Invited Review
Asymmetric Synthesis in Ionic Liquids

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Summary. In the last decades catalytic enantioselective transformations have became one of the most studied fields in synthesis chemistry. With the advancement of biphasic catalysis several of these reactions have been adapted to be run in ionic liquids. The variability of ionic liquids provides the means to fine tune catalytic processes, and even more importantly, the ionic liquids might be used to immobilize the catalyst and allow its easy recycling. The present review aims to provide an overview of the state of the art of enantioselective homogeneous catalytic transformations in ionic liquids.

Keywords. Metal catalysis; Organocatalysis; Stereoselectivity.

Introduction

Ionic liquids (ILs) are ionic compounds that have a melting point below 100°C. Most of the commonly used ILs are liquid at room temperature. Ionic liquids have a high polarity (usually between acetonitrile and methanol) and low (negligible) vapor pressure. These features combined with the fact that most ionic liquids are immiscible with less polar organic solvents led to their burgeoning use as media or co-solvent in catalysis. The importance of this area is highlighted by the increasing number of reviews and books dedicated to the topic [1].

The first example of the use of ILs in biphasic asymmetric catalysis was reported by *Chauvin et al.* [2] in 1995, while the first examples of their use as media in such transformations appeared five ye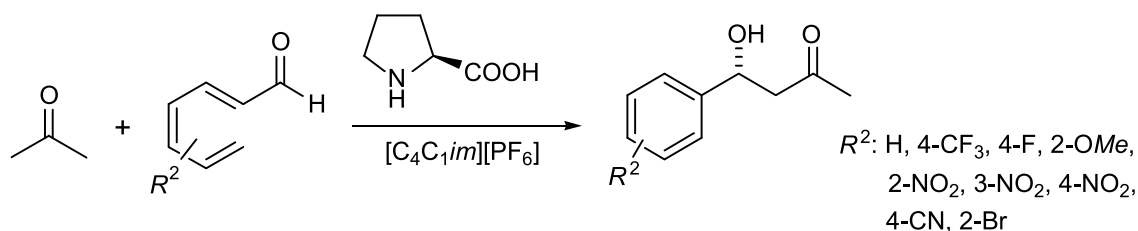ars later [3]. Since then a multitude of reports appeared in literature using several different classes of ionic liquids. The most common ionic liquids in asymmetric transformations are the N,N'-disubstituted imidazolium salts (C_xC_yim, where C_x and C_y are normal alkyl groups of n carbon atoms). Ammonium, phosphonium, pyridinium (*py*), and pyrrolidinium (*pyr*) salts have also been used, although less frequently. ILs can be chiral in the cation or anion alike. Such ILs offer a unique approach to asymmetric synthesis through the presence of a chiral medium.

There are three major classes of catalytic enantioselective transformations in ILs: biocatalysis, organocatalysis, and metal catalysis. Due to the limits of this review we only present here an arbitrary selection of representative examples of the two latter classes.
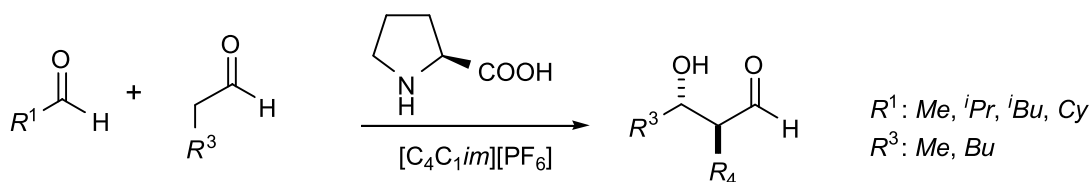
Organocatalysis in Ionic Liquids

