Applications of Ionic Liquids in Organic Synthesis†

*Hua Zhao and Sanjay V. Malhotra**
Department of Chemistry and Environmental Science
New Jersey Institute of Technology
University Heights
Newark, NJ 07102, USA
E-mail: malhotra@njit.edu

Outline

1. Introduction
2. Composition of Ionic Liquids
3. Transition-Metal-Mediated Catalyses
   - 3.1. Hydrogenation
   - 3.2. Oxidation
   - 3.3. Hydroformylation
   - 3.4. Hydrodimerization
   - 3.5. Heck Reaction
   - 3.6. Alkoxycarbonylation
   - 3.7. Trost–Tsuji Coupling
   - 3.8. Ring-Closing Metathesis (RCM)
   - 3.9. Suzuki Cross-Coupling
4. Other Organic Reactions
   - 4.1. Diels–Alder Reaction
   - 4.2. Friedel–Crafts Reaction
   - 4.3. Esterification
   - 4.4. Regioselective Alkylation
   - 4.5. Displacement Reaction with Cyanide
   - 4.6. Stereoselective Halogenation
   - 4.7. Reduction of Aldehydes and Ketones
   - 4.8. Fischer Indole Synthesis
   - 4.9. Beckmann Rearrangement
   - 4.10. Cycloaddition
5. Biocatalysis in Ionic Liquids
6. Summary
7. References and Notes

1. Introduction

An ionic liquid (IL) is a liquid consisting of ions only, but this definition is different from the classic definition of a molten salt.[1] The latter is a high-melting, highly viscous, and highly corrosive liquid, while an ionic liquid is liquid at a much lower temperature (< 100 °C) and has a lower viscosity. Currently, a major drive is underway in industry and academia to substitute more environmentally friendly technologies for traditional ones in which damaging and volatile organic solvents are heavily used. Ionic liquids are considered as environmentally friendly substitutes for volatile organic solvents, not only because of their low vapor pressures, but, more importantly, also because of their ability to act as catalysts. Moreover, ionic liquids possess several other attractive properties, including chemical and thermal stability, nonflammability, high ionic conductivity, and a wide electrochemical potential window.

Ambient-temperature, alkylpyridinium (RPy^+) chloroaluminate based ionic liquids were first reported in the early 1950s.[2] However, the report by Wilkes and co-workers[3a] of 1,3-dialkylimidazolium-based chloroaluminate ionic liquids, that possess favorable physical and electrochemical properties, provided the impetus for a dramatic increase in activity in this area.[3b] Ionic liquids usually consist of inorganic anions and nitrogen-containing organic cations, and their chemical and physical properties can be finely tuned for a range of applications by varying the cations or anions.[4] For example, varying the anion X in [EMIM][X] changes the melting point of the ionic liquid in the range of –14 to 87 °C.[5] The fact that they can now be produced with melting points at or below room temperature (as low as –96 °C) has been an important reason why ionic liquids have been explored in many applications.[1]

Recent reviews have surveyed the behavior of halogenoaluminate(III) ionic liquids in many reactions including dimerization, polymerization, and multiphase hydrogenation.[5,6] Since halogenoaluminate(III)-type ionic liquids are sensitive to moisture, their applications in chemical reactions have been limited. Stable, room-temperature ionic liquids (RTILs) have been studied in many chemical processes, for example, bio-processing operations,[7] as electrolytes in electrochemistry,[8,9] in gas separations such as the capturing of CO_2,[10] in liquid–liquid extractions,[11,12] and as heat-transfer fluids.[13] However, since most studies have employed ionic liquids as green solvents or catalysts for organic synthesis, this review will summarize recent research on the applications of RTILs in organic reactions.

2. Composition of Ionic Liquids

The most commonly used cations in room-temperature ionic liquids are alkylammonium, alkylphosphonium, *N*,*N*′-dialkylimidazolium ([RR′IM]), and *N*-alkylpyridinium ([RPy]) cations (**Figure 1**).[5] The most commonly utilized alkyl chains are methyl, ethyl, butyl, hexyl, octyl, and decyl. The most commonly investigated IL anions are shown in **Table 1**.[4,14-22]

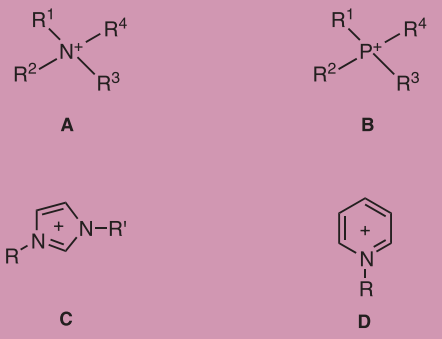
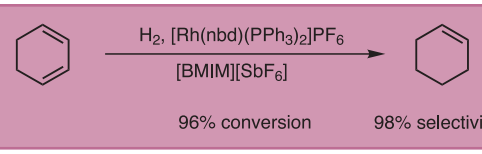


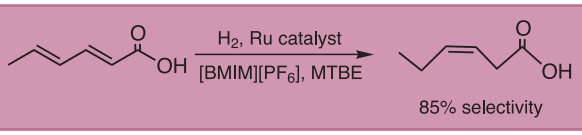
Figure 1. Important Cation Types in Room-Temperature Ionic Liquids.

Table 1. Examples of Anions Commonly Found in Ionic Liquids

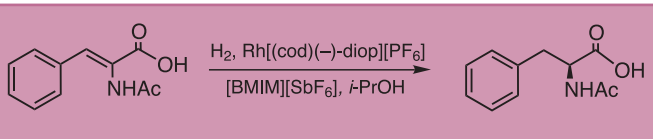
Anion	Reference	Anion	Reference
BF_4^-	4	$(CF_3SO_2)_2N^-$	17
PF_6^-	14	$CF_3CO_2^-$	17
SbF_6^-	15	$HexBEt_3^-$	18
$CH_3CO_2^-$	4	OTs^-	19
HSO_4^-	16	$AuCl_4^-$	20
NO_3^-	4	$AlCl_4^-$	21
NO_2^-	4	Carborane anions	22
$CF_3SO_3^-$	17		



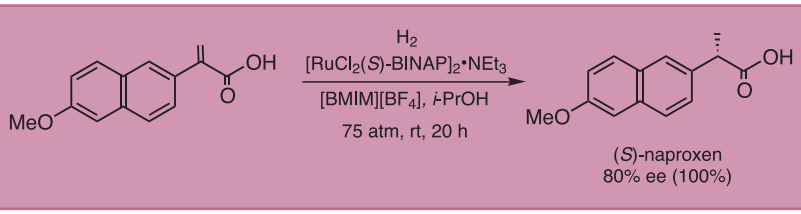
eq 1



eq 2



eq 3



eq 4

3. Transition-Metal-Mediated Catalyses

3.1. Hydrogenation

Ionic liquids can dissolve organometallic compounds and provide a polar, weakly coordinating medium for transition-metal catalysts. In this case, ionic liquids are used as inert solvents or co-catalysts.

The [Rh(nbd)(PPh_3)$_2$][PF_6] (nbd = norbornadiene) catalyzed biphasic hydrogenation of 1-pentene in ionic liquids [BMIM][PF_6] (BMIM = 1-*n*-butyl-3-methylimidazolium) and [BMIM][SbF_6] was first reported in 1995 by Chauvin and co-workers.[23] The reaction rate in the IL was five times higher than the one obtained by using acetone as solvent. Furthermore, the catalyst solution in the ionic liquid was reused without significant loss of rhodium. Chauvin's group also reported a selective hydrogenation of 1,3-cyclohexadiene to cyclohexene (98% selectivity at 96% conversion) by taking advantage of the biphasic reaction system (**eq 1**):[24] the solubility of 1,3-cyclohexadiene in [BMIM][SbF_6] is about five times that of cyclohexene. It is worth noting that complete suppression of the hydrogenation activity was observed when ionic liquids containing Cl^- impurities were used.

