcohols including aromatic ring substituted by an alkyl chain with a hydroxyl group were examined as well. To this group belongs 1-phenylethanol that in reaction with vinyl acetate is used as a model system for analysis of influence of many parameters on the outcome of the reactions [14, 16, 19, 21].

Kim et al. developed markedly enhanced enantioselectivity for aliphatic alcohols containing aromatic rings (0.15 mmol) in reaction with vinyl acetate (1.5–3 equiv.). They performed reactions in presence of CAL B and PCL (20 mg) enzymes in tetrahydrofuran (*THF*), or toluene, or [*emim*][BF_4], or [*bmim*]-[PF_6] (1 cm^3) at room temperature. Transesterification catalyzed by CAL B proceeded with better enantiopurity and higher enantiomeric ratio in ionic liquid than in organic solvents ($ee_p = 95.5\%$, $E = 141$ in *THF*, $ee_p = 99.0\%$, $E = 648$ in [*emim*]-[BF_4], and $ee_p > 99.5\%$, $E > 967$ in [*bmim*][PF_6] for 4-phenyl-2-butanol). The presence of an ester group in an alcohol, *i.e.* in benzyl 3-hydroxybutanoate, leads to high ee_p in case of ionic liquids, however, E is higher for more polar ionic liquid (for [*emim*][BF_4] $E = 651$ and for [*bmim*][PF_6] $E = 155$). *Kim et al.* also studied alcohols containing a chloride atom in the aliphatic alcohol chain catalyzed by PCL. In all cases ee_p and E was equal or higher when ionic liquids where used as solvents compared to organic solvents. All analyzed results for alcohols presented by *Kim et al.* clearly prove that alcohols were esterified effectively in ionic liquids and in some cases even with impressively high enantioselectivity. Moreover, taking into account that volatility of ionic liquids is negligible, the ionic liquids are great substitute for *THF* or toluene for enantioseparation studies [20]. Ionic liquid [*bmim*][PF_6] seems to be a good solvent for reactions with some alcohols; however, data presented by *Schöfer et al.* [19] indicate that transesterification of 1-phenylethanol with the same acylating agent provides poor results for eight enzymes. *Schöfer et al.* made a screening of [*bmim*]-[PF_6], eight other imidazolium-based ILs, and one *N*-butylpyridinium ionic liquid either. Reactions between 54 mm^3 1-phenylethanol and 122 mm^3 vinyl acetate were performed in presence of 1 mg enzyme in 4.4 cm^3 ionic liquid at 24°C for 72 h. They tested eight different enzymes, nevertheless the best resolution of secondary alcohols has been achieved for CAL B (1 mg) where conversion of 1-phenylethanol is equal to 50% with $ee_p > 98\%$ for [*bmim*][NTf_2] and [*bmim*][CF_3SO_3]. For *Pseudomonas* sp. conversions were 50% and 47% with maintained $ee_p > 98\%$ for [*bmim*][CF_3SO_3] and [*bmim*][NTf_2]. Reactions with CAL B in other ionic liquids gave always high enantiopurity of product ($ee_p > 98\%$) but it was accompanied by lower conversion of (*R*)-1-phenylethanol. Some examined ionic liquids facilitate acylation of (*S*)-1-phenylethanol what leads to lower enantioselectivity ($3\% < ee_p < 84\%$). The interesting aspect is that the mentioned ionic liquids improved conversion of (*R*) enantiomer while ee_p and reaction velocity stayed at the same high level comparing to the result obtained for reactions when *tert*-butyl methyl ether has been used [19]. Other interesting results have been presented by *Rasalkar et al.* who tested one anhydride. They performed reactions between alcohol (2 mmol) and succinic anhydride (2 mmol) in [*bmim*][PF_6] (4 cm^3) with PCL (44 mg, 1300 units). One of alcohols tested by them was 1-phenylethanol. *Rasalkar et al.* [21] found that the use of succinic anhydride resulted in 43% conversion of reacted enantiomers of 1-phenylethanol with $ee_p = 96\%$, while *Schöfer et al.* for *Pseudomonas* sp. did not notice any conversion for the same alcohol [19]. Only for all *Alcaligenes* sp. *Schöfer et al.* obtained 44% conversion with $ee_p = 77\%$ [19].