It is not surprising that proline, the grandfather of organocatalysts [4], is one of the first and most frequently used compounds that was used as organocatalyst in ILs. In the aldol reaction of benzaldehyde derivatives and acetone (Scheme 1) interestingly the nature of the IL used was found to have a significant influence on the chemoselectivity of the process. The most efficient media was $[C_4C_1im][PF_6]$, in which enantioselectivities were acceptable (58–82%) and the catalyst could be recycled several times without apparent degradation of the *ee* [5]. The use of immobilized ILs in the same transformation led to a moderate decrease of the efficiency [6]. Extension of this
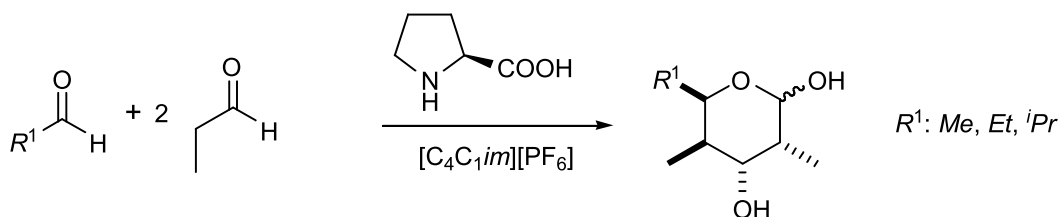
* Corresponding author. E-mail: kotschy@elte.hu

Scheme 1

R^2: H, 4-CF$_3$, 4-F, 2-O*Me*, 2-NO$_2$, 3-NO$_2$, 4-NO$_2$, 4-CN, 2-Br

Scheme 2

R^1: *Me*, ^{i}*Pr*, ^{i}*Bu*, *Cy*
R^3: *Me*, *Bu*

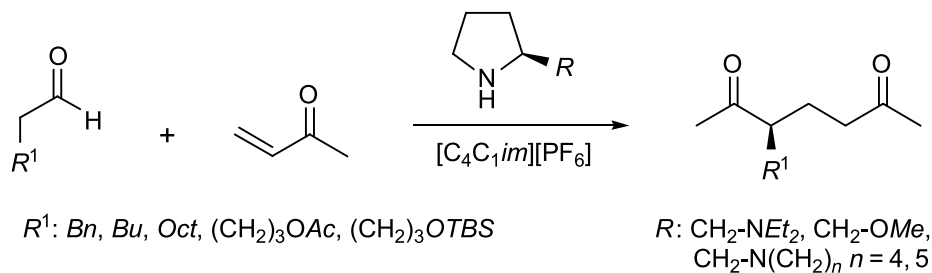**Scheme 3**

R^1: *Me*, *Et*, ^{i}*Pr*

protocol to the cross aldol reaction of two different aldehydes proceeded very efficiently (Scheme 2) and in certain cases nearly complete enantioselectivity was observed even after several recyclings. The addition of a co-solvent to the IL was advantageous to the chemoselectivity of the reaction [7]. By slightly modifying the conditions the same reactants could be converted to pyrane reactants (Scheme 3).

ILs as media were found to accelerate the reaction of methyl vinyl ketone and various aliphatic aldehydes (Scheme 4). Several proline derivatives were tested as organocatalyst but the observed enantio-
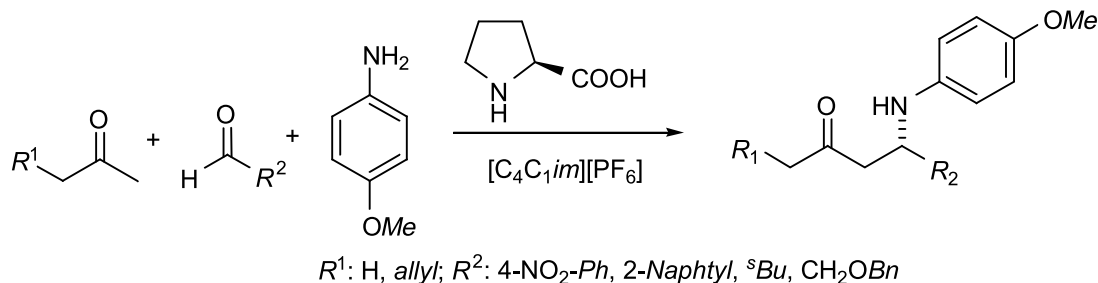
selectivities, however, were only modest (below 60%) in most cases [8].