Similarly, other rhodium- and cobalt-catalyzed hydrogenations, such as the hydrogenation of butadiene,[25] aromatic compounds,[26] or acrylonitrile–butadiene copolymers have been conducted successfully in ionic liquids.[27] More recently, a ruthenium-catalyzed stereoselective hydrogenation of sorbic acid to *cis*-3-hexenoic acid was performed in the biphasic [BMIM][PF_6]–MTBE system (**eq 2**).[28]

Enantioselective hydrogenation in ionic liquids has attracted special attention, since it provides a means for recycling metal complexes of expensive chiral ligands. In the presence of [Rh(cod)(–)-(diop)][PF_6] catalyst {cod = 1,3-cyclooctadiene; diop = 4,5-bis[(diphenylphosphanyl)methyl]-2,2-dimethyl-1,3-dioxolan-4,5-diol} in [BMIM][SbF_6], the enantioselective hydrogenation of α-acetamidocinnamic acid to (*S*)-phenylalanine was achieved with 64% enantiomeric excess (ee) (**eq 3**).[23]

Another successful example of enantioselective hydrogenation was reported by Monteiro et al., who used [$RuCl_2$(*S*)-BINAP]$_2$•NEt_3 as the chiral catalyst.[29] (*S*)-Naproxen was thus synthesized in 80% ee from 2-(6-methoxy-2-naphthyl)acrylic acid in [BMIM][BF_4] and isopropyl alcohol (**eq 4**).

Very recently, biphasic systems containing an ionic liquid and supercritical CO_2 ($scCO_2$) have been investigated for catalytic hydrogenation.[30,31] Tumas and co-workers[30] observed that the hydrogenation of olefins could be achieved in a biphasic [BMIM][PF_6]–$scCO_2$ system. The ionic liquid phase containing the catalyst was decanted and reused in up to four consecutive reactions. Jessop's group[31] performed the successful asymmetric hydrogenation of tiglic acid (**eq 5**) and the precursor of the anti-inflammatory drug ibuprofen (**eq 6**) by using Ru(OAc)$_2$((*R*)-tolBINAP) as catalyst. In both cases, the product was separated by $scCO_2$ extraction upon completion of the reaction.

Molecular hydrogen was found four times more soluble in [BMIM][BF_4] than in [BMIM][PF_6] at the same pressure.[32] Systematic studies of the effect of hydrogen concentration on enantioselectivity have been conducted by Berger et al. in the asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid and the kinetic resolution of methyl (±)-3-hydroxy-2-methylenebutanoate by Rh(I) and Ru(II) catalysts.[32] The concentration of molecular hydrogen in the ionic liquid rather than its pressure in the gas phase was found to have the most significant influence on the conversion and enantioselectivity of these reactions.

3.2. Oxidation

Although ionic liquids are highly stable and have been evaluated as media for oxidation reactions,[17] surprisingly little attention has been focused on carrying out catalytic oxidations in ionic liquids. A recent publication by Song and Roh is one of the earliest studies of catalytic oxidations in ionic liquids.[33] In this study, asymmetric Jacobsen–Katsuki epoxidations were performed with NaOCl in [BMIM][PF_6] and were catalyzed by a chiral Mn complex (Jacobsen's catalyst) (**eq 7**). A clear improvement of the catalytic activity was observed by adding the ionic liquid to the dichloromethane solvent. The ionic liquid containing the catalyst was reused in four consecutive runs without significant loss in yield; however, after the 5th run, the conversion dropped from 83% to 53%. This drop in conversion is believed to be due to a degradation of the [Mn^{III}(salen)] complex.

Another example of catalytic oxidation is the methyltrioxorhenium (MTO)-catalyzed epoxidation of olefins with the urea–H_2O_2 adduct (UHP) in [EMIM][BF_4].[34] High conversions and yields were observed, except for 1-decene (46% conversion, > 99% yield), which was attributed to its lower solubility in the ionic liquid. In the case of sensitive epoxides, ring opening was observed in the presence of large amounts of water.

A more exciting study utilized a chiral Mn(salen) complex in [BMIM][PF_6] for the electroassisted biomimetic activation of molecular oxygen.[35] It was observed that a highly reactive oxomanganese(V) intermediate could transfer its oxygen to an olefin, which hints at a promising future for clean oxidations with molecular oxygen in ionic liquid media.

3.3. Hydroformylation

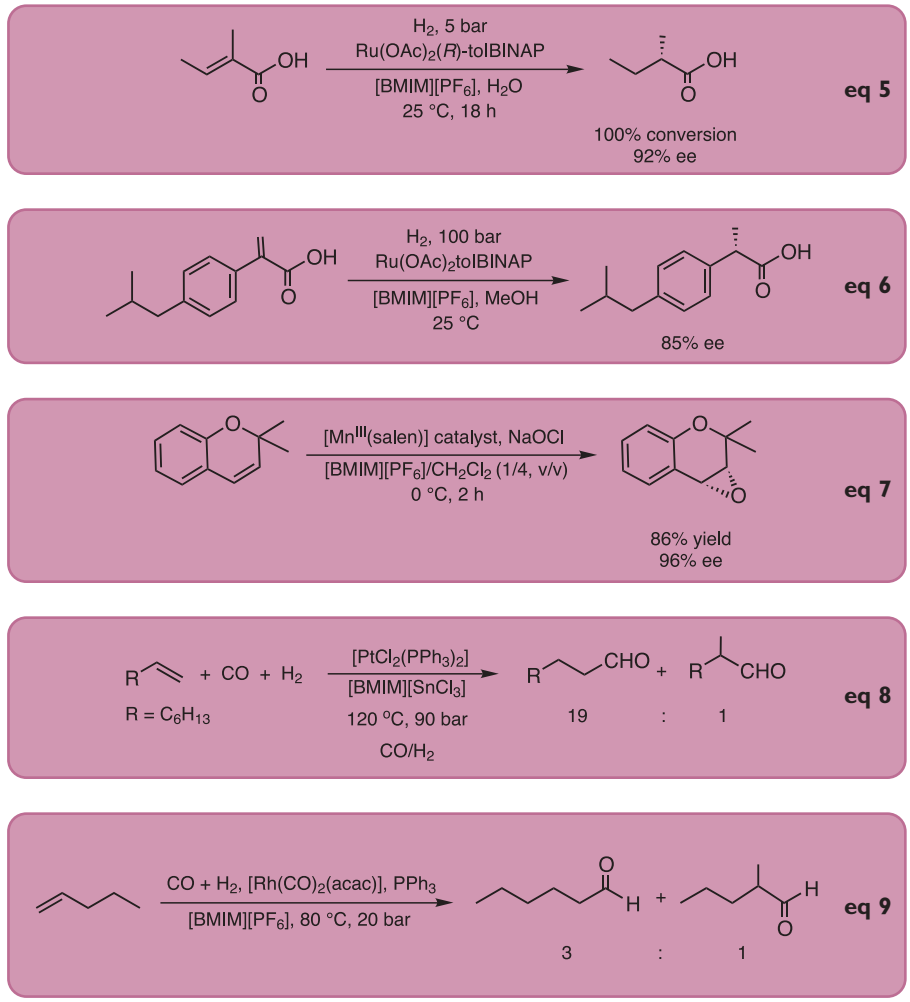
The platinum-catalyzed hydroformylation of ethene in tetraethylammonium trichlorostannate melts was conducted by Parshall as early as 1972.[36] The ionic liquid used in this case has a high melting point of 78 °C. Recently, Waffenschmidt and Wasserscheid reported the platinum-catalyzed hydroformylation of 1-octene in the room-temperature ionic liquid [BMIM][$SnCl_3$] (**eq 8**).[37] This biphasic system offered the advantage of simple product isolation and easy recovery of the platinum catalyst.

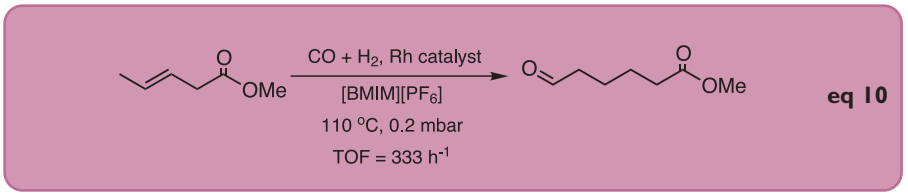
The ruthenium- and cobalt-catalyzed hydroformylation of internal and terminal alkenes in molten tetra-*n*-butylphosphonium bromide was reported by Knifton in 1987.[38] The rhodium-catalyzed hydroformylation of 1-hexene was investigated in higher-melting phosphonium tosylates, such as [Bu_3PEt][TsO] (mp 81–83 °C) and [Ph_3PEt][TsO] (mp 94–95 °C).[39] The product was easily separated from the solid catalyst medium at room temperature, and the catalyst was reused without loss of activity.

