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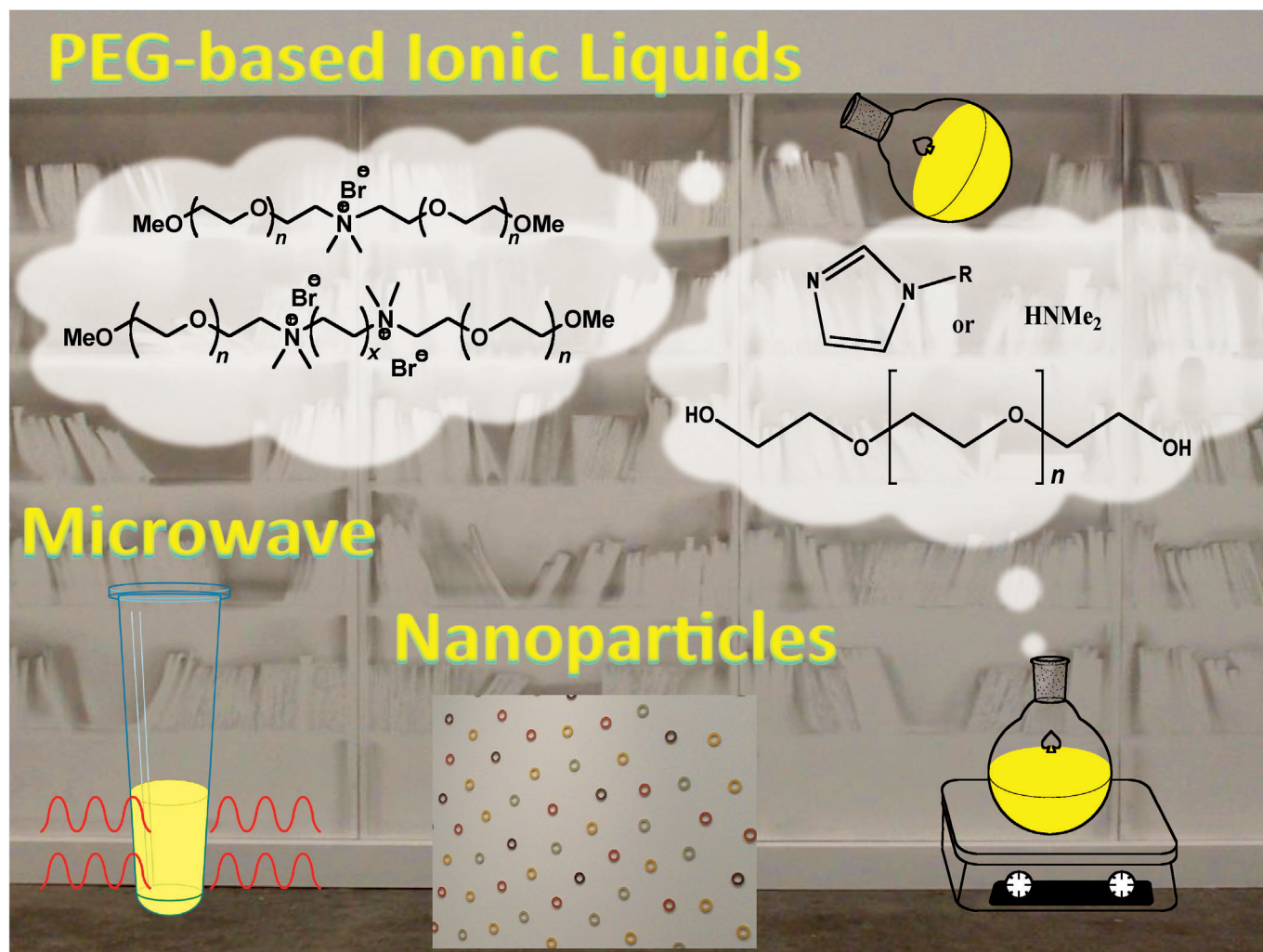
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# Poly(ethylene glycol)-Based Ionic Liquids: Properties and Uses as Alternative Solvents in Organic Synthesis and Catalysis

Martina Maya Cecchini,<sup>[a, b]</sup> Clarence Charnay,<sup>\*,[c]</sup> Francesco De Angelis,<sup>[b]</sup> Frédéric Lamaty,<sup>[a]</sup> Jean Martinez,<sup>[a]</sup> and Evelina Colacino<sup>\*,[a]</sup>



PEG-based ionic liquids are a new appealing group of solvents making the link between two distinct but very similar fluids: ionic liquids and poly(ethylene glycol)s. They find applications across a range of innumerable disciplines in science, technology, and engineering. In the last years, the possibility to use these as alternative solvents for organic synthesis and catalysis has been increasingly explored. This Review highlights strategies for their synthesis, their physical properties (critical point,

glass transition temperature, density, rheological properties), and their application in reactions catalyzed by metals (such as Pd, Cu, W, or Rh) or as organic solvent (for example for multi-component reactions, organocatalysis, CO<sub>2</sub> transformation) with special emphasis on their toxicity, environmental impact, and biodegradability. These aspects, very often neglected, need to be considered in addition to the green criteria usually considered to establish ecofriendly processes.

## 1. Introduction

Ionic liquids (ILs)<sup>[1,2]</sup> and poly(ethylene glycol)s (PEGs)<sup>[3–6]</sup> have experienced a tremendous explosion in applications in recent decades and are distinguished from classical organic solvents by considering their intrinsic chemical and physical properties. They have good stability (thermal, chemical, redox, radiochemical), low or null vapor pressure, high thermal and ionic conductivity suitable for microwave (MW)-assisted heating,<sup>[7,8]</sup> the possibility of recycling, and the ability to act as efficient solvents (also for gaseous reagents) or supports for reagent and catalyst immobilization.

Among the abundance of differently functionalized ILs, those incorporating PEG moieties (IL<sub>PEG</sub>) into the cationic (or anionic) units, making the link between the two distinct but very similar fluids, yield a new appealing group of solvents that find applications across a range of disciplines, including science, technology, and engineering.<sup>[9]</sup> They find widespread applications in dissolving carbohydrates and polymers (cellulose, lignin),<sup>[10]</sup> in protein and enzyme stabilization and activation [e.g., IL<sub>PEG</sub> **4** (ECOENG 500); Figure 1],<sup>[11]</sup> in partitioning inorganic salts (HgCl<sub>2</sub>) from aqueous solutions (e.g., IL<sub>PEG</sub> **11**; Figure 2),<sup>[12]</sup> or in acting as reductants and stabilizers for the synthesis of nanoparticles (NPs).<sup>[13,14]</sup> The possibility of tuning their properties through cation and/or anion modification allows the design of new functional solvents and materials while retaining the characteristics exhibited by the parent counterion. For example, among the dicationic IL<sub>PEG</sub> **11** (Figure 2), those functionalized with polyfluoroalkyl substituents are used as high-temperature lubricants,<sup>[15,16]</sup> whereas those with alkyl or hydroxyalkyl substituents on the imidazolium (Im) ring are used as stationary phases in analytical chromatography systems.<sup>[17]</sup> IL<sub>PEG</sub> **14**<sup>[18,19]</sup> (Figure 2), with a cationic

azabicyclo moiety, have found applications in gas absorption (e.g., CO<sub>2</sub>).

Despite the plethora of possible applications for the IL<sub>PEG</sub> systems, the scope of this Review is to highlight the use of IL<sub>PEG</sub>s as solvents for organic synthesis and catalysis. Depending on the intrinsic characteristics issued by a specific synthetic design of the solvent to answer particular needs, their physico-chemical properties, toxicity, environmental impact, and biodegradability are underlined if possible.<sup>[20]</sup> Attention is focused on the IL<sub>PEG</sub> solvents composed of one or two PEG or monomethyl ether (mPEG) chains (bridged or not) on the cationic part of the molecule (Figures 1 and 2). The overview is restricted to derivatives with at least four oxyethylene units because derivatives with shorter chain lengths cannot be classified as proper PEGs. Different to PEGs or ILs, PEG-based ILs have been scarcely investigated and often neglected in recent literature. For this reason, we estimate that this Review, highlighting their preparation, applications in organic synthesis and catalysis, and describing their physical properties, will be a valuable tool to understand their full potential. If possible, we have also highlighted their toxicity, biodegradability, and environmental persistence. These important aspects, usually poorly investigated and discussed in the current literature, are particularly important, especially in a green chemistry context. For the first time, data have been collected and discussed critically around poorly investigated and rarely discussed concerns.