The proline catalyzed *Mannich* reaction of aldimines and various aldehydes and ketones ran smoothly in ILs to give high *ee*s through several cycles. The three-component variant of this reaction has also been studied (Scheme 5), where the yields and selectivities were also comparable to those obtained in organic solvents, although certain substrates gave only poor yields in ILs [9].
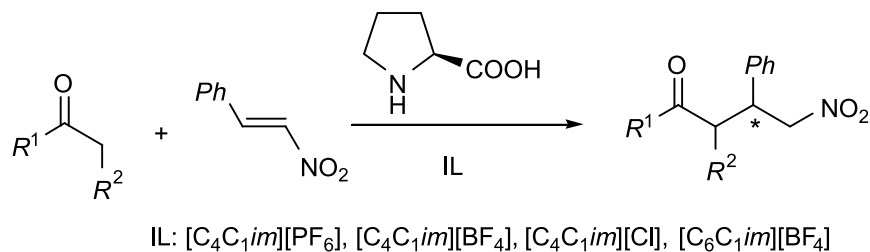
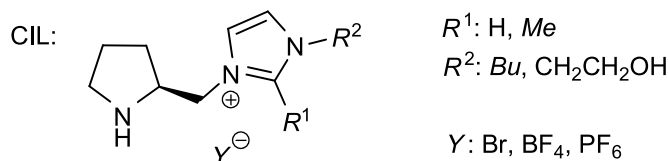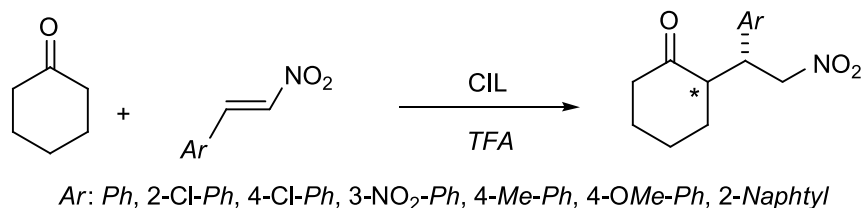Several asymmetric *Michael* additions were conducted in ILs with β-ketoesters and analogues [10],

R^1: *Bn*, *Bu*, *Oct*, (CH$_2$)$_3$O*Ac*, (CH$_2$)$_3$O*TBS*

R: CH$_2$-N*Et$_2$*, CH$_2$-O*Me*, CH$_2$-N(CH$_2$)$_n$ n = 4, 5

Scheme 4

R^1: H, allyl; R^2: 4-NO$_2$-Ph, 2-Naphtyl, ^{s}Bu, CH$_2$OBn

Scheme 5

IL: [C$_4$C$_1$im][PF$_6$], [C$_4$C$_1$im][BF$_4$], [C$_4$C$_1$im][Cl], [C$_6$C$_1$im][BF$_4$]

Scheme 6

Ar: Ph, 2-Cl-Ph, 4-Cl-Ph, 3-NO$_2$-Ph, 4-Me-Ph, 4-OMe-Ph, 2-Naphtyl

CIL:

R^1: H, Me
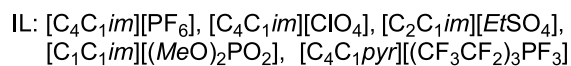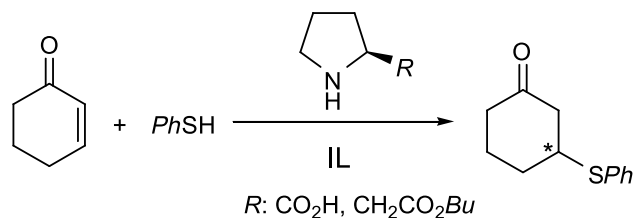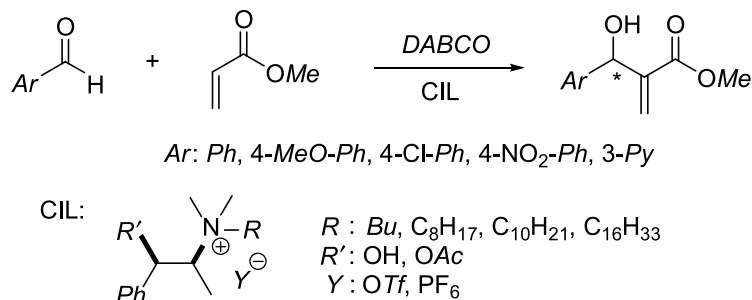R^2: Bu, CH$_2$CH$_2$OH

Y: Br, BF$_4$, PF$_6$

Scheme 7

and interestingly change of the IL could result in the reversal of the enantioselection of the process in certain cases [11]. Proline [12] and other organocatalysts [13] were also tested in the addition of aldehydes and ketones to nitroolefins (Scheme 6), proline giving usually the best selectivity. The recycling of the catalyst led to deteriorating selectivity.