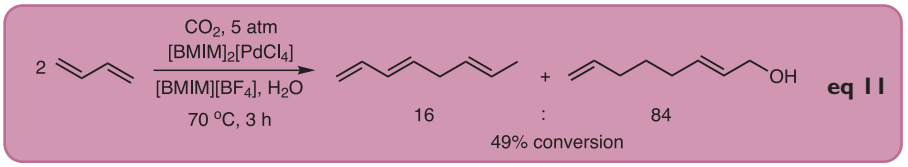
By employing room-temperature ionic liquid [BMIM][PF_6] as the reaction medium, the rhodium-catalyzed hydroformylation of 1-pentene was performed by Chauvin et al. (**eq 9**).[23] A higher activity [turnover frequency (TOF) = 333 h^{-1}] was observed as compared to the same reaction in toluene (TOF = 297 h^{-1}). Another report also indicated that a higher activity (TOF = 810 h^{-1}) and higher regioselectivity (*n/iso* = 16) were possible in the biphasic hydroformylation of 1-octene in [BMIM][PF_6] using a Rh-based catalyst.[40] Catalyst loss in the organic phase was less than 0.5%, and the ionic liquid catalyst solution was recycled. A high regioselectivity (20:1) was also obtained in the hydroformylation of 1-octene in [BMIM][PF_6] by using cationic guanidine-modified diphosphine ligands containing a xanthene backbone.[41]

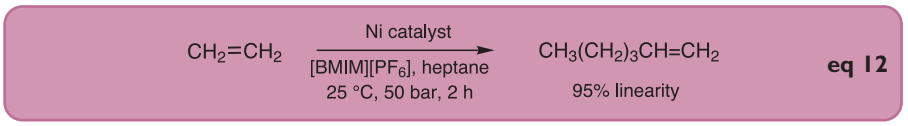
Not only have the biphasic hydroformylation reactions in ionic liquids shown their process advantages, but so has the rhodium-catalyzed monophasic reaction of methyl 3-pentenoate in [BMIM][PF_6] (**eq 10**).[42] The recovered catalyst was reused ten times under the same conditions without loss of activity.

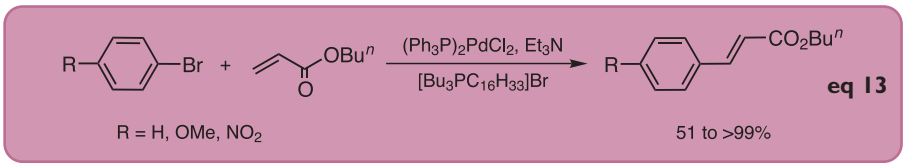
An interesting continuous flow process was utilized for the rhodium-catalyzed biphasic hydroformylation of 1-octene in [BMIM][PF_6]–$scCO_2$.[43] The product was synthesized at a fixed rate for 72 h with *n/iso* regioselectivity of 3.8, and only <1 ppm of Rh was lost in the organic phase.

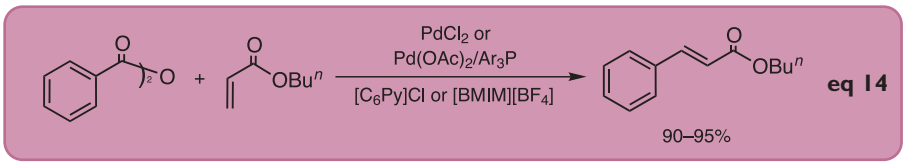


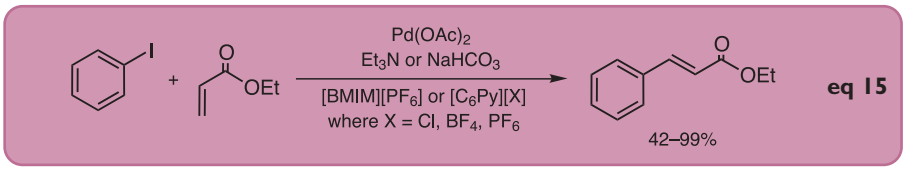












3.4. Hydrodimerization

Nickel(II)-catalyzed dimerization reactions in ionic liquids were first investigated in chloroaluminate(III) ionic liquid [BMIM][$AlCl_4$].[44] The product hexenes were separated from the ionic liquid by decantation. Due to the dissociation of ionic metal complexes caused by ionic liquids, it was believed that the ionic liquids were beneficial for the reactions. This application was extended to the oligomerization of butenes[45] and to the selective dimerization of ethene.[46]

Hydrodimerizations in ionic liquids can have many advantages over traditional hydrodimerizations, including higher selectivity for dimers due to their low solubility in ionic liquids, smaller reactor size, lower disposal costs, absence of corrosion, and wider applicability to less reactive and higher olefins.[15]

In recent years, chloroaluminate-free ionic liquids have become a new development in hydrodimerizations, because these new types of ionic liquids are more stable and easier to handle than the moisture-sensitive chloroaluminate(III) ionic melts. For example, [BMIM][BF_4] in water (1:1 v/v) was investigated in the hydrodimerization of 1,3-butadiene catalyzed by [BMIM]$_2$[$PdCl_4$].[47] In addition to the dimer, 1,3,6-octatriene, 2,7-octadienol was also produced (**eq 11**). However, by using $PdCl_2$/Ph_3P (1:4) as catalyst in [BMIM][X] (X = BF_4^-, PF_6^-, $CF_3SO_3^-$), the dimer, 1,3,6-octatriene, was obtained exclusively.[48]

Nickel(II)-catalyzed hydrodimerization reactions have also been studied in room-temperature ionic liquids. Wasserscheid and co-workers obtained a dimer selectivity of 98% and a TOF of 1240 h^{-1} at 25 °C in the linear dimerization (64% linearity) of 1-butene.[5,49] Recently, Wasserscheid, Gordon, and their co-workers also reported a biphasic oligomerization of ethene to higher α-olefins by nickel complexes in [BMIM][PF_6] (**eq 12**).[50] The product was separated easily as a clear layer, and the catalyst-containing ionic liquid layer was recovered without any detectable loss of catalyst activity.

3.5. Heck Reaction

The first use of ionic liquids as reaction media for the palladium-catalyzed Heck coupling was reported by Kaufmann et al. in 1996.[51] Moderate-to-high yields of butyl *trans*-cinnamates were obtained in molten tetraalkylammonium and tetraalkylphosphonium bromides by reaction of bromobenzenes with butyl acrylate (**eq 13**). The ionic liquid is believed to stabilize the palladium catalyst, and, in most reactions, no precipitation of palladium was observed even after complete conversion of the aromatic halide to the product.

Bohm and Hermann have extended this work to low-melting salts.[52] Their results indicate that molten [NBu_4][Br] (mp 103 °C) performs better in the Heck reaction than organic solvents such as DMF. In the reaction of bromobenzene with styrene, the yield of stilbene is increased from 20% in DMF to 99% in [NBu_4][Br] by using diiodobis(1,3-dimethylimidazolium-2-ylidene)palladium(II) as catalyst. Additional advantages of this solvent are the excellent solubility of all reacting molecules in it and its possible application as an inexpensive inorganic base. The authors also claim that the use of ionic liquids could become part of a standard method for carrying out Heck reactions in the future.

Earle, Seddon, and their co-workers described Heck couplings in [BMIM][PF_6] or *n*-hexylpyridinium hexafluorophosphate by using $PdCl_2$ or $Pd(OAc)_2$/Ar_3P as the catalyst (**eq 14**, **15**).[53] They reported a workup procedure in the three-phase system [BMIM][PF_6]/water/hexane. The products were soluble in the organic phase, while the used catalyst remained in the ionic layer. The salt formed as a by-product, [Hbase]X, dissolved in the aqueous phase.