## 2. Preparation of PEG-Based ILs

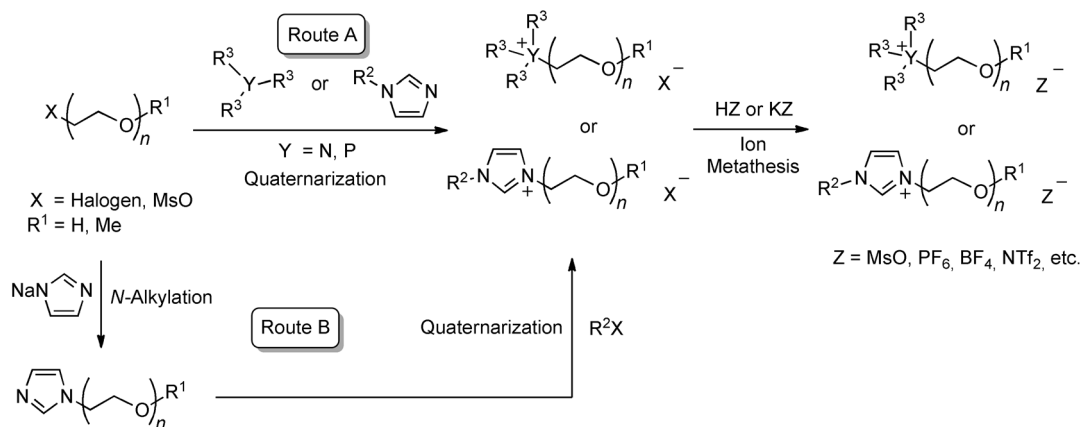
The more straightforward method to access the IL<sub>PEG</sub>s described herein consists of an alkylation reaction of a tertiary amine, phosphine, or N-substituted imidazole with a functionalized PEG (or mPEG) with a suitable leaving group (halogen or mesyl substituent) (Scheme 1, Route A). Reactions usually require a long time (24 h to two weeks), and are performed at room temperature or under reflux conditions in a suitable organic solvent (toluene, THF, ethanol, acetonitrile) or in neat conditions. The functionalization of PEGs with halogens or sulfonate esters is classically achieved by using thionyl chloride,<sup>[21,22]</sup> phosphorous tribromide,<sup>[23–25]</sup> or methanesulfonyl chloride.<sup>[26,27]</sup>

Alternatively, the synthesis of IL<sub>PEG</sub>s can be achieved according to an alkylation/quaternarization two-step procedure. In the first step, a functionalized PEG (or mPEG) reacts with a nucleophilic imidazole anion, leading to a PEG-substituted imidazole. Then, quaternarization is performed in the presence

[a] M. M. Cecchini, Dr. F. Lamaty, Prof. J. Martinez, Dr. E. Colacino  
Institut des Biomolécules Max Mousseron (IBMM)  
UMR 5247 CNRS—UM I-UM II, Université Montpellier II  
Place E. Bataillon, 34095 Montpellier Cedex 5 (France)  
E-mail: evelina.colacino@univ-montp2.fr

[b] M. M. Cecchini, Prof. F. De Angelis  
Dipartimento di Scienze Fisiche e  
Chimiche Università dell'Aquila e Consorzio INCA  
Via Vetoio, Coppito, 67100 L'Aquila (Italy)

[c] Dr. C. Charnay  
Institut Charles Gerhardt Montpellier (ICGM), Equipe CMOS  
CNRS UMR 5253, Université Montpellier II  
Place E. Bataillon, 34095 Montpellier Cedex 5 (France)  
E-mail: clarence.charnay@univ-montp2.fr



Scheme 1. General methods for the preparation of IL<sub>PEG</sub>s.

of a suitable alkyl halide, eventually followed by ion metathesis (Scheme 1, Route B). Formally, the two approaches result in the same product and the choice of the suitable synthetic method is a case-to-case study directly related to the experimental out-

comes. Almost quantitative conversions, easy workup, and purification of the final IL<sub>PEG</sub> are the main goals to pursue, bearing in mind that it is generally impossible to use conventional purification techniques to separate byproducts with similar properties (e.g., Br-PEG-Br from MeO-PEG-Br).

The recovery of IL<sub>PEG</sub> from the crude reaction mixture can be achieved by simple evaporation, by liquid-liquid extraction, precipitation from diethyl ether (or isopropanol), or (scarcely) by column chromatography; this leads to variable quantities of IL<sub>PEG</sub>s on a scale ranging from less than 1 g to 10–20 g. Hexabutyl diammonium [Bu<sub>3</sub>NPEG<sub>6000</sub>NBu<sub>3</sub>][Br] (**1a**),<sup>[28]</sup> diphosphonium [Bu<sub>3</sub>PPEG<sub>6000</sub>PBu<sub>3</sub>][Br] (**1b**),<sup>[23]</sup> and diguanidinium-PEG (**2**)<sup>[29]</sup> salts were obtained by Route A through amination of PEG-6000 dibromide<sup>[23]</sup> (Scheme 2). Amination of mesylated PEG methyl ether<sup>[30]</sup> afforded waxy salts [mPEG<sub>n</sub>NEt<sub>3</sub>][OMs] (**3**)<sup>[31]</sup> ( $n=7, 12, 17$ ), after two weeks, although sulfonates are excellent leaving groups under S<sub>N</sub>2 conditions. No indication of the yield was reported.

A mixture of IL<sub>PEG</sub>s **3** with *n*-heptane or toluene affords a temperature-dependent phase separation system, allowing a so-called monophasic reaction/two-phase separation, suitable for straightforward workup procedures. Similarly, mono-[mPEG<sub>350</sub>NMe<sub>2</sub>][Br] (**5**) and dicationic [(mPEG<sub>350</sub>NMe<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>][Br] (**6**) ammonium-based IL<sub>PEG</sub>s were synthesized from brominated PEG methyl ether and gaseous *N,N*-dimethylamine or *N,N,N',N'*-tetramethylethylenediamine (TMEDA), respectively, in an alcoholic solvent<sup>[32]</sup> (Scheme 2).

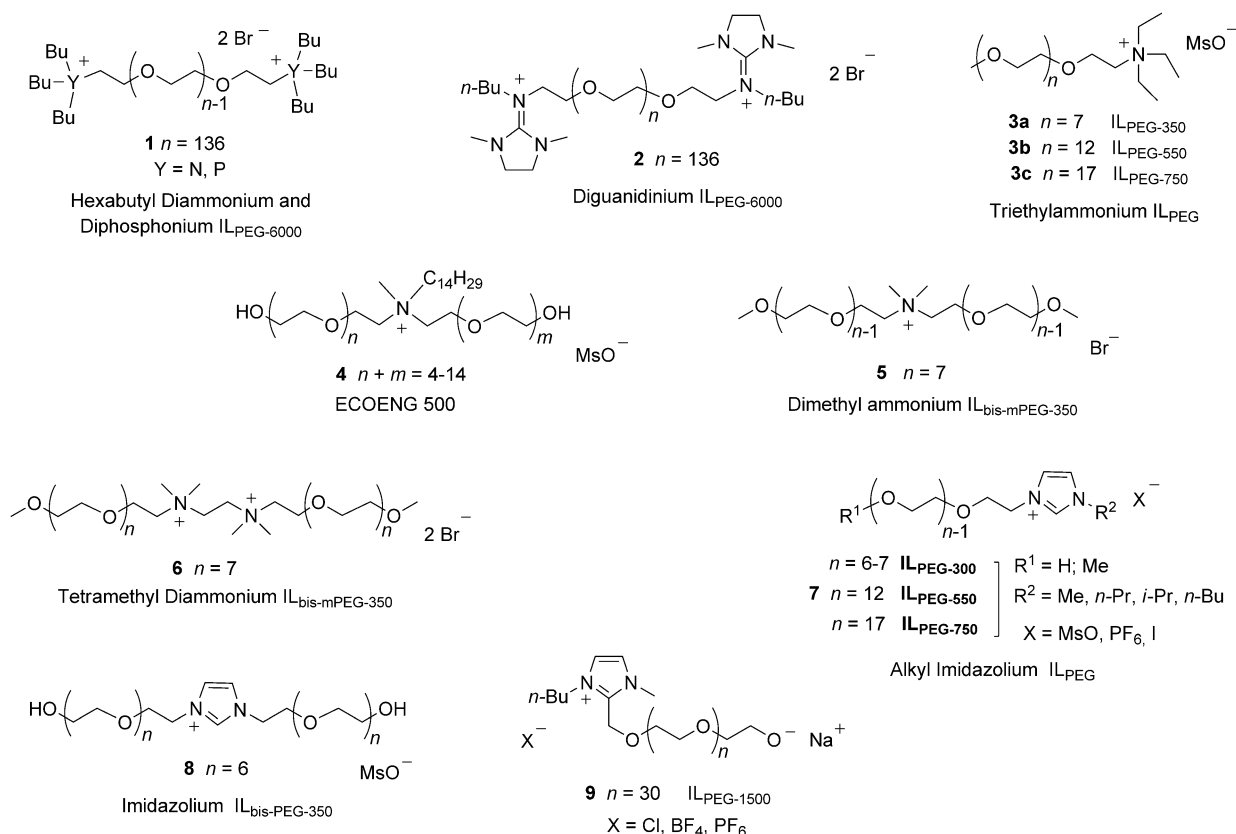
Nucleophilic substitution with alkyl imidazoles on PEG methane sulfonate derivatives in solution or in neat conditions afforded the corresponding water-soluble butylimidazolium [mPEG<sub>350</sub>Bulm][PF<sub>6</sub>] (**7a**)<sup>[27]</sup> after ion metathesis, alkyl-IL<sub>PEG</sub>s [mPEG<sub>550</sub>R<sup>2</sup>Im][PF<sub>6</sub>] (**7b**)<sup>[33]</sup> (R<sup>2</sup>=Me, *n*Pr, *i*Pr) after chromatographic purification, and oligoether [PEG<sub>300</sub>Melm][OMs] (**7c**)<sup>[34]</sup> after precipitation/filtration workup from diethyl ether. Similarly, [(PEG<sub>300</sub>)<sub>2</sub>Im][OMs] (**8**),<sup>[34]</sup> containing two oligoether moieties, was obtained through two consecutive substitution reactions: in the first step, imidazole was alkylated with monobrominated PEG-300,<sup>[34]</sup> then a second substitution reaction with monomesylated PEG-300 afforded the final product after precipitation from diethyl ether (Scheme 3). IL<sub>PEG-1500</sub> (**9**),<sup>[35]</sup> with a polyether