Rasalkar et al. examined also influence of triethylamine (Et_3N) on the results. The aim of using Et_3N is to increase the catalytic activity of enzyme [29]. The reaction rate increased more than 1.5 times compared to the original rates for studied alcohols. *Rasalkar et al.* [21] and *Schöfer et al.* [19] presented results for acylation of 2-chloro-1-phenylethanol by succinic anhydride and vinyl acetate. They obtained various ee_p values (91% and 99.5%). The difference may come from the acylating agent, dissimilar starting compositions of performed reactions, but what is also important, in both papers, is lack of information about the water activity (a_w), which is a crucial parameter determining enzyme activity [28]. *Noël et al.* determined the effects of water activity and temperature in a comprehensive study on the separation

of secondary alcohols. As a model example they chose the reaction between 2-pentanol (46 mm^3, 414 μmol) and vinyl propionate (46 mm^3, 414 μmol) in [*bmim*][NTf_2] (300 mm^3) catalyzed by CAL B solution in 15 m*M* phosphate buffer (3.73 mg cm^{-3}). Transesterification at 60°C and at 2% (*v*/*v*) water content leads to $ee_p > 99.99\%$ what demonstrates the excellent enantioselectivity of CAL B. They analyzed the activity and selectivity profiles (activity/selectivity *vs.* temperature) for CAL B in [*bmim*]-[NTf_2] and *n*-hexane at 2% (*v*/*v*) water content detecting the highest synthetic activity at 60°C [27]. The activity is almost 2.5 times higher in ionic liquid than in *n*-hexane, however, the selectivity is not strongly dependent on temperature. At a temperature above 60°C, the difference between IL and *n*-hexane can be explained by the strong protective effect of ionic liquid against enzyme thermal deactivation described already in literature [16, 30–32]. *Noël et al.* present in details effects of water activity on synthetic activity of CAL B. The enzyme activity strongly depends on the water content and for CAL B reaches a maximum for a_w higher than 0.8 increasing exponentially from synthetic activity of 0% at $a_w = 0.1$ to 100% at $a_w > 0.8$ [28]. The system involving ionic liquid, an enzyme, and water is very complicated but explanation of this phenomenon is presented in literature [18, 32–35].

Bogel-Łukasik et al. studied acylation of the model substrate 2-octanol (400 mmol dm^{-3}) with succinic anhydride (800 mmol dm^{-3}) catalyzed by *Candida antarctica* lipase B (40 g dm^{-3}) in ionic liquids and organic solvents (750 mm^3) at water activity 0.1 and at 35°C. They screened a wide range of ionic liquids and organic solvents for this purpose. *Bogel-Łukasik et al.* examined nine 1-alkyl-3-methylimidazolium, two quaternary ammonium ionic liquids, two water-miscible organic solvents, and two water-immiscible ones. Novelty of their work is the fact that they obtained diester from double esterification of 2-octanol. In many cases, the diester was even produced in higher quantity than the expected acidic hemiester. The major reaction products were the (*R*)-hemiester and the (*R*,*R*)-diester. In the less polar solvents the conversion of 2-octanol was higher, but the enzyme was also less enantioselective and the (*S*)-hemiester, the (*S*,*S*)-diester, and the *meso*-(*R*,*S*)-diester were detected as well. The correlation between solvent polarity and the distribution of reaction products also held for solvent mixtures. In the less polar solvents, the amount of (*R*)-hemiester peaked at the early stages of reaction, and typically decayed afterwards. This behavior they explained as a coupling of two reaction pathways: the hydrolysis of the hemiester, and the esterification of the hemiester. In the less polar solvents the lower solubility of succinic acid, produced in the former pathway, leads to its precipitation and acts as a driving force for the process. Indeed in tetrahydrofuran, which in spite of its low polarity can solubilize at least three times more succinic acid than the other three organic solvents tested, the amount of (*R*)-hemiester peaked and remained constant thereafter. In ILs, the reaction was less favorable and the solubility limit of succinic acid was no longer a discriminating parameter [13].