The in situ identification of N-heterocyclic carbene complexes of palladium was performed by Xiao's group.[54] It was observed that [BMIM][Br] is more efficient in improving the Heck reaction rate than [BMIM][BF_4]. Two catalyst complexes, [PdBr(μ-Br)(bmiy)]$_2$ and [$PdBr_2$(bmiy)]$_2$, were isolated in [BMIM][Br] but not in [BMIM][BF_4] under the same reaction conditions. It was presumed that the stronger basicity of bromide as compared to tetrafluoroborate was a major factor in the formation of the carbene in [BMIM][Br]. Recently, Xiao and co-workers obtained >99% regioselectivity for the α-arylation

product in the Heck coupling of 1-bromonaphthalene with butyl vinyl ether in [BMIM][BF_4].[55] Similarly, [BMIM][BF_4] and [BMIM][PF_6] have also been employed in the palladium-catalyzed Stille[56] and Negishi couplings,[57] and in the nickel-catalyzed coupling of aryl halides.[58]

Other recent studies of the Heck coupling in ionic liquids include the Heck reaction of β-substituted acrylates in [NBu_4][Br] catalyzed by a palladium–benzothiazole carbene complex,[59] and the synthesis of pterocarpans by a Heck–oxyarylation reaction sequence in [BMIM][PF_6] in the presence of [$PdCl_2(PhCN)_2$]/Ph_3P/Ag_2CO_3 as the catalyst system.[60]

3.6. Alkoxycarbonylation

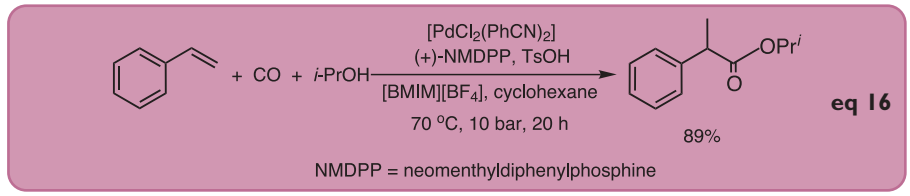
Carbonylation reactions in ionic liquids have received much less attention than the previously discussed transition-metal-catalyzed reactions. An example of palladium-catalyzed alkoxycarbonylation of styrene was reported by Monteiro and co-workers (**eq 16**).[61] In the reaction medium [BMIM][BF_4]/cyclohexane, styrene reacted with isopropyl alcohol and carbon monoxide to form isopropyl 2-phenylpropionate. Using (+)-neomenthyldiphenylphosphine [(+)-NMDPP] as ligand, the product was obtained in 89% yield and 99.5% regioselectivity, but with a very low asymmetric induction (ee < 5%).

A study of the palladium-catalyzed alkoxycarbonylation of aryl bromides and iodides in [BMIM][BF_4] and [BMIM][PF_6] was reported by Mizushima et al.,[62] who observed improved reactivities in the ionic liquids.

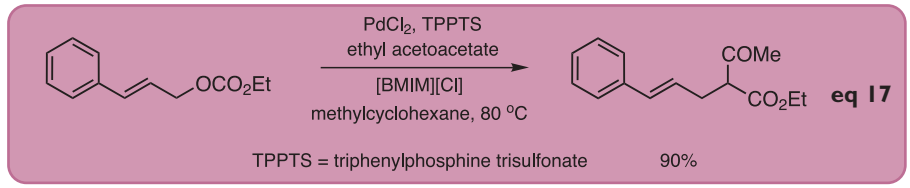
3.7. Trost–Tsuji Coupling

The Trost–Tsuji coupling is an important method for synthesizing carbon–carbon bonds through nucleophilic, allylic substitution. An interesting example is the monophasic reaction of 3-acetoxy-1,3-diphenylpropene with dimethyl malonate in [BMIM][BF_4].[63] The product is obtained in 91% yield after 5 h at room temperature using $Pd(OAc)_2$/PPh_3 as the catalyst system and K_2CO_3 as the base.

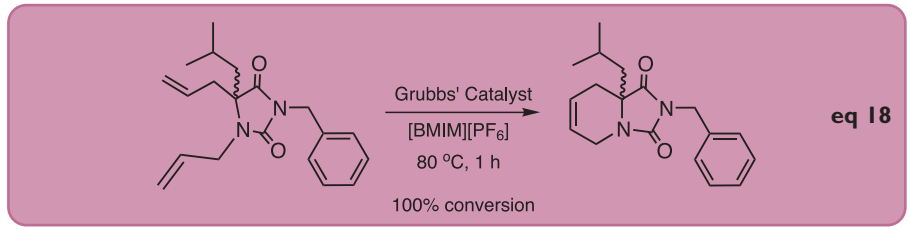
Biphasic Trost–Tsuji couplings have been conducted by de Bellefon et al. in [BMIM][Cl]/methylcyclohexane.[64] These workers observed a tenfold improvement in the catalytic activity due to the higher solubility of the substrates in the ionic liquid (**eq 17**). Enhanced selectivity was also achieved, since the formation of cinnamyl alcohol and phosphonium salts was suppressed.



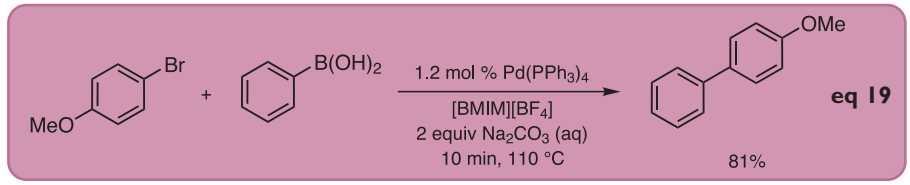
eq 16



eq 17



eq 18



eq 19

3.8. Ring-Closing Metathesis (RCM)

Ring-closing metathesis (RCM) is widely recognized as a powerful method for creating heterocycles, constrained peptides, and complex natural products.[65] [BMIM][PF_6] was used as an effective medium for ring-closing metathesis (RCM) that is induced by Grubbs' catalysts (**eq 18**).[66] After extraction of the product, [BMIM][PF_6] and the ruthenium catalyst were reused for three cycles. High conversions and a broad substrate tolerance were observed.

3.9. Suzuki Cross-Coupling

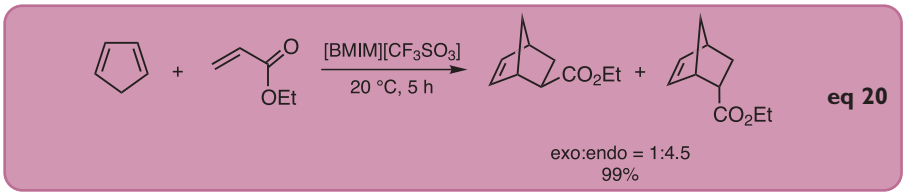
The Suzuki cross-coupling reaction is another versatile method for generating new carbon–carbon bonds. However, the traditional reaction suffers from several drawbacks such as incorporation of the catalyst into the product, decomposition of the catalyst, and/or poor reagent solubility. In order to overcome these drawbacks, a study of the palladium-catalyzed Suzuki cross-coupling reaction of aryl halides with arylboronic acids has recently been conducted in the room-temperature ionic liquid [BMIM][BF_4] (**eq 19**). Unprecedented reactivities were observed in addition to the easy isolation of product and recovery of catalyst.[67] This study identified several advantages of the Suzuki cross-coupling carried out in ionic liquids, namely: (a) a significant increase in reactivity is observed at a reduced catalyst concentration, especially for nonactivated aryl bromides; (b) homocoupling is avoided; (c) the reaction can be conducted under air without loss of yield or degradation of catalyst; and (d) repetitive runs can be performed without loss of catalyst activity.