Proline-like ILs were used both as media and catalyst in the addition of ketones and aldehydes to nitrostyrene (Scheme 7). The model reaction of cyclohexanone showed an excellent yield and enantioselectivity, but the activity of the catalyst decreased on recycling. Michael donors other than cyclohexanone reacted also with decreased selectivity [14].
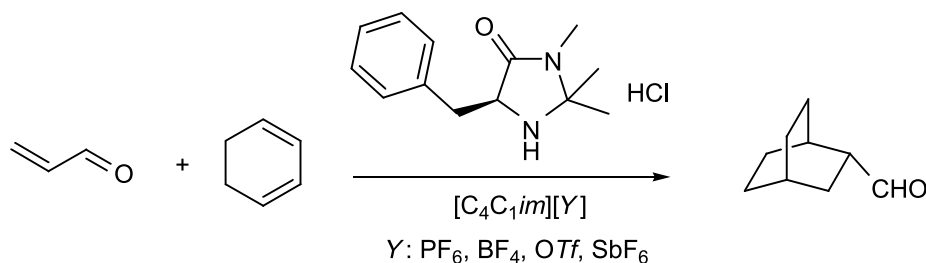
The Michael addition of thiophenol to chalcone was also carried out in ILs (Scheme 8), but in this reaction the addition of proline had no effect on the

R: CO$_2$H, CH$_2$CO$_2$Bu

IL: [C$_4$C$_1$im][PF$_6$], [C$_4$C$_1$im][ClO$_4$], [C$_2$C$_1$im][EtSO$_4$], [C$_1$C$_1$im][(MeO)$_2$PO$_2$], [C$_4$C$_1$pyr][(CF$_3$CF$_2$)$_3$PF$_3$]

Scheme 8

Scheme 9

Scheme 10

enantioselectivity, suggesting that the uncatalyzed process is so much accelerated in the IL, that there is no time for the formation of the chiral iminium intermediate from chalcone [15].

In the *Bayliss-Hillman* reaction of methyl acrylate and benzaldehyde (Scheme 9) several chiral ILs were tested as media. Only moderate enantioselectivities were observed in the *DABCO* catalyzed process. In the screening of different ILs and substrates in order to approach selectivities that can be obtained in conventional organic solvents improve remained futile [16].

N-Butyl-*N'*-methylimidazolium salts containing different anions were used as media in the *Diels-Alder* reaction of cyclohexadiene and acrolein in the presence of the *MacMillan* catalyst (Scheme 10). Surprisingly, the nature of the anion had a dramatic effect both on the selectivity and efficiency of the transformation. In PF$_6$ and SbF$_6$ salts good yields and enantioselectivities (up to 93%) were obtained, while in the tetrafluoroborate and triflate salts racemic products were formed in low yield [17].

Metal Catalysis in Ionic Liquids

The most studied transition metal catalyzed enantioselective transformation is most likely the asymmetric reduction of carbon–carbon and carbon–heteroatom double bonds. In these reactions usually molecular hydrogen is used as the reagent. When changing the common solvents in hydrogenation the solubility of hydrogen might become an issue. Comprehensive solubility studies revealed that ILs dissolve H$_2$ poorly alike water (less efficiently than organic solvents) [18], so kinetics of the hydrogenation and the selectivity of the process can both vary considerably depending on the nature of the IL [19].