Some authors performed the separation of secondary alcohols conjugated with direct extraction of products by employing supercritical fluids [14–16]. The application of ionic liquids together with supercritical fluids offers very interesting prospects because supercritical fluid can be dissolved up to 0.6 mole fraction in [*bmim*][PF_6], while no ionic liquid is detected in the vapor phase [36]. This allows to develop new methods of products separation after reactions. For example, *Lozano et al.* performed reactions between model alcohol, 1-phenylethanol (100 mmol dm^{-3} in *n*-hexane), and vinyl propionate (50 mmol dm^{-3} in *n*-hexane) at 0.1 cm^3 min^{-1} flow with $scCO_2$ at 15 MPa in presence of CAL B (1.3 mg in 150 mm^3 water) dissolved in [*emim*][NTf_2] and [*bmim*][NTf_2] (4 cm^3) in a continuous mode. In both ionic liquids $ee_p > 99.9\%$ but higher temperature increases the selectivity (for 50°C selectivity = 86.3% when at 100°C equals 95.2% for [*emim*][NTf_2]). Besides, the activity decay was enhanced by the increase in temperature [16, 31]. However, the increase in polarity of ionic liquid slightly enhances all the activity and operational stability parameters due to a more appropriate microenvironment for the enzyme [16]. *Reetz et al.* deliberated an enzymatic reaction linked with extraction of products formed during reaction of 1-phenylethanol (10 mmol) with vinyl acetate (5.5 mmol) and CAL B (100 mg) in [*bmim*][NTf_2] (2 cm^3) in a batch process at 11 MPa at 40°C. They separated enantiomers of 1-phenylethanol very efficiently. After 1.2 h and 2 cycles the conversion was 46.7% with $ee_s = 95.2\%$ ((*S*)-1-phenylethanol) and $ee_p = 99.4\%$ ((*R*)-1-phenylethyl acetate) [14]. In their other paper [15] they tested isooctane,

[*bmim*][PF_6], [*bmim*][BF_4], and [*bmim*][NTf_2] together with CO_2 to extract the product of enzymatic reaction between 2-octanol (0.5 mmol) and vinyl acetate (1 mmol). They achieved the best results for Novozym 435 (5 mg) in [*bmim*][NTf_2] (1 cm^3) at 45°C reaching $ee_s > 99.9\%$ and $ee_p = 99.6\%$ at 50.9% conversion. The outcome of this reaction was used for the separation study. Other ionic liquids [*bmim*][PF_6], [*bmim*][BF_4], and isooctane gave high ee_s similar to [*bmim*][NTf_2] but much lower ee_p (88.6, 89.8, and 85.7% for isooctane, [*bmim*][PF_6], and [*bmim*][BF_4]). Separation of products from a reaction performed in [*bmim*][NTf_2] was carried out in two steps (1st step 9 MPa, 60°C and 2nd step 20 MPa, 45°C). *Reetz et al.* obtained from separation the products with very high purity $ee_s = 98.9\%$ and $ee_p > 99.5\%$ [15].

Accordingly, ionic liquids exhibit the feasibility to improve the resolution of secondary alcohols *via* enzyme catalytic acylation.

Conclusions

Lipase-catalyzed acylation of alcohols is a way to resolve enantiomers with $ee_p > 99\%$ and with $E > 100$. Lipase enzymes catalyze efficiently reactions with (*R*)-enantiomer leaving the second enantiomer unreacted.

Separation of secondary alcohols is a field of chemistry now widely studied. Enzymatic catalysis is a great tool that guides to obtain optically pure enantiomers. Ionic liquids are suitable media for enzymatic reactions due to their unique properties. ILs stabilize enzymes and reactants better than organic solvents. Besides, they influence the synthetic activity of an enzyme what leads to reduction of reaction time compared to the traditional solvents, and by employing different ionic liquids we can easily control the reaction pathways to achieve the required products. Due to negligible vapor pressure of ionic liquids, new feasibilities are opened for extraction of products after enzyme catalytic reaction by liquid extraction or by the minimum-waste separation with supercritical fluids. Extraction with using supercritical fluids makes possible to link reaction and separation into one conjugated process which is required to reduce impact on environment. In addition, because of that we can reduce emission of organic solvents what makes the processes sustainable.

Acknowledgements

I am grateful for support by the European Commission in the frame of *Marie Curie* Research Training Network SUPERGREENCHEM (EC Contract No.: MRTN-CT-2004-504005).

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