4. Other Organic Reactions

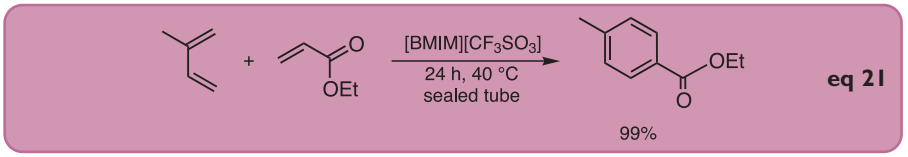
4.1. Diels–Alder Reaction

An early study of the Diels–Alder reaction of cyclopentadiene with methyl acrylate or methyl vinyl ketone in [$EtNH_3$][NO_3] was reported in 1989.[68] Although the reaction rate and selectivity were lower than those in water, the study showed that ionic liquids could be employed in this type of reaction. Encouraged by these findings, Diels–Alder reactions were conducted in several other ionic liquids such as [EMIM][PF_6],[69,70] [EMIM][BF_4],[70] [EMIM][CF_3SO_3],[70] [BMIM][ClO_4],[69] [EMIM][Cl]–$AlCl_3$,[71] and [BMIM][CF_3SO_3].[72] Two examples of these reactions are illustrated in **eq 20** and **21**.[72]

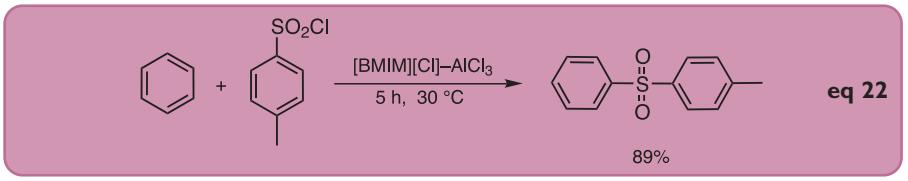
The use of $LiClO_4$ in diethyl ether has become one of the biggest developments in Diels–Alder chemistry. The $LiClO_4$–Et_2O



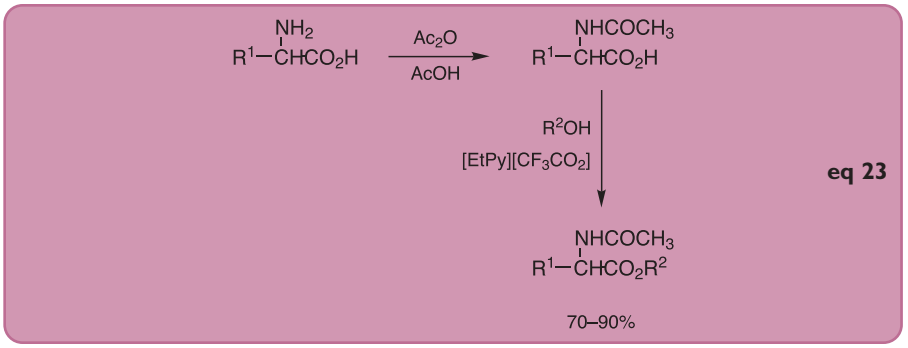
eq 20



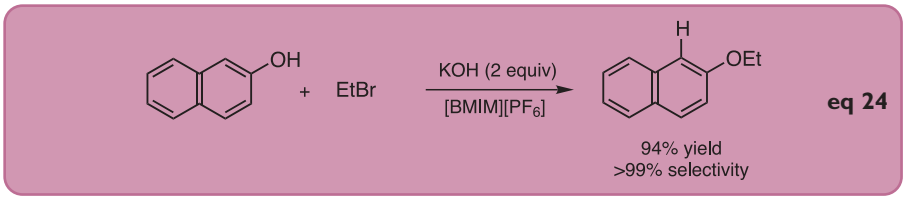
eq 21



eq 22



eq 23



eq 24

system can accelerate the Diels–Alder reaction due to the high concentration of electrolyte. By using ionic liquids instead of $LiClO_4$–Et_2O, reactivities can be improved and the need for potentially explosive perchlorate-based reaction media is eliminated.[72]

A recent study of the scandium triflate catalyzed Diels–Alder reaction investigated the use of ionic liquids as polar media for facilitating catalyst recovery and increasing reaction rate and selectivity.[73] For example, when 1,4-naphthoquinone was dissolved in [BMIM][PF_6] and reacted with 1,3-dimethylbutadiene in the presence of $Sc(OTf)_3$, the corresponding product was obtained in > 99% yield.

4.2. Friedel–Crafts Reaction

Friedel–Crafts acylations are of industrial importance and are associated with a massive consumption of aluminum(III) chloride. It has been demonstrated that acylation reactions can be carried out in acidic chloroaluminate(III) ionic liquids.[74,75] The regioselectivities and rates observed in these reactions are comparable to the best values known for the traditional acylations. The Friedel–Crafts acylation of benzene has been conducted in acidic chloroaluminate(III) ionic liquid.[75] The monoacylated products were obtained as a result of the deactivation of the aromatic ring by the acyl substituent. In addition to benzene and other simple aromatic rings, a range of organic and organometallic substrates (e.g., ferrocene) have been acylated in acidic chloroaluminate(III) ionic liquids.[76,77]

An in situ IR spectroscopic study was performed on the Friedel–Crafts acetylation of benzene in ionic liquids using $AlCl_3$ and $FeCl_3$.[78] The results revealed that the mechanism of the Friedel–Crafts acetylation of benzene in ionic liquids was exactly the same as that in 1,2-dichloroethane.

Another interesting development is the use of [BMIM][chloroaluminate] as Lewis acid catalyst for the Friedel–Crafts sulfonylation of benzene and substituted benzenes with TsCl (**eq 22**).[79] The substrates exhibited enhanced reactivity, and furnished the corresponding unsymmetrical diaryl sulfones in 83–91% yields under ambient conditions.

4.3. Esterification

Esterifications of alcohols and acetic acids in the room-temperature ionic liquid 1-butylpyridinium chloride–aluminum(III) chloride as a "green" catalyst have been reported by Deng et al.[80] Satisfactory conversions and selectivities were obtained, and most of the ester products were easily recovered due to their immiscibility with the ionic liquid.

Amino acid esters are very important intermediates in the chemical and pharmaceutical industry. They are usually difficult to prepare because amino acids exist as zwitterions (dipolar ions), in which the carboxyl group is not in the free form. Our group has recently developed a successful method for synthesizing amino acid esters using [EtPy][CF_3CO_2] (EtPy = *N*-ethylpyridinium) as a "green" catalyst.[81] Excellent conversions have generally been achieved for the ethyl and isopropyl esters of many amino acids (**eq 23**).

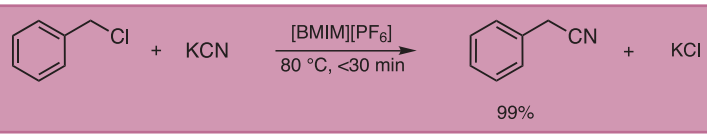
4.4. Regioselective Alkylation

Alkylation of indole or 2-naphthol is usually achieved by preformation of the ambident indolate[82] or 2-naphtholate[83] anion and subsequent treatment with alkyl halide. Regioselective alkylation at the heteroatom of these anions is solvent-dependent, and can be achieved by using a dipolar aprotic solvent such as DMF.[83,84] As an environmentally friendly alternative, [BMIM][PF_6] has been utilized for the regioselective alkylation at the heteroatom of indole and 2-naphthol (**eq 24**).[85] Advantages of this process include simple operation, easy product isolation, no measurable solvent vapor pressure, high regioselectivity, and the potential for recycling the solvent.

4.5. Displacement Reaction with Cyanide

Nucleophilic displacement reactions are often achieved using phase-transfer catalysis (PTC) to facilitate reaction between the organic reactants and the inorganic ionic

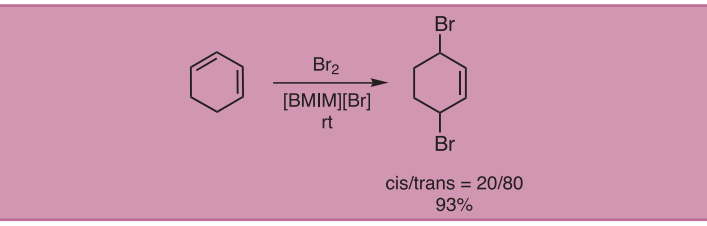
salts that provide the nucleophiles.[86] In conventional PTC, the typical organic solvents used, such as dichloroethane or *o*-dichlorobenzene, are environmentally undesirable. In addition, catalyst separation and recovery are very difficult. It has been demonstrated that the use of room-temperature ionic liquids as catalytic, environmentally benign solvents for the displacement of benzylic chloride with cyanide can replace phase-transfer-catalyzed biphasic systems (**eq 25**).[87] This eliminates the need for a volatile organic solvent and hazardous catalyst disposal.