Evelina Colacino obtained her Ph.D. in 2002 at the Universities of Montpellier II (France) and of Calabria (Italy). She was a Research Fellow at the Catholic University of Louvain (Belgium) in 2003, Research Scientist at Sigma-Tau Pharmaceuticals (Italy) in 2004, and Post-Doctoral Fellow and Research Assistant at the University of Montpellier II until 2007, at which she has been appointed Assistant Professor of Organic Chemistry since. Her main research interests focus on the development of ecofriendly protocols for the synthesis of biomolecules and small heterocyclic compounds by metal-catalyzed processes using mechanistic investigations of metal-catalyzed processes using alternative energy inputs.

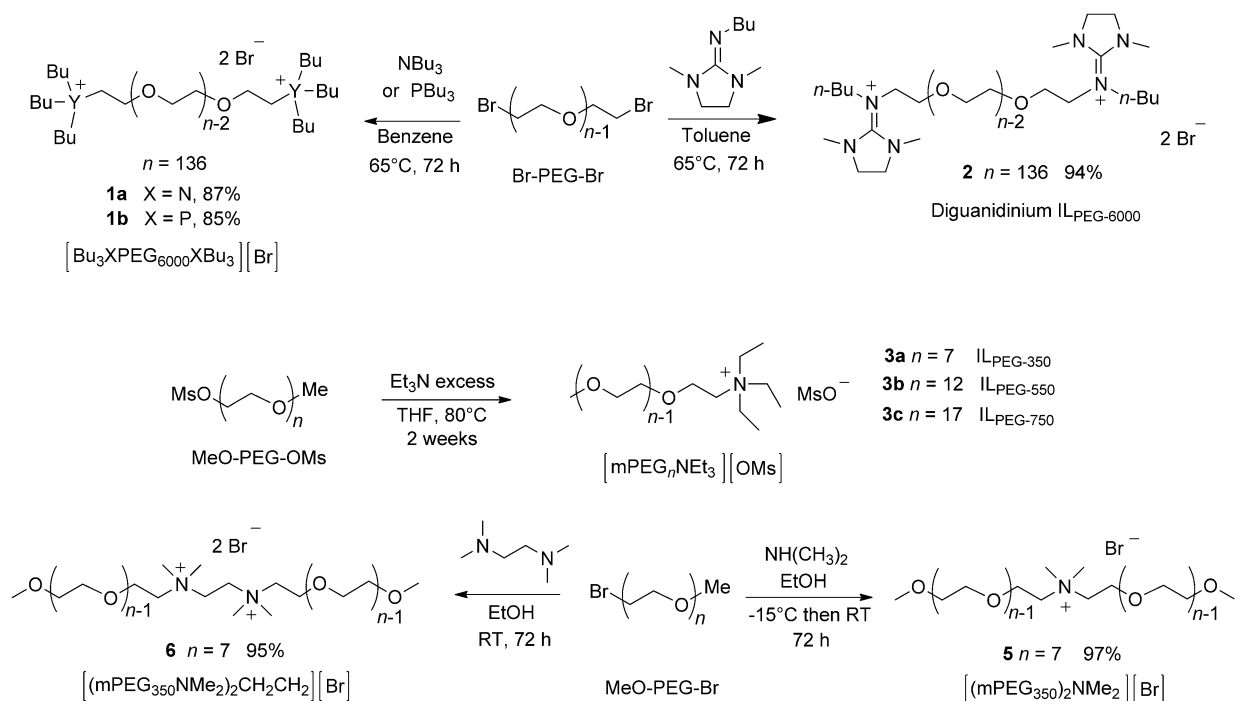


Clarence Charnay obtained his Ph.D. from the University of Montpellier II (France) in 1999. After working as a researcher at the Paul Pascal Research Center (Bordeaux, France) with Dr. V. Schmitt and at Montpellier II with Professor J. M. Devoisselle on drug encapsulation into porous nanoparticles, he joined the Halas Nanophotonics group (Rice University, USA) and studied the design of new plasmonic nanostructures with Professor Naomi Halas. His has been Maitre de Conférences (Assistant Professor) at the University Montpellier II since 2002 and has research interests in nanoparticle science, colloids, and surfactants (PEGylated amphiphiles).





**Figure 1.** PEG-based ILs as mono- and bridged dicationic ammonium, phosphonium, guanidinium, or monocationic imidazolium salts. Ms = mesyl.