The rhodium catalyzed hydrogenation of enamides (Scheme 11) was found to work well and high enantioselectivities (95%) were obtained. The catalyst could be recycled and for some reactions the IL extended the lifetime of the catalyst [20]. This phenomenon is not general, however since in other cases the catalytic activity of the rhodium complex de-
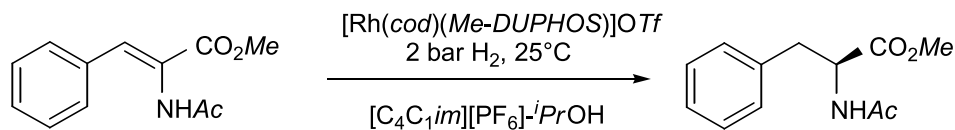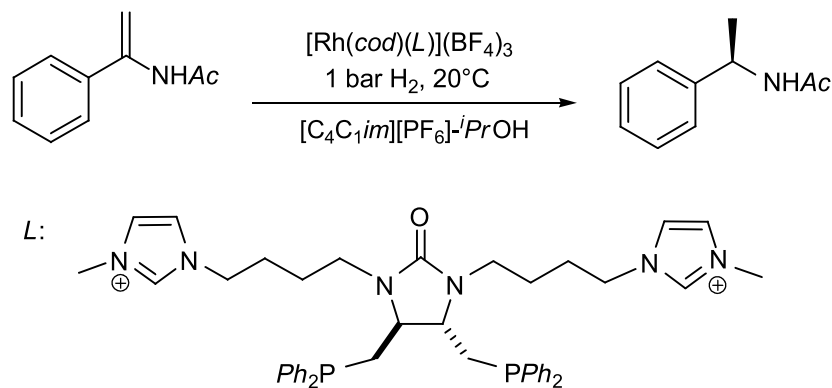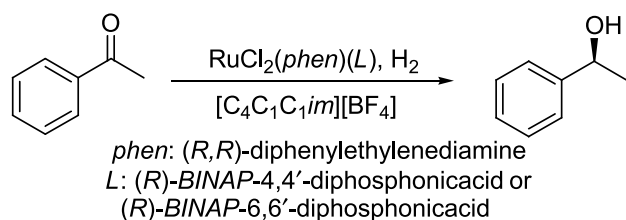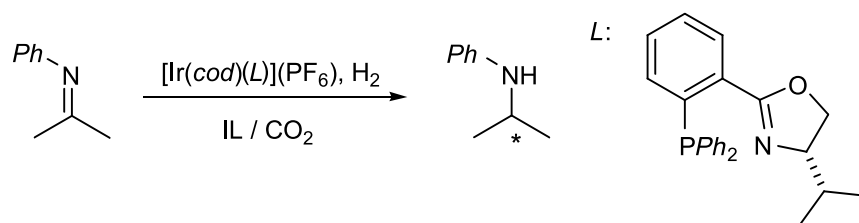

Scheme 11

Scheme 12

creased considerably on recycling, which might be attributed to leaching or partial deactivation.

In order to anchor the catalyst to the IL phase imidazolium moieties were attached covalently to a chiral diphosphine (Scheme 12). The so obtained catalyst system was efficient in enamide reduction and it could also be recycled without apparent loss of its activity [21].

Ruthenium-based catalyst systems were also tested in ILs. The fine tuning of *Noyori*'s Ru-*BINAP* system by functionalizing the ligand led to excellent enantioselectivity in the reduction of β-ketoesters [22]. The similar catalyst system having a diphenyl-ethylenediamine supporting ligand was efficient in the reduction of aromatic ketones (Scheme 13). In this transformation the nature of the IL was found to have a major influence on catalyst activity [23]. The same transformation was also achieved in phospho-

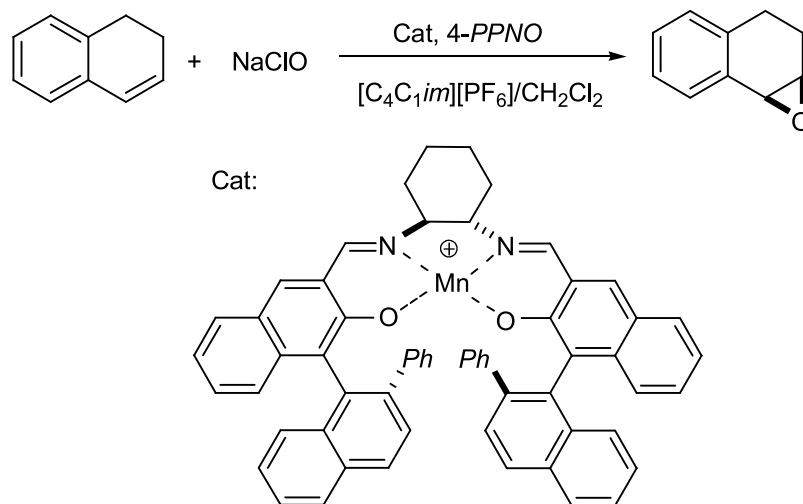nium ILs and in this case instead of molecular hydrogen isopropanol was used as "reducing agent" (transfer hydrogenation) [24].
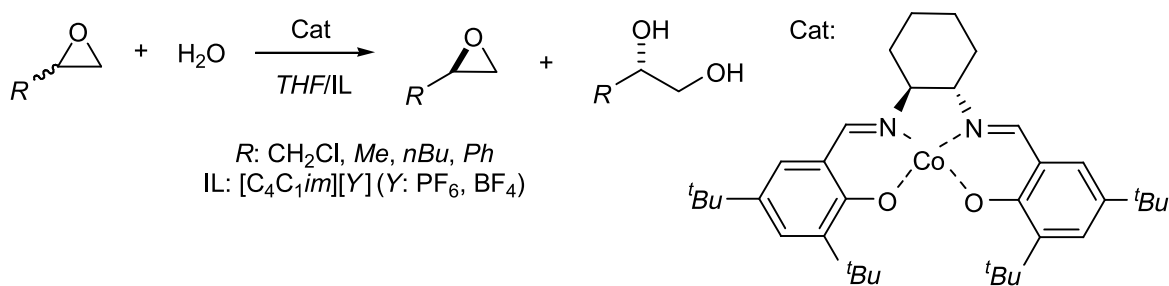
The use of a biphasic IL-carbon dioxide system was found to accelerate the iridium catalyzed reduction of imines without the apparent loss of selectivity (Scheme 14). The rate enhancement was attributed to the increased solubility of hydrogen and the decreased viscosity of the biphasic system [25].