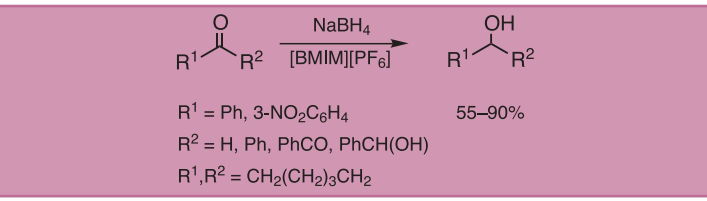
eq 25

4.6. Stereoselective Halogenation

The analysis of alkenes in a complex hydrocarbon mixture, such as gasoline, is a difficult process. The analysis of alkenes in the presence of alkanes, however, can be achieved after their transformation into the corresponding dihalo derivatives.[88] Several ionic liquids—[BMIM][PF_6], [BMIM][BF_4], [BMIM][Br], and [BMIM][Cl]—have been studied as alternatives to toxic chlorinated solvents for the stereoselective halogenation of alkenes and alkynes (**eq 26**).[89]



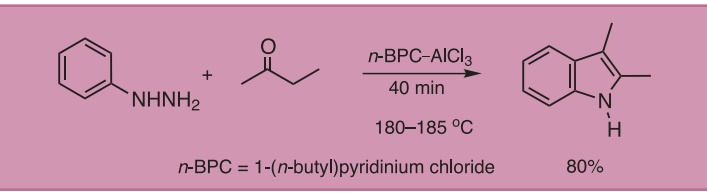
eq 26



eq 27

4.7. Reduction of Aldehydes and Ketones

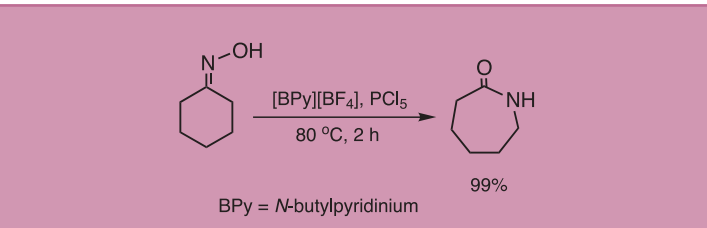
Howarth et al. have investigated the reduction of aldehydes and ketones with $NaBH_4$ in [BMIM][PF_6].[90] In this study, six common aldehydes and ketones were converted into the corresponding alcohols in moderate-to-high yields (**eq 27**). The ionic liquid was recycled, and, in some cases, the product alcohol was distilled directly from the ionic liquid.



eq 28

4.8. Fischer Indole Synthesis

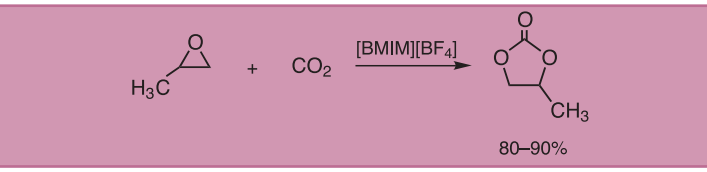
The Fischer indole synthesis using a chloroaluminate ionic liquid both as a solvent and catalyst was achieved with product yields in the 41–92% range (**eq 28**).[91] The amount of $AlCl_3$ used was much less than that of other reported catalysts such as $ZnCl_2$ or PPA, and the procedure followed proved safer with respect to the amount of catalyst employed, its hazard, and cost.



eq 29

4.9. Beckmann Rearrangement

The Beckmann rearrangement is typically carried out in strong Brønsted or Lewis acids, such as concentrated sulfuric acid, phosphorus pentachloride in ether, or hydrogen chloride in a mixture of acetic acid and acetic anhydride. These conditions give rise to significant amounts of by-products and serious corrosion problems.[92] In a recent study by Peng and Deng,[93] the catalytic Beckmann rearrangement of several ketoximes was achieved with satisfactory conversion and selectivity in 1,3-dialkyl-imidazolium or alkylpyridinium salts and phosphorated compounds (PCl_5, $POCl_3$, or P_2O_5) (**eq 29**).



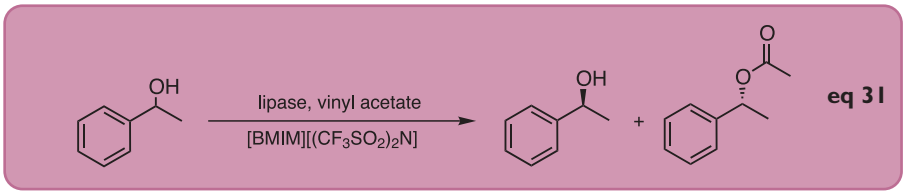
eq 30

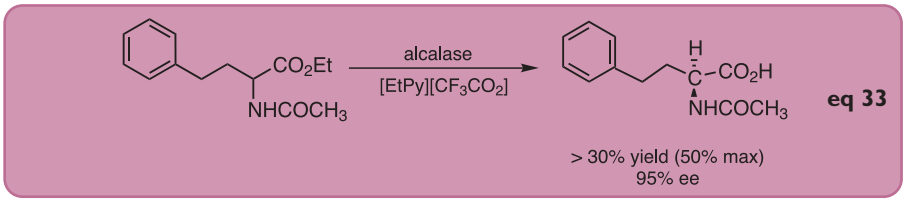
4.10. Cycloaddition

The cycloaddition of propylene oxide (PO) and carbon dioxide has been conducted in ionic liquids based on [BMIM] or [BPy] salts and in the absence of any organic solvent. Optimal results were obtained with [BMIM][BF_4] as catalyst (**eq 30**).[94] It was found that both the cations and anions of the room-temperature ionic liquids exerted a strong influence on catalytic activity, and a suitable CO_2/PO molar ratio was required for the reaction. The conversion of propylene oxide increased with increasing reaction temperature, and the ionic liquid catalyst was recycled.

5. Biocatalysis in Ionic Liquids

In recent years, a lot of attention has been focused on enzymatic reactions in ionic liquids. As early as 1984, it was observed that the enzyme alkaline phosphatase is relatively stable in a 4:1 (v/v) mixture of triethylammonium nitrate and water.[95] Erbeldinger et al. reported the first enzymatic synthesis of *Z*-aspartame in [BMIM][PF_6] containing 5% (v/v) water.[96] The enzyme





thermolysin exhibited excellent stability and a competitive rate in the same ionic liquid as compared to the enzymatic reaction in organic solvents.

Lipase has frequently been reported as a biocatalyst of organic reactions in ionic liquids. Nine lipases were investigated for the dynamic kinetic resolution of 1-phenylethanol by transesterification in various ionic liquids.[97] Improved enantioselectivities were observed as compared to when these same reactions were carried out in MTBE (**eq 31**). Kim et al. also obtained enhanced enantioselectivities in the transesterifications of alcohols using lipase in [BMIM][BF_4] and [BMIM][PF_6].[98] In the lipase-catalyzed enantioselective acylation of allylic alcohols in [BMIM][X] (X = PF_6^-, $CF_3CO_2^-$, TsO^-, SbF_6^-), Itoh et al. found that the anions of the imidazolium salts had a significant influence on the outcome of the reaction (**eq 32**).[99]

More systematic studies on lipase-catalyzed enantio- and regioselective acylations were conducted by Park and Kazlauskas in several imidazolium- and *N*-alkylpyridinium-based ionic liquids.[100] In these studies, the *Pseudomonas cepacia* lipase (PCL) catalyzed acylation of 1-phenylethanol with vinyl acetate proceeded with high enantioselectivity. Regioselective acetylation of β-D-glucose in ionic liquids yielded more 6-*O*-acetylglucose than 3,6-*O*-diacetylglucose (13–50:1), while the acetylation in organic solvents gave a selectivity of only 2–3:1. The epoxidation of cyclohexene by peroxyoctanoic acid, generated in situ by the immobilized enzyme Novozyme® 435 catalyzed reaction of octanoic acid with 60% aqueous H_2O_2, was achieved successfully.[101] Another study showed that the enantioselectivity of a lipase-catalyzed kinetic resolution could be increased at higher temperatures.[102] This study indicated that, for a galactosidase-catalyzed synthesis of a disaccharide, the secondary hydrolysis was suppressed thus doubling the yield. It was also observed that three different lipases exhibited both excellent activity and stability in the synthesis of an ester in [BMIM][PF_6].[103]

Recently, we showed that high enantioselectivities and yields could be achieved in the kinetic resolution of amino acid esters such as that of homophenylalanine in [EtPy][CF_3CO_2] by using the enzyme *Bacillus licheniforms* alcalase (**eq 33**).[104] This same alcalase also exhibited high selectivity and activity in low concentrations of ionic liquid in water.