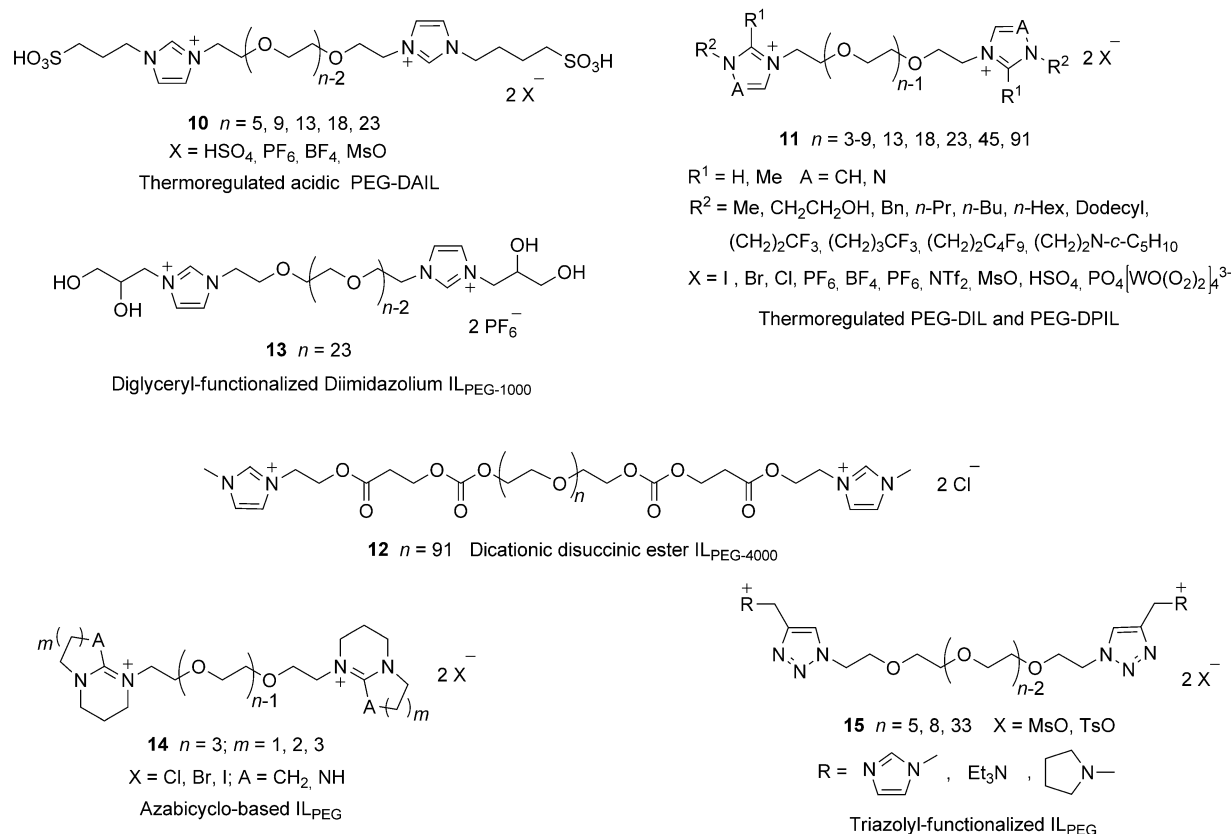


**Scheme 2.** Synthesis of ammonium, phosphonium, and guanidinium IL<sub>PEG</sub>s.

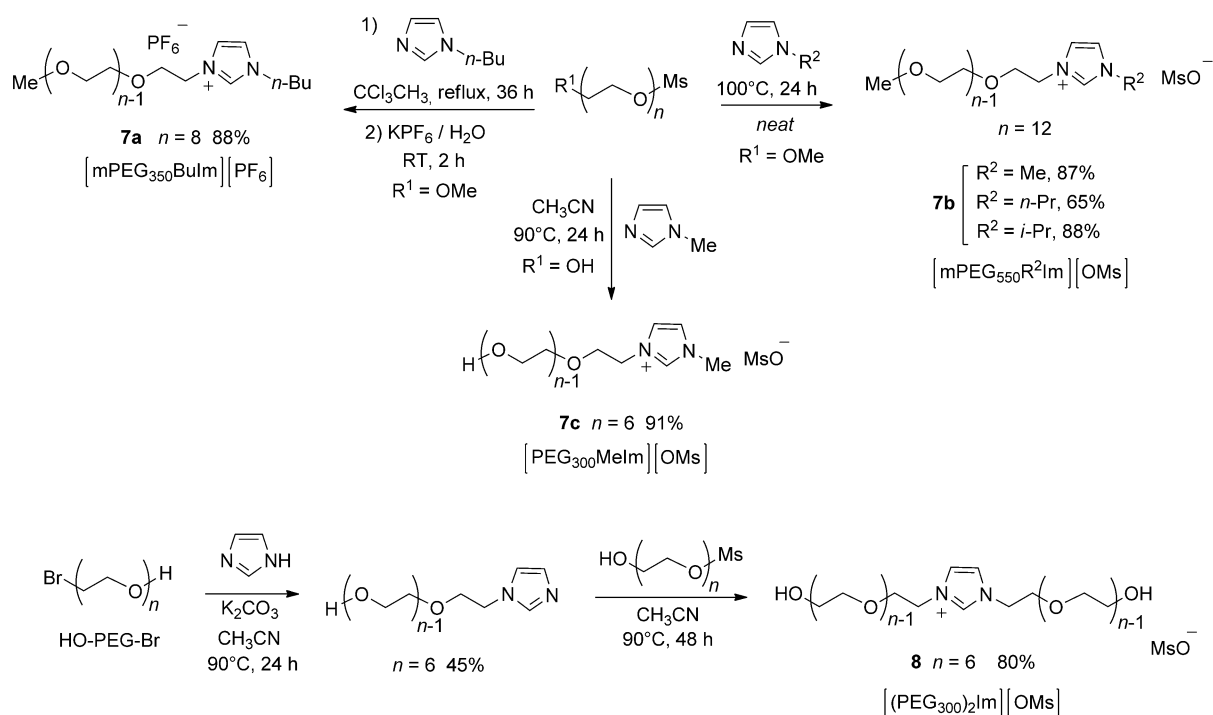
chain at the carbene position, was obtained by anionic polymerization of ethylene oxide in the presence of paraformal-

dehyde, initiated by Im IL in basic medium. No side reaction was detected, and the product was exclusively a low-molecular-





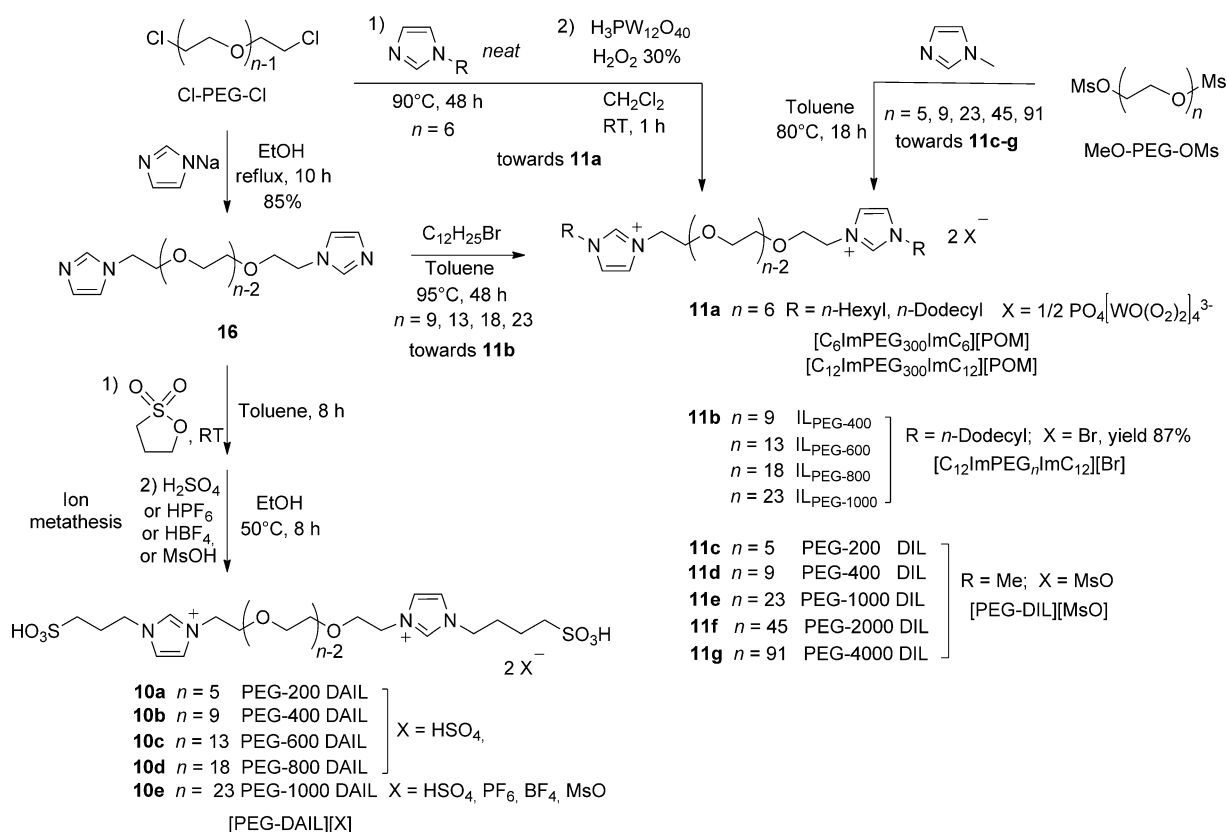
**Figure 2.** Bridged PEG-based dicationic ILs. Bn = benzyl,  $n\text{Hex} = n\text{-hexyl}$ ,  $\text{NTf}_2 = \text{bis(trifluoromethylsulfonyl) imide}$ .



**Scheme 3.** Synthesis of mono- and di-polyether imidazolium IL<sub>PEGs</sub>.

weight PEG with a degree of polymerization ( $\text{DP}_n$ ) of up to 30. Thermoregulated acidic IL<sub>PEGs</sub> **10**, referred to as [PEG-DAIL]

[X],<sup>[36–41]</sup> with different lengths of polyether chains were also described (Scheme 4). They have been tailored using two