The epoxidation of different substrates using either *Katsuki* or *Jacobsen* type *salen* complexes was found to proceed well in ILs without the apparent loss of selectivity in most cases [26]. Dihydronaphthalene was epoxidized efficiently and the catalyst could be recycled without any significant change in its activity and selectivity (Scheme 15). A similar *salen* complex could ring open one of the enantiomers of terminal epoxides with acceptable selectivity in an IL containing solvent mixture (Scheme 16). It is worth mentioning that the IL seems to have blocked the deactivation of the catalyst [27].
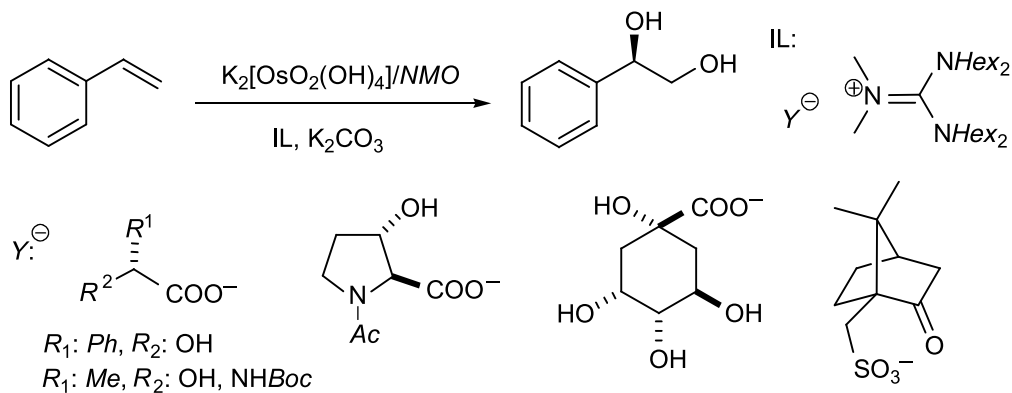
The asymmetric dihydroxylation of olefins was achieved both in IL containing biphasic systems and in pure ILs [28]. The asymmetric dihydroxylation of olefins was also realized in the absence of the usual chiral ligands using chiral ILs as media (Scheme 17). Guanidinium salts having different

phen: (*R,R*)-diphenylethylenediamine
L: (*R*)-*BINAP*-4,4′-diphosphonicacid or
(*R*)-*BINAP*-6,6′-diphosphonicacid

Scheme 13

Scheme 14

Scheme 15

R: CH$_2$Cl, *Me*, *nBu*, *Ph*
IL: [C$_4$C$_1$*im*][*Y*] (*Y*: PF$_6$, BF$_4$)

Scheme 16

R_1: *Ph*, R_2: OH
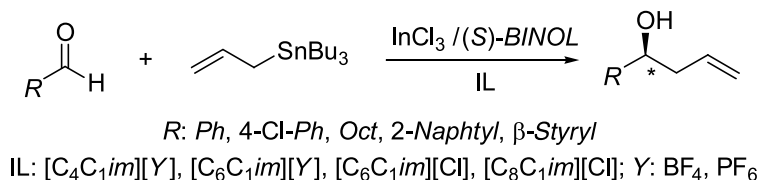R_1: *Me*, R_2: OH, NH*Boc*