6. Summary

The use of ionic liquids as solvents or catalysts has a profound effect on the observed activities and selectivities. As a result, there is growing interest in developing applications for them in a wide range of synthetic reactions. The present review was not designed to be comprehensive, but rather to summarize some of the recent advances in the application of ionic liquids in organic synthesis. We hope that readers will find it helpful in their day-to-day work.

7. References and Notes

(†) This review is dedicated to Professor Herbert C. Brown on his 90th birthday.

(1) Seddon, K. R. *J. Chem. Technol. Biotechnol.* **1997**, *68*, 351.

(2) Hurley, F. H.; Wier, T. P. *J. Electrochem. Soc.* **1951**, *98*, 203.

(3) (a) Wilkes, J. S.; Levisky, J. A.; Wilson, R. A.; Hussey, C. L. *Inorg. Chem.* **1982**, *21*, 1263. (b) Wilkes, J. S.; Zaworotko, M. J. *J. Chem. Soc., Chem. Commun.* **1992**, 965.

(4) Freemantle, M. *Chem. Eng. News* **1998**, *76(13)*, 32.

(5) Wasserscheid, W.; Keim, W. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3772.

(6) Welton, T. *Chem. Rev.* **1999**, *99*, 2071.

(7) Cull, S. G.; Holbrey, J. D.; Vargas-Mora, V.; Seddon, K. R.; Lye, G. J. *Biotechnol. Bioeng.* **2000**, *69*, 227.

(8) Fuller, J.; Breda, A. C.; Carlin, R. T. *J. Electroanal. Chem.* **1998**, *459*, 29.

(9) Kosmulski, M.; Osteryoung, R. A.; Ciszewska, M. *J. Electrochem. Soc.* **2000**, *147*, 1454.

(10) Bates, E. D.; Mayton, R. D.; Ntai, I.; Davis, J. H., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 926.

(11) Sheng, D.; Ju, Y. H.; Barnes, C. E. *J. Chem. Soc., Dalton. Trans.* **1999**, 1201.

(12) Fadeev, A. G.; Meagher, M. M. *Chem. Commun.* **2001**, 295.

(13) Brennecke, J. F.; Maginn, E. J. *AIChE J.* **2001**, *47*, 2384.

(14) Fuller, J.; Carlin, R. T.; De Long, H. C.; Haworth, D. *J. Chem. Soc., Chem. Commun.* **1994**, 299.

(15) Chauvin, Y.; Olivier-Bourbigou, H. *CHEMTECH* **1995**, *25*(9), 26.

(16) Keim, W.; Korth, W.; Wasserscheid, P. Intl. Patent 0016,902, Mar 30, 2000; *Chem. Abstr*. **2000**, *132*, P 238691v.

(17) Bonhôte, P.; Dias, A.-P.; Papageorgiou, N.; Kalyanasundaram, K.; Grätzel, M. *Inorg. Chem.* **1996**, *35*, 1168.

(18) Ford, W. T.; Hauri, R. J.; Hart, D. J. *J. Org. Chem.* **1973**, *38*, 3916.

(19) Karodia, N.; Guise, S.; Newlands, C.; Andersen, J.-A. *Chem. Commun*. **1998**, 2341.

(20) Hasan, M.; Kozhevnikov, I. V.; Siddiqui, M. R. H.; Steiner, A.; Winterton, N. *Inorg. Chem.* **1999**, *38*, 5637.

(21) Fannin, A. A.; Floreani, D. A.; King, L. A.; Landers, J. S.; Piersma, B. J.; Stech, D. J.; Vaughn, R. L.; Wilkes, J. S.; Williams, J. L. *J. Phys. Chem.* **1984**, *88*, 2614.

(22) Larsen, A. S.; Holbrey, J. D.; Tham, F. S.; Reed, C. A. *J. Am. Chem. Soc.* **2000**, *122*, 7264.

(23) Chauvin, Y.; Mussman, L.; Olivier, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2698.

(24) Chauvin, Y.; Mussman, L.; Olivier, H. *Angew. Chem*. **1995**, *107*, 2941.

(25) Suarez, P. A. Z.; Dullius, J. E. L.; Einloft, S.; de Souza, R. F.; Dupont, J. *Inorg. Chim. Acta* **1997**, *255*, 207.

(26) Dyson, P. J.; Ellis, D. J.; Parker, D. G.; Welton, T. *Chem. Commun*. **1999**, 25.

(27) Muller, L. A.; Dupont, J.; de Souza, R. F. *Makromol. Chem., Rapid Commun*. **1998**, *19*, 409.

(28) Steines, S.; Drieben-Holscher, J.; Wasserscheid, P. *J. Prakt. Chem*. **2000**, *342*, 348.

(29) Monteiro, A. L.; Zinn, F. K.; de Souza, R. F.; Dupont, J. *Tetrahedron: Asymmetry* **1997**, *8*, 177.

(30) Liu, F.; Abrams, M. B.; Baker, R. T.; Tumas, W. *Chem. Commun*. **2001**, 433.