**Scheme 4.** Synthesis of bridged PEG diimidazolium IL-PEGs. POM = peroxopolyoxometalate.

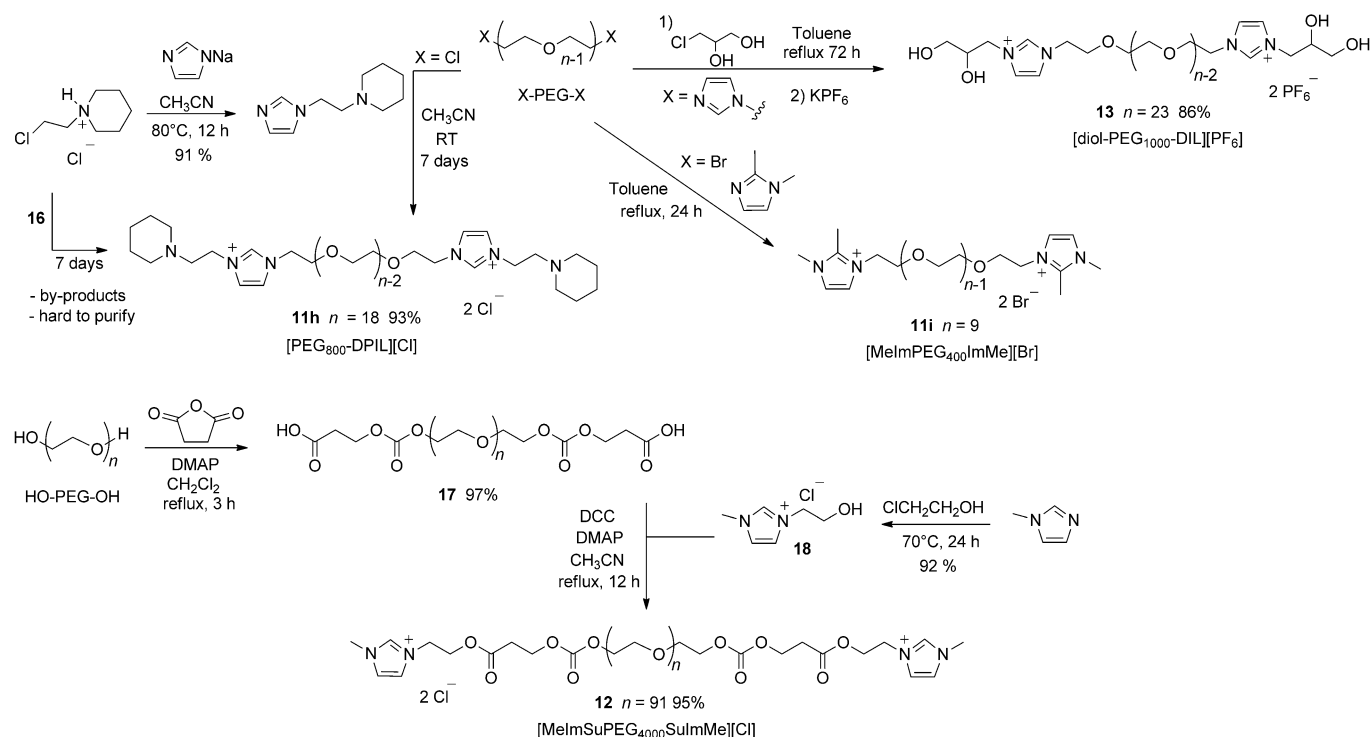
Brønsted acidic functionalities “built on purpose” [task-specific ILs (TSILs)]. The synthesis involves the formation of a common PEG–diimidazole intermediate, **16**, according to Route B (Scheme 1), followed by a two-step alkylation process with 1,3-propane and a sulfone/acidic treatment to introduce the acidic functionality. Then, ion metathesis allows the introduction of the desired counterion. The [PEG-DAIL][X] solvents **10** are viscous liquids, but no data are available concerning their purity or yields. In the presence of a suitable organic solvent, they form a temperature-dependent biphasic system, with a miscibility temperature ( $T_m$ ) that strictly depends on the intrinsic characteristic of the selected [PEG-DAIL][X]. In general, IL-PEG derivatives are soluble to a certain degree in common organic solvents, such as chloroform, ethyl acetate, and toluene. This is a problem when the product of the reaction needs to be separated from the crude mixture and the IL-PEG or IL-PEG/catalyst recovered, especially for homogeneous catalysis. In the case of heterogeneous systems, the recovery of both product and IL-PEG/catalyst is easier, but mass transfer is less efficient. The gap is filled with the thermoregulated systems discussed in Section 5.

PEG-300 dichloride and a suitably alkylated imidazole reacted in neat conditions to afford the corresponding precursors IL-PEGs  $[\text{C}_6\text{ImPEG}_{300}\text{ImC}_6][\text{Cl}]$  and  $[\text{C}_{12}\text{ImPEG}_{300}\text{ImC}_{12}][\text{Cl}]$  (Scheme 4). Introduction of the POM (Venturello’s) anion was achieved by ion metathesis, leading to the temperature-depen-

dent miscibility with of  $[\text{C}_6\text{ImPEG}_{300}\text{ImC}_6][\text{POM}]$  and  $[\text{C}_{12}\text{ImPEG}_{300}\text{ImC}_{12}][\text{POM}]$  (**11a**).<sup>[42]</sup> On the other hand, IL-PEGs  $[\text{C}_{12}\text{ImPEG}_n\text{ImC}_{12}][\text{Br}]$  (**11b**)<sup>[43]</sup> ( $n = 9, 13, 18, 23$ ) were synthesized by alkylation of the PEG-bridged diimidazolium intermediate **16** with *n*-dodecylbromide (Scheme 4). Similarly, [PEG-DIL][MsO] solvents **11c–g**<sup>[40,44,45]</sup> were obtained, starting from mesylated mPEG (Scheme 4). [PEG<sub>800</sub>-DPIL][Cl] (**11h**).<sup>[46]</sup> [Melm-PEG<sub>400</sub>ImMe][Br] (**11i**).<sup>[18]</sup> and the diglycerol-functionalized [diol-PEG<sub>1000</sub>DIL][PF<sub>6</sub>] (**13**).<sup>[47]</sup> containing two vicinal hydroxyl groups, were synthesized starting from native PEG through Route A after three steps<sup>[12]</sup> (Scheme 5). The alternative synthesis of [PEG<sub>800</sub>DPIL][Cl] (**11h**) by alkylation of intermediate **16** with *N*-(2-chloroethyl)piperidine requires a long time (7 days) and also results in notable byproduct formation, tedious workup, and impossible purification.

A different strategy has been described to access the dicationic disuccinic ester [MelmSuPEG<sub>4000</sub>SulmMe][Cl] (**12**).<sup>[48]</sup> which was obtained after condensation of the PEG–succinic acid backbone **17** with **18**. It was easily recovered after precipitation from diethyl ether (Scheme 5).

Triazolyl IL-PEGs **15**<sup>[49]</sup> were recently prepared through the Cu<sup>I</sup>-catalyzed microwave-assisted azide/alkyne click reaction under microwave activation of diazoethylene glycols<sup>[50]</sup> and the corresponding alkyne-containing (cat)ionic liquid head group. No data have yet been reported on their possible applications.



Scheme 5. Synthesis of various IL-PEGs. DMAP = 4-dimethylaminopyridine, DCC = *N,N'*-dicyclohexylcarbodiimide.

### 3. Physicochemical Properties of PEG-Based ILs

The physicochemical properties of specific ILs with long functional mPEG-derivatized cations depend on the cation structure and the nature of the counteranion.<sup>[9,49,51–53]</sup> Although few results have been reported for ILs with long PEG chains, the number of ether units in the PEG chains is expected to influence intermolecular interactions (van der Waals interactions and hydrogen bonding), chain flexibility, and conformation.<sup>[13,16,54,55]</sup> The thermophysical properties, viscosity, liquid density, polarity, and hydrophilicity are largely dependent on the mPEG cation length.<sup>[9,56–58]</sup> For example, [(mPEG<sub>350</sub>)<sub>2</sub>NMe<sub>2</sub>][Br] (**8**) was fully miscible with water and, similar to the parent PEG-derived solvent, it was also soluble in polar alcoholic solvents (MeOH, EtOH).<sup>[32]</sup> Furthermore, it was reported that slight changes in the chemical structure of PEG-based ILs might have a significant effect on the properties of the ILs.<sup>[13,56–58]</sup> The rheological behavior, ionic conductivity, or thermophysical properties can be finely tuned by chemical modifications of the anion or cation for specific applications, for use as solid electrolytes in electrochemical devices for energy conversion, or for use as dipolar media in chemical applications, especially for reactions under microwave irradiation.<sup>[7,52,59–61]</sup>

#### 3.1. Thermal analysis: Glass transition and melting point

The glass transition temperature ( $T_g$ ) and the melting point temperature ( $T_m$ ) of PEGylated ILs, determined by differential scanning calorimetry (DSC), are related to cation–anion interactions and to the intra-/intermolecular interactions between

mPEG chains or with the cationic groups.<sup>[62]</sup> However, it was reported that crystallization did not occur for several ILPEGs because of the rotational freedom of the ethylene ether group, which hindered the chain organization.<sup>[9,63]</sup>

#### 3.2. Glass-transition temperature

Values of  $T_g$  (Table 1) decrease as the number of ether units in the molecule increases because the longest PEG chains exhibit higher flexibility and more conformational degrees of freedom, and therefore, higher free volume. Moreover, the values of  $T_g$  reported by Binder and co-workers<sup>[49]</sup> for dicationic ILs also depended on the PEG size, as well as on the chemical nature of both the counteranion and cationic group.<sup>[49,51,59]</sup> Indeed, the reported  $T_g$  values for IL-PEGs with the same counteranion, [MeSO<sub>3</sub>], and PEG size of five ether units (PEG-200) for the cation increase in the order [NEt<sub>3</sub>] (−15 °C) < [Pyr] (−14 °C) < [Melm] (−5 °C), whereas for a large PEG chain composed of 33 units (PEG-1500), the opposite trend is observed for the cations Melm (−41 °C) < Pyr (−30 °C). The higher  $T_g$  value for IL-PEGs with the Im cation and a short PEG chain is essentially attributed to intermolecular hydrogen bonding between PEG moieties and Im groups.<sup>[13,62]</sup> The opposite trend observed for a large PEG chain indicates that the PEG moieties are long enough to develop intramolecular interactions with Im groups, and therefore, overcome intermolecular hydrogen bonding.<sup>[49]</sup> Furthermore, the ILs with Pyr groups exhibit higher  $T_g$  values because the positive charge is more localized compared with the high charge distribution of the aromatic Im groups, thus weakening the strength of the cation–anion interactions in the



**Table 1.** Physicochemical properties of the PEG-based ILs: glass transition temperature ( $T_g$ ), melting temperature ( $T_m$ ), decomposition temperature ( $T_d$ ), and density ( $\rho$ ).