Scheme 17

chiral anions induced enantiomeric excesses comparable with conventional asymmetric dihydroxylation reactions conducted in the presence of cinchona-based ligands [29].
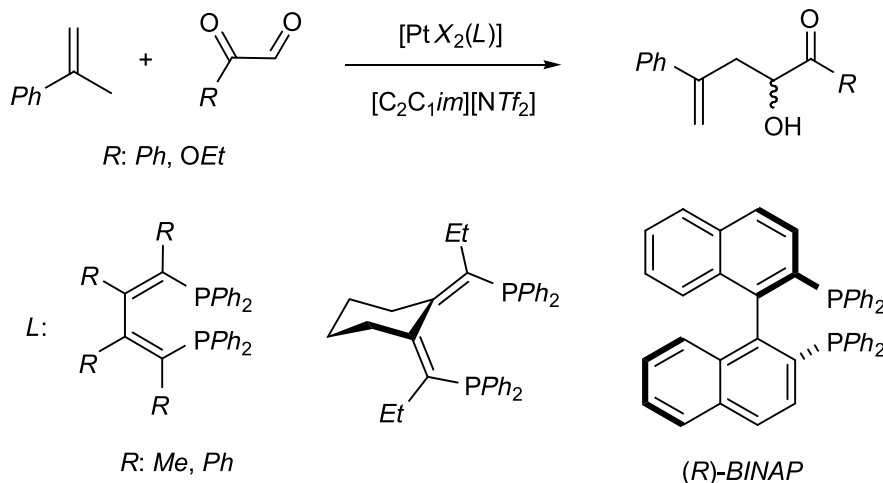
The indium(III) catalyzed allylation of aldehydes with allyltributyltin has been performed with a great variety of ligands in a series of ILs (Scheme 18).

Catalysts containing *BINOL* as ligand could not be recycled since they decomposed on work-up [30]. Selectivities and yields were mediocre in the process.
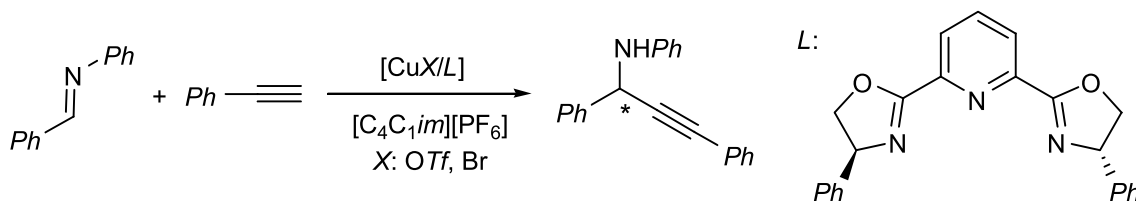
The palladium-catalyzed reaction of glyoxal derivatives and alkenes ran smoothly in ILs and both yield and selectivity were usually superior compared with the same reactions run in *DCM* (Scheme 19)

R: *Ph*, 4-Cl-*Ph*, *Oct*, 2-*Naphtyl*, β-*Styryl*

IL: [C$_4$C$_1$*im*][*Y*], [C$_6$C$_1$*im*][*Y*], [C$_6$C$_1$*im*][Cl], [C$_8$C$_1$*im*][Cl]; *Y*: BF$_4$, PF$_6$

Scheme 18

R: *Ph*, O*Et*


R: *Me, Ph*

(*R*)-*BINAP*

Scheme 19

Scheme 20

[31]. A possible explanation for the increased selectivity might be the decreased rate of racemization of the ligand in ILs.

A propargylamine was prepared in the copper(I)-*PyBox*-catalyzed enantioselective addition of terminal acetylenes to imines (Scheme 20). Interestingly the efficiency of the transformation showed a marked dependence both on the copper counter ion and the nature of the imidazole C2-substituent [32].