(31) Brown, R. A.; Pollet, P.; McKoon, E.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. *J. Am. Chem. Soc*. **2001**, *123*, 1254.
(32) Berger, A.; de Souza, R. F.; Delgado, M. R.; Dupont, J. *Tetrahedron: Asymmetry*. **2001**, *12*, 1825.
(33) Song, C. E.; Roh, E. J. *Chem. Commun*. **2000**, 837.
(34) Owens, G. S.; Abu-Omar, M. M. *Chem. Commun*. **2000**, 1165.
(35) Gaillon, L.; Bedioui, F. *Chem. Commun*. **2001**, 1458.
(36) Parshall, G. W. *J. Am. Chem. Soc*. **1972**, *94*, 8716.
(37) Waffenschmidt, H.; Wasserscheid, P. *J. Mol. Catal. A: Chem*. **2000**, *164*, 61.
(38) Knifton, J. F. *J. Mol. Catal*. **1987**, *43*, 65.
(39) Karodia, N.; Guise, S.; Newlands, C.; Andersen, J.-A. *Chem. Commun*. **1998**, 2341.
(40) Brasse, C. C.; Englert, U.; Salzer, A.; Waffenschmidt, H.; Wasserscheid, P. *Organometallics* **2000**, *19*, 3818.
(41) Wasserscheid, P.; Waffenschmidt, H.; Machnitzki, P.; Kottsieper, K. W.; Stielzer, O. *Chem. Commun*. **2001**, 4510.
(42) Keim, W.; Vogt, D.; Waffenschmidt, H.; Wasserscheid, P. *J. Catal*. **1999**, *186*, 481.
(43) Sellin, M. F.; Webb, P. B.; Cole-Hamilton, D. J. *Chem. Commun*. **2001**, 781.
(44) Chauvin, Y.; Gilbert, B.; Guibard, I. *J. Chem. Soc., Chem. Commun*. **1990**, 1715.
(45) Chauvin, Y.; Olivier, H.; Wyrvalski, C. N.; Simon, L. C.; de Souza, R. F. *J. Catal*. **1997**, *165*, 275.
(46) Einloft, S.; Dietrich, F. K.; de Souza, R. F.; Dupont, J. *Polyhedron* **1996**, *15*, 3257.
(47) Dullius, J. E. L.; Suarez, P. A. Z.; Einloft, S.; de Souza, R. F.; Dupont, J.; Fischer, J.; De Cian, A. *Organometallics* **1998**, *17*, 815.
(48) Silva, S. M.; Suarez, P. A. Z.; de Souza, R. F.; Dupont, J. *Polym. Bull*. **1998**, *40*, 401.
(49) Ellis, B.; Keim, W.; Wasserscheid, P. *Chem. Commun*. **1999**, 337.
(50) Wasserscheid, P.; Gordon, C. M.; Hilgers, C.; Muldoon, M. J.; Dunkin, I. R. *Chem. Commun*. **2001**, 1186.
(51) Kaufmann, D. E.; Nouroozian, M.; Henze, H. *Synlett* **1996**, 1091.
(52) Bohm, V. P. W.; Hermann, W. A. *Chem. Eur. J*. **2000**, *6*, 1017.
(53) Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett*. **1999**, *1*, 997.
(54) Xu, L.; Chen, W.; Xiao, J. *Organometallics* **2000**, *19*, 1123.
(55) Xu, L.; Chen, W.; Ross, J.; Xiao, J. *Org. Lett*. **2001**, *3*, 295.
(56) Handy, S. T.; Zhang, X. *Org. Lett*. **2001**, *3*, 233.
(57) Sirieix, L.; Ossberger, M.; Betzemeier, B.; Knochel, P. *Synlett* **2000**, 1613.
(58) Howarth, J.; James, P.; Dai, J. *Tetrahedron Lett*. **2000**, *41*, 10319.
(59) Calo, V.; Nacci, A.; Monopoli, A.; Lopez, L.; di Cosmo, A. *Tetrahedron* **2001**, *57*, 6071.
(60) Kiss, L.; Papp, G.; Joo, F.; Antus, S. *Heterocycl. Commun*. **2001**, *7*, 417.
(61) Zim, D.; de Souza, R. F.; Dupont, J.; Monteiro, A. L. *Tetrahedron Lett*. **1998**, *39*, 7071.
(62) Mizushima, E.; Hayashi, T.; Tanake, M. *Green Chem*. **2001**, *3*, 76; *Chem. Abstr.* **2001**, *136*, 118248.
(63) Chen, W.; Xu, L.; Chatterton, C.; Xiao, J. *Chem. Commun*. **1999**, 1247.
(64) de Bellefon, C.; Pollet, E.; Grenouillet, P. *J. Mol. Catal*. **1999**, *145*, 121.
(65) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
(66) Buijsman, R. C.; van Vuuren, E.; Sterrenburg, J. G. *Org. Lett.* **2001**, *3*, 3785.
(67) Mathews, C. J.; Smith, P. J.; Welton, T. *Chem. Commun*. **2000**, 1249.
(68) Jaeger, D. A.; Tucker, C. E. *Tetrahedron Lett.* **1989**, *30*, 1785.
(69) Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793.
(70) Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem*. **1999**, *1*, 23; *Chem. Abstr.* **1999**, *131*, 87674.
(71) Lee, C. W. *Tetrahedron Lett*. **1999**, *40*, 2461.
(72) Holbrey, J. D.; Seddon, K. R. *Clean Prod. Proc*. **1999**, *1*, 223.
(73) Song, C. E.; Shim, W. H.; Roh, E. J.; Lee, S.-g.; Choi, J. H. *Chem. Commun*. **2001**, 1122.
(74) Adams, C. J.; Earle, M. J.; Roberts, G.; Seddon, K. R. *Chem. Commun*. **1998**, 2097.
(75) Boon, J. A.; Levisky, J. A.; Pflug, J. L.; Wilkes, J. S. *J. Org. Chem.* **1986**, *51*, 480.
(76) Surette, J. K. D.; Green, L.; Singer, R. D. *J. Chem. Soc., Chem. Commun*. **1996**, 2753.
(77) Dyson, D. J.; Grossle, M. C.; Srinivasan, N.; Vine, T.; Welton, T.; Williams, D. J.; White, A. J. P.; Zigras, T. *J. Chem. Soc., Dalton Trans*. **1997**, 3465.
(78) Csihony, S.; Mehdi, H.; Horvath, I. T. *Green Chem*. **2001**, *3*, 307.
(79) Nara, S. J.; Harjani, J. R.; Salunkhe, M. M. *J. Org. Chem*. **2001**, *66*, 8616.
(80) Deng, Y.; Shi, F.; Beng, J.; Qiao, K. *J. Mol. Catal. A: Chem*. **2001**, *165*, 33.
(81) Zhao, H.; Malhotra, S. V. Esterification of Amino Acids by Using Ionic Liquid as a Green Catalyst. In *Catalysis of Organic Reactions*; Morrell, D., Ed.; Marcel Dekker: New York, 2002; Volume 83; pp 667-672.
(82) Nunomoto, S.; Kawakami, Y.; Yamashita, Y.; Takeuchi, H.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 111.
(83) Kornblum, N.; Seltzer, R.; Haberfield, P. *J. Am. Chem. Soc*. **1963**, *85*, 1148.
(84) Cardillo, B.; Casnati, G.; Pochini, A.; Ricca, A. *Tetrahedron* **1967**, *23*, 3771.
(85) Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Chem. Commun*. **1998**, 2245.
(86) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis*; Chapman and Hall: New York, 1994.
(87) Wheeler, C.; West, K. N.; Liotta, C. L.; Eckert, C. A. *Chem. Commun*. **2001**, 887.
(88) Delaet, M.; Tilquin, B. *Talanta* **1992**, *39*, 769.
(89) Chiappe, C.; Capraro, D.; Conte, V.; Pieraccini, D. *Org. Lett*. **2001**, *3*, 1061.
(90) Howarth, J.; James, P.; Ryan, R. *Synth. Commun*. **2001**, *31*, 2935.
(91) Rebeiro, G. L.; Khadilkar, B. M. *Synthesis* **2001**, 370.
(92) Izumi, Y.; Sato, S.; Urabe, K. *Chem. Lett.* **1983**, 1649.
(93) Peng, J.; Deng, Y. *Tetrahedron Lett*. **2001**, *42*, 403.
(94) Peng, J.; Deng, Y. *Cuihua Xuebao* **2001**, *22*, 598; *Chem. Abstr.* **2002**, *136*, 218602.
(95) Magnusson, D. K.; Bodley, J. W.; Adams, D. F. *J. Solution Chem*. **1984**, *13*, 583.
(96) Erbeldinger, M.; Mesiano, A. J.; Russell, A. J. *Biotechnol. Prog*. **2000**, *16*, 1129.
(97) Schoefer, S. H.; Kaftzik, N.; Wasserscheid, P.; Kragl, U. *Chem. Commun*. **2001**, 425.
(98) Kim, K.-W.; Song, B.; Choi, M.-Y.; Kim, M.-J. *Org. Lett*. **2001**, *3*, 1507.
(99) Itoh, T.; Akasaki, E.; Kudo, K.; Shirakami, S. *Chem. Lett*. **2001**, 262.
(100) Park, S.; Kazlauskas, R. J. *J. Org. Chem*. **2001**, *66*, 8395.
(101) Langer, R.; Klausener, A.; Rodefeld, L. Intl. Patent Appl. W0 01 02,596, Jan 11, 2001; *Chem. Abstr.* **2001**, *134*, 85168u.
(102) Kragl, U.; Kaftzik, N.; Schoefer, S. H.; Eckstein, M.; Wasserscheid, P.; Hilgers, C. *Chim. Oggi*. **2001**, *19*(7/8), 22.
(103) Husum, T. L.; Jorgensen, C. T.; Christensen, M. W.; Kirk, O. *Biocatal. Biotransform.* **2001**, *19*, 331.
(104) Zhao, H.; Malhotra, S. V. *Biotechnol. Lett*. **2002**, *24*, 1257.

About the Authors

Sanjay Malhotra was born in New Delhi, India. He received a Bachelor of Science degree from Gujrat University, India. After three years of industrial experience as an R&D scientist working on agrochemicals, he moved to the U.S. for further studies. He obtained a Ph.D. in 1995 from Seton Hall University under the direction of Professor Robert L. Augustine. Subsequently, he moved to Purdue University to work with Professor Herbert C. Brown, and spent the next four years as his research associate. In 1999, he joined the faculty of the New Jersey Institute of Technology. His research interests include the development of new methodologies and catalysts for asymmetric organic transformations. He is also active in research on ionic liquids, especially the study of enzymatic reactions in ionic liquids. He has authored several publications in the area of asymmetric catalysis, heterogeneous catalysts, and enzymatic reactions in ionic liquids. He is currently working on a book on new methodologies in asymmetric catalysis.

Hua Zhao received both his B.S. degree in chemistry and M.S. degree in chemical engineering from Tianjin University (China). In 2002, he obtained his Ph.D. degree in chemical engineering from the New Jersey Institute of Technology under the direction of Professor Sanjay Malhotra. His research interests are focused on the study of ionic liquids in enzymatic reactions.