Entry	Cation	Anion	$T_g$ [°C]	$T_m$ [°C]	$T_d$ [°C]	$\rho$ [g mL <sup>-1</sup> ]	Ref.
1	[mPEG <sub>150</sub> Melm]	[MeSO <sub>3</sub> ]	−59	n.r. <sup>[a]</sup>	196	1.23	[13]
2	[(mPEG <sub>350</sub> ) <sub>2</sub> NMe <sub>2</sub> ]	[Br]	n.r. <sup>[a]</sup>	n.r. <sup>[a]</sup>	285	n.r. <sup>[a]</sup>	[32]
3	[mPEG <sub>300</sub> Melm]	[I]	−50.5	n.o. <sup>[b]</sup>	281	1.363	[63]
4	[mPEG <sub>550</sub> Melm]	[I]	−50.9	7	282	1.294	[63]
5	[mPEG <sub>750</sub> Melm]	[I]	−54.5	23	284	1.262	[63]
6	[poly(PEG <sub>150</sub> Melm) <sub>n</sub> ]	[N(SO <sub>2</sub> CF <sub>3</sub> ) <sub>2</sub> ]	−23.5	n.o. <sup>[b]</sup>	403	n.r. <sup>[a]</sup>	[59]
7	[poly(PEG <sub>100</sub> Melm) <sub>n</sub> ]	[N(SO <sub>2</sub> CF <sub>3</sub> ) <sub>2</sub> ]	−12.5	n.o. <sup>[b]</sup>	414	n.r. <sup>[a]</sup>	[59]
8	[MelmPEG <sub>250</sub> ImMe]	[MeSO <sub>3</sub> ]	−5	n.o. <sup>[b]</sup>	305	n.r. <sup>[a]</sup>	[49]
9	[MelmPEG <sub>1500</sub> ImMe]	[MeSO <sub>3</sub> ]	−41	30	345	n.r. <sup>[a]</sup>	[49]
10	[MePyrrPEG <sub>250</sub> PyrrMe] <sup>[c]</sup>	[MeSO <sub>3</sub> ]	−14	n.o. <sup>[b]</sup>	318	n.r. <sup>[a]</sup>	[49]
11	[MePyrrPEG <sub>1500</sub> PyrrMe] <sup>[c]</sup>	[MeSO <sub>3</sub> ]	−30	38	310	n.r. <sup>[a]</sup>	[49]
12	[MePyrrPEG <sub>250</sub> PyrrMe] <sup>[c]</sup>	[p-MeC <sub>6</sub> H <sub>4</sub> SO <sub>3</sub> ]	−5	n.o. <sup>[b]</sup>	320	n.r. <sup>[a]</sup>	[49]
13	[Et <sub>3</sub> NPEG <sub>250</sub> NEt <sub>3</sub> ]	[MeSO <sub>3</sub> ]	−15	n.o. <sup>[b]</sup>	290	n.r. <sup>[a]</sup>	[49]
14	[Et <sub>3</sub> NPEG <sub>250</sub> NEt <sub>3</sub> ]	[p-MeC <sub>6</sub> H <sub>4</sub> SO <sub>3</sub> ]	−6	n.o. <sup>[b]</sup>	297	n.r. <sup>[a]</sup>	[49]

[a] n.r.: not reported. [b] n.o.: not observed. [c] Pyrr = pyrrolidinium.

salts.<sup>[62,64]</sup> The higher  $T_g$  observed for the toluene sulfonate salts is ascribed to the large volume and low flexibility of the aromatic cycle, which prevails over the effect of its high charge distribution.<sup>[49]</sup>

### 3.3. Melting point

The melting point ( $T_m$ ) of PEG-functionalized ILs is determined by the strength of the crystal lattice, which arises from different effects, mostly cation–anion interactions, intermolecular interactions, and the conformational degrees of freedom of the cation or anion (or molecular rigidity), similar to conventional ILs. Moreover, a highly symmetric anion or cation leads to better molecular stacking in the crystal with more efficient intermolecular interactions, which results in a higher lattice energy; therefore,  $T_m$  increases.<sup>[13,64,65]</sup> The results reported for IL<sub>PEG</sub>s highlight the significance of the length of PEG in determining the value of  $T_m$ . Indeed, the dominant effect for the short PEG chains, which is the flexibility of the ether groups that lower the value of  $T_m$ , is limited for long PEG chains because the chain polarity strengthens the solid-state cohesion. As a result, the melting point,  $T_m$ , increases with increasing PEG chain length because of strong interactions (polar, van der Waals, hydrogen bonds) between PEG chains.<sup>[63]</sup> For example,  $T_m$  is not observed for the [mPEG<sub>300</sub>Melm] (Table 1, entry 3) or [MelmPEG<sub>250</sub>ImMe] (Table 1, entry 8) cations because the PEG chain flexibility hinders crystallization, whereas IL<sub>PEG</sub>s with longer PEG chains exhibit a  $T_m$  that increases with the number of ethylene oxide moieties [7 and 23 °C for [mPEG<sub>550</sub>Melm] (Table 1, entry 4) and [mPEG<sub>750</sub>Melm] (Table 1, entry 5), respectively, and 30 °C for [MelmPEG<sub>1500</sub>ImMe] (Table 1, entry 9)].

### 3.4. Liquid density

Generally, the density of the IL<sub>PEG</sub>s depends on the cation–anion interactions and molecular packing.<sup>[62]</sup> It is thus expected that there will be a decrease in density with an increase in the

PEG chain length, as observed for [mPEG<sub>750</sub>Melm][I] (Table 1, entry 5), [mPEG<sub>550</sub>Melm][I] (Table 1, entry 4) and [mPEG<sub>350</sub>Melm][I] (Table 1, entry 3) for which the measured liquid densities at 25 °C are 1.262, 1.294, and 1.363 g cm<sup>-3</sup>, respectively (Table 1). This trend is consistent with previous reports on the effect of the alkyl chain length on the density of some ILs with bis(trifluoromethylsulfonyl)imide ([Tf<sub>2</sub>N]) as a counterion.<sup>[65]</sup>

### 3.5. Thermogravimetric analysis

The thermal stability of IL<sub>PEG</sub>s depends on the chemical nature of the counteranion, the chemical nature of the cation head, and the side chain in the cation.<sup>[9,59]</sup> Therefore, the decomposition temperatures ( $T_d$ ) of the IL<sub>PEG</sub>s were increased by a PEG chain long enough to wrap around the cationic head, which was expected to hinder nucleophilic attack of the anion involved in the thermal decomposition of the IL cation.<sup>[63]</sup> Therefore, [mPEG<sub>350</sub>Melm][I] and [mPEG<sub>750</sub>Melm][I] have  $T_d$  values that are higher than those of [mPEG<sub>150</sub>Melm][MsO] (281, 284, and 196 °C, respectively; Table 1; entries 3, 5, and 1). The  $T_d$  values of IL<sub>PEG</sub>s additionally depend on the chemical structure of the cation head [290 °C for [Et<sub>3</sub>NPEG<sub>250</sub>NEt<sub>3</sub>] (Table 1, entry 13) versus 305 °C for [MelmPEG<sub>250</sub>ImMe] (Table 1, entry 8)]. However, not enough data were reported for IL<sub>PEG</sub>s with long chains to allow classification of the thermal stability of the different cation groups. The decomposition temperature as a function of the anion was reported to decrease in the order [N(SO<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>] > [BF<sub>4</sub>] > [p-MeC<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>] > [MeSO<sub>3</sub>] > [PF<sub>6</sub>] > [I] ≈ [Br].<sup>[13,32,49,65]</sup>