The catalytic *Michael* addition of a β-ketoester to *MVK* was achieved in the presence of a Pd-*BINAP* catalyst system (Scheme 21). The reaction could be fine-tuned by screening different *BINAP* derivatives as ligands (*ees* up to 84%) [33]. Efficient recycling of the catalyst could also be achieved in the presence of a moderately acidic additive.
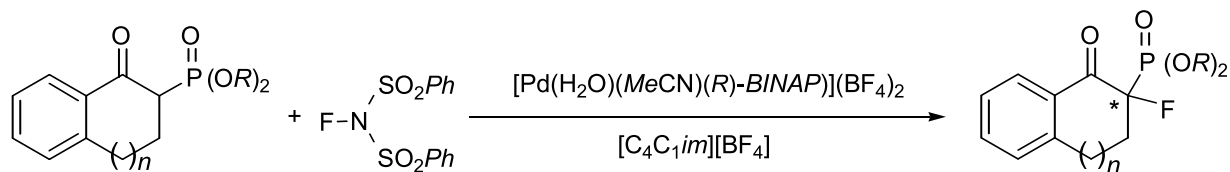
Ferrocene based ligands were found to give acceptable enantioselectivities in the palladium catalyzed
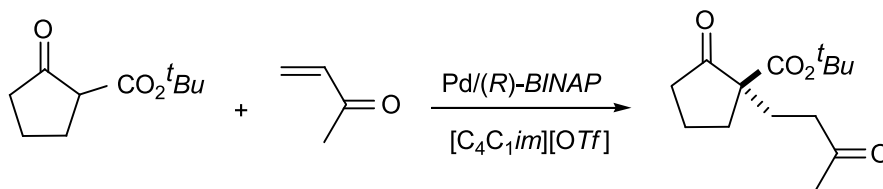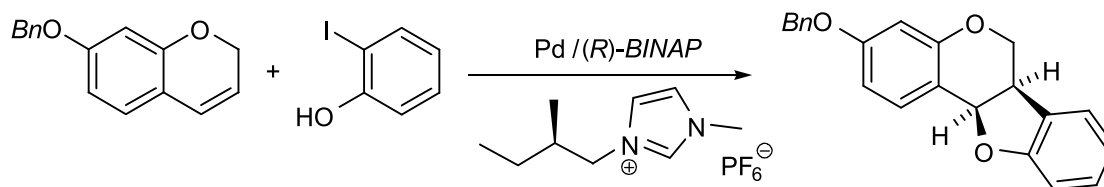

Scheme 21
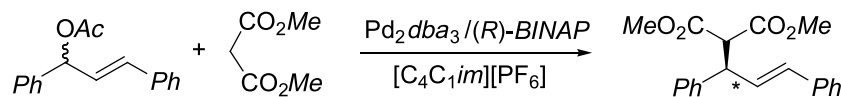
Scheme 22

Scheme 23

Scheme 24

allylation of dimethyl malonate in ILs [34]. The catalyst efficiency remained constant on recycling. The performance of the Pd-*BINAP* system (Scheme 22) on the other hand deteriorated considerably on recycling due probably to increased leaching.

The enantioselective fluorination of β-ketoesters and β-ketophosphonates was achieved in ILs using chiral palladium complexes (Scheme 23). The transformations proceeded with good selectivity and *ee*s above 90% were obtained in most cases [35].

Attempts were also made at carrying out the *Heck* oxyarylation of a benzopyrene derivative in a chiral IL (Scheme 24). The reaction proceeded however with poor selectivity (*ee* < 10%) [36].

ILs were tested not only for fine chemicals synthesis but also in the preparation of polymers (Scheme 25). Carbon monoxide and propene were co-polymerized in the presence of a palladium catalyst. The nature of the ILs was found to influence the properties (polydispersity, M_w, *etc.*) of the formed polymer [37].

Amongst several other transformations the copper catalyzed enantioselective cyclopropanation of

alkenes with diazo compounds was also studied using various ILs. The nature of the IL, as in other cases, had a significant influence on the process [38].

Concluding Remarks

Although this review did not intend to provide a comprehensive and detailed description of the state-of-the-art in asymmetric catalysis in ionic liquids, the authors hope that they could convince the reader that the field is burgeoning. The uniqueness of chiral ILs, namely that they can provide a chiral environment that can be easily available and interacts strongly with the reactants has been barely tapped so far and promises to be an interesting field for future investigations.

Acknowledgements

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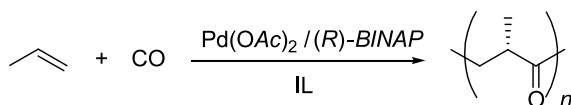
IL: [C$_4$C$_1$*im*][PF$_6$], [C$_6$C$_1$*im*][PF$_6$], [C$_4$C$_1$*im*][BF$_4$], [C$_8$C$_1$*im*][BF$_4$]

Scheme 25

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