### 3.6. Rheological behavior

The viscosity of IL<sub>PEG</sub>s used as media in different chemical and electrochemical applications is an important parameter involved in the rate of mass transport, which is a limiting factor for the considered applications. The viscosity of ILs largely depends on van der Waals interactions, hydrogen bonding, and also on the nature of the counteranion and rotational freedom within both ionic moieties.<sup>[9,62,64,66]</sup> For example, the viscosities of [EG–Melm][BF<sub>4</sub>], [EG–Melm][PF<sub>6</sub>], and [EG–Melm][NTf<sub>2</sub>] (EG = ethylene glycol) are 86, 336, and 541 cP, respectively, at 25 °C.<sup>[52]</sup> Hence, the viscosity increases as follows: [BF<sub>4</sub>] < [PF<sub>6</sub>] < [NTf<sub>2</sub>]. The high viscosity found with [NTf<sub>2</sub>] is probably attributable to hydrogen bonding with the hydroxyl group of the EG chain attached to the Im ring. In the same way, the increase in the length of the EG chain makes the IL<sub>PEG</sub> more viscous: [mPEG<sub>150</sub>Melm][NTf<sub>2</sub>] has a viscosity of 2249 cP at room temperature.<sup>[52]</sup> Moreover, the viscosity increases proportionally

to the length of the side chains grafted to the cation. In particular, [mPEG<sub>350</sub>Bulm][I], with a bulky *n*-butyl group attached to the N atom, has a higher viscosity at 25 °C than its homologue, [mPEG<sub>350</sub>Melm][I]: 1675.0 and 1094.9 cP, respectively.<sup>[63]</sup>

The same trends in the variation of viscosity were also reported for IL<sub>PEG</sub>s based on an ethylene oxide number greater than three moieties and different cationic groups, such as Im, Pyr, piperidinium (Pip), oxazolidinium (Oxa), ammonium (NR<sub>3</sub>), and phosphonium (PR<sub>3</sub>).<sup>[62,67]</sup> However, few results were reported for IL<sub>PEG</sub>s with long PEG chains. For example, ammonium- and phosphonium-based ILs with oxyethylene chains have been synthesized. The rheological behavior of these new ILs suggests that the viscosity of ILs with a PEG chain is lower than that with an alkyl chain because the relaxation time of the former is faster than that of the latter. Shiota et al. also suggested that the differences between ammonium- and phosphonium-based ILs could be attributed to different molar volumes.<sup>[67]</sup> The higher molar volume of phosphonium-based IL leads to a decrease in the shear viscosity through a reduction of interionic Coulombic interactions. The same effect was reported for ammonium, Im, and Pip cationic groups, for which the viscosity decreased with the bulkiness of the group: 184, 174, and 119 cP for [Et<sub>3</sub>NPEG<sub>400</sub>Et<sub>3</sub>N], [EtImPEG<sub>400</sub>ImEt], and [EtPipPEG<sub>400</sub>PipEt], respectively.<sup>[67]</sup> Considering the effect of the PEG chain length, it was reported that a longer PEG chain decreased the viscosity: 900.9 cP for [mPEG<sub>750</sub>Melm][I], 1025.7 cP for [mPEG<sub>550</sub>Melm][I], and 1094.9 cP for [mPEG<sub>350</sub>Melm][I] at 25 °C. The same trend was observed for other cationic groups, for example, [Et<sub>3</sub>NPEG<sub>200</sub>NEt<sub>3</sub>][OAc], [Et<sub>3</sub>NPEG<sub>400</sub>NEt<sub>3</sub>][OAc], and [Et<sub>3</sub>NPEG<sub>600</sub>NEt<sub>3</sub>][OAc] displayed viscosities of 230, 184, and 174 cP, respectively, at 50 °C.<sup>[63]</sup> Krishnan et al. attributed this behavior to wrapping of the Im ring with the PEG chain, leading to screening of Coulombic interactions between the Im cation and the anion and, thereby, to a decrease in viscosity.<sup>[63]</sup> Furthermore, [(mPEG<sub>350</sub>)Me<sub>2</sub>Im][Br] (**5**) displays a high viscosity (2230 MPa s) at room temperature because of the presence of two long PEG chains, which are responsible for enhanced van der Waals interactions associated with reduced rotational freedom of the cation, as well as to a larger and less flexible molecule compared with a cation with a single PEG chain.<sup>[32]</sup>

The temperature dependence of the viscosity of IL<sub>PEG</sub>s is also important because reactions in these new media are often performed at temperatures higher than room temperature. The viscosity of IL<sub>PEG</sub>s decreases as *T* increases according to an Arrhenius-type law,  $\eta = \eta_0 e^{E_a/RT}$ . Moreover, it was reported that the activation energy slightly decreased for longer poly(oxyethylene) (POE) groups, in agreement with a nonlinear conformation of the PEG chain:  $E_a = 36.02$  and  $39.30$  kJ mol<sup>-1</sup> for [mPEG<sub>750</sub>Melm][I] and [mPEG<sub>350</sub>Melm][I], respectively.<sup>[63]</sup> The high conformational and rotational flexibility of the ether moieties leads to an increase in the free volume of the IL<sub>PEG</sub> cation. As a result, the related effect of the PEG chain on the viscosity decrease was ascribed to a larger number of holes available for efficient mass transport and low viscosity, which is in agreement with the hole theory.<sup>[68,69]</sup>

## 4. Applications in Organic Synthesis and Catalysis

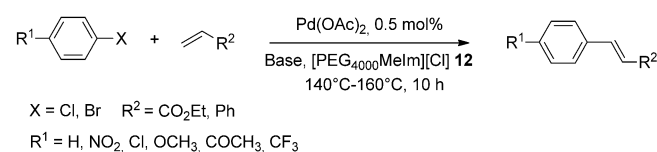
The various PEG-based ILs previously described have applications in different areas of organic synthesis, including metal-catalyzed reactions, organocatalysis, multicomponent reactions (MCRs), and aromatic substitution. They may serve as solvents, additives, or ligands in these reactions. Details are presented for every reaction.

### 4.1. Metal-catalyzed reactions

#### 4.1.1. Reactions with palladium

Two families of cross-coupling reactions have been studied in the presence of PEG-based ILs: the Heck reaction and Suzuki coupling.

Wang et al. investigated the possibility of conducting a Heck reaction in an alternative medium consisting of IL<sub>PEG</sub>.<sup>[48]</sup> ILs are already well established as solvents in such transformations, and PEGs have been described in the literature as an alternative to ILs.<sup>[48]</sup> Consequently, a hybrid of both media could provide interesting properties that affect the outcome of the reaction. For this purpose, the use of [PEG<sub>4000</sub>Melm][Cl] (**12**) in a Heck reaction was investigated (Scheme 6).

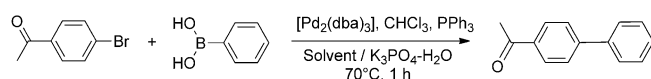


Scheme 6. Heck reaction in [PEG<sub>4000</sub>Melm][Cl] (**12**).

IL **12** (3 g) and Pd(OAc)<sub>2</sub> (0.5 mol%) were mixed together in the absence of any other ligand to catalyze the reaction of bromoanisole with styrene. Various bases were tested: K<sub>3</sub>PO<sub>4</sub> and K<sub>2</sub>CO<sub>3</sub> gave rise to the best results, yielding *trans*-stilbene selectively as the only product. The reaction was performed at 140 °C; the temperature could not be decreased without a loss in conversion. The same reaction was also performed in different reaction media, such as PEG 4000-OH, but the conversion decreased to 52%, whereas in [BMIm][Cl] only traces of product were obtained. To delineate the scope of the reaction, several olefins were synthesized, starting from bromoarenes with electron-donating (CH<sub>3</sub>, OMe) or -withdrawing groups (NO<sub>2</sub>, COCH<sub>3</sub>, Cl) with styrene or ethylacrylate. Yields ranged from 91 to 97%. Because of the efficiency of this catalytic system it was tested in the reaction with chlorobenzene derivatives. The reactivity of these substrates was low, but switching the base from K<sub>2</sub>CO<sub>3</sub> to Cs<sub>2</sub>CO<sub>3</sub> and increasing the reaction time to 24–48 h and the temperature to 160 °C provided good yields of the expected product, as long as the chloroarene contained an electron-withdrawing group (NO<sub>2</sub>, COCH<sub>3</sub>, CF<sub>3</sub>). Recycling of the catalytic system was also evaluated using the reaction of bromobenzene with styrene. After completion of the reaction,

the mixture was extracted with diethyl ether and the residual mixture was used again in a next cycle. 100% conversion was obtained in the first five cycles, but then the reactivity dropped. This could be attributed to the degradation of IL<sub>PEG</sub> through hydrolysis of the ester bonds and accumulation of salts in the solvent as byproducts of the reaction. The combination of this PEG-based IL and Pd(OAc)<sub>2</sub> provided a ligandless catalytic system for the Heck reaction.

Livingston et al. reported results on the effects of ILs on the yield and catalyst activity in Suzuki cross-coupling.<sup>[70]</sup> They studied this reaction in organic solvents, in ILs, and in mixtures of these solvents. Among others, they considered the use of PEG-based ILs of the ECOENG family (Figure 1). In the reaction of 4-bromoacetophenone and boronic acid catalyzed by [Pd<sub>2</sub>(dba)<sub>3</sub>] (dba = dibenzylideneacetone) and in the presence of PPh<sub>3</sub> as a ligand, the presence of organic solvents (ethyl acetate or dioxane) resulted in a good yield (up to 77%) of the reaction product, whereas the reaction in ILs provided average-to-low yields (Scheme 7).

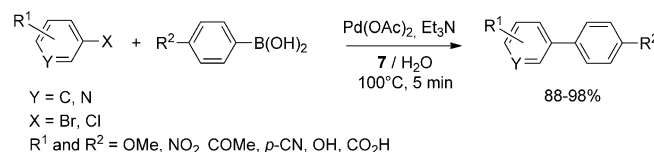


Scheme 7. Suzuki cross-coupling in PEG-ILs.

Among the various ILs used, ECOENG 500 (**4**) demonstrated the best performance (47.5%). Nevertheless, a large amount of palladium black precipitated when the reaction was performed in an organic solvent. This was in sharp contrast to the use of an IL, such as **4**, for which no catalyst decomposition was observed, except when exposed to air overnight. The idea of mixing the solvents arose from the possibility of combining the best results from the two experimental conditions: the yield from the organic solvent and the catalyst stability of the IL. A more systematic study was performed with a mixture of ECOENG 500/ethyl acetate (dioxane gave similar results and was more toxic). The reaction conditions could be optimized by lowering the temperature from 70 to 30 °C and the catalyst loading from 5 to 2.5 mol%. The expected product was obtained in 75% yield. Although complementary structural analyses or recycling experiments were not performed in this study, from visual observations it could be concluded that this mixed solvent system sufficiently stabilized the catalyst to avoid the formation of palladium black and that the presence of ethyl acetate decreased the viscosity of the reaction mixture. A small amount of water was added as indicated by the experimental data. This probably influenced the physicochemical properties of the solvent mixture.

The Suzuki–Miyaura coupling was also investigated by Liu et al., who used PEG-functionalized Im salts in water (Figure 1; **7**).<sup>[33]</sup> The presence of the Im moiety provides an N-heterocyclic carbene (NHC) ligand, which can efficiently bind to metal, enhancing its stability and efficacy. Different monoimidazolium salts **7** were used in a Suzuki–Miyaura reaction. The model reaction was the coupling of 4-bromoanisole with phenylboronic

acid in water at 100 °C by using Pd(OAc)<sub>2</sub> as a source of palladium catalyst and **7a** or **7b** as ligand. The investigation consisted of screening various bases in this reaction together with [PEG–Melm]. Inorganic bases did not promote the transformation. Among the organic bases, triethylamine gave rise to the best results, supposedly by stabilizing the active NHC palladium species present in the reaction mixture. The three PEG–Im **7** were then compared in terms of reaction kinetics, with triethylamine as the base. The use of the *i*Pr-substituted compound resulted in faster reactions due, according to the authors, to the importance of steric bulk on the ligand in this palladium-catalyzed reaction (Scheme 8). With these optimized ex-



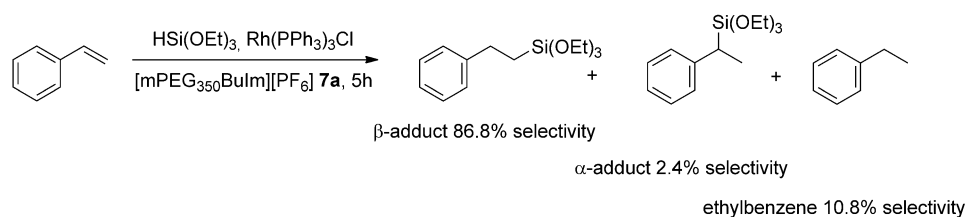
Scheme 8. Suzuki cross-coupling in water/IL<sub>PEG</sub> **7**.

perimental conditions in hand, the scope of the reaction could be delineated by using 0.5 mol% of Pd(OAc)<sub>2</sub>. Substituted bromobenzene resulted in excellent yields with either electron-donating or -withdrawing groups. One example with 4-nitrochlorobenzene was reported, but it needed a higher catalyst loading (1 mol%), an additive [tetrabutylammonium bromide (TBAB)], and a longer reaction time to obtain the coupling product in good yield. Recovery of the products was performed by extraction with ethyl acetate after quenching of the reaction with brine. No data of feasible recycling was reported.

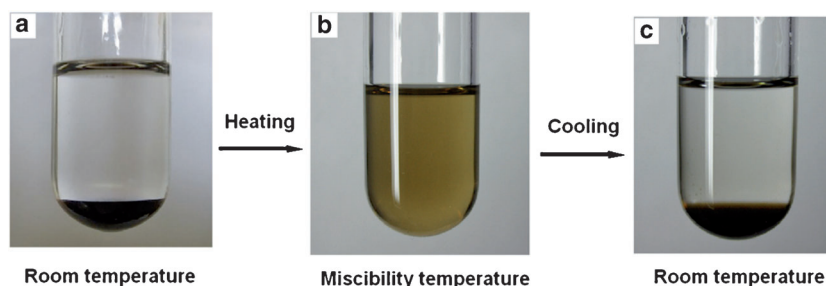
#### 4.1.2. Reactions with rhodium

The rhodium-catalyzed reactions carried out in PEG-based ILs are hydrogenation, hydrosilylation, and hydroformylation, some of which form a thermoregulated system with an organic solvent. In 2008, a rhodium-catalyzed hydrosilylation was reported by Peng et al.<sup>[27]</sup> The reaction of styrene and triethoxysilane with a rhodium salt was investigated in various solvents. In classic organic solvents (THF or benzene), the conversion was not complete and the selectivity was poor. This was also the case with a classical IL, such as [BMIm][PF<sub>6</sub>]. In contrast, when an aliphatic starting material was used, **7a** (Scheme 3), it provided high and selective conversion towards the formation of the  $\beta$  adducts, along with some hydrogenation product (Scheme 9). In the case of styrene, some of the  $\alpha$  isomer was also detected. The expected product was recovered by extraction with diethyl ether, and the IL could be reused for more than five runs with an aliphatic alkene. A decrease in the catalytic activity was observed when the reaction was performed with styrene.

The groups of Jiang<sup>[31]</sup> and Wang<sup>[71]</sup> described different approaches to rhodium-catalyzed reactions with IL<sub>PEG</sub>. They developed a thermoregulated catalytic system with IL<sub>PEG</sub>/organic solvent (Figure 3). At room temperature, two phases are present:



**Scheme 9.** Rhodium-catalyzed hydrosilylation in IL-PEG **7a**.



**Figure 3.** Illustration of the thermoregulated phase-transition properties of IL-PEGs.

one organic phase containing the substrate of the reaction and one IL phase containing the catalyst. Under gas pressure and heating, only one homogeneous phase is obtained, in which the reaction takes place. Upon cooling and depressurization, a binary system is obtained again to allow separation of the catalytic system into the IL-PEG phase and the product in the organic phase.

The first reaction investigated was the hydroformylation of 1-dodecene by using  $\text{RhCl}_3 \cdot \text{H}_2\text{O}$  with 3,3',3''-phosphinidynetris-(benzenesulfonic acid) (TPPTS) as the metal catalyst.<sup>[31]</sup> Various IL-PEG sulfonates  $[\text{mPEG}_n\text{NEt}_3][\text{MsO}]$  (**3**) were considered, based on different PEG sizes: 350 (**3a**), 550 (**3b**), or 750 (**3c**). These IL-PEGs were evaluated for their ability to provide a thermoregulated system in the presence of *n*-heptane and toluene.  $[\text{mPEG}_{750}\text{NEt}_3][\text{MsO}]$  (**3c**) presented a better miscibility gap and was chosen for this study. This system has another advantage: it can immobilize the phosphine used in the reaction by exchanging the sodium ion of TPPTS with the ammonium ion of the IL. The first parameter explored in this study was the phosphine/rhodium ratio at a temperature of 110 °C, which is close to the miscibility of PEG-IL with the organic solvent (heptane or toluene) of 108 °C, and a pressure of 5 MPa. These conditions should preserve the catalytic activity and stabilize the catalyst. The optimum ratio for this reaction was eight. Reaction time and temperature were also varied to obtain conditions (110 °C, 5 MPa for 5 h) that yielded 99% conversion and 97% of the aldehyde. After cooling, the product could be easily separated from the catalytic system. Recycling was also evaluated, and the reaction could be performed eight more times without loss of activity. Less than 1 wt% of rhodium leached at every cycle.

The second application of the thermoregulated organic solvent/ $[\text{mPEG}_{750}\text{NEt}_3][\text{MsO}]$  (**3c**) system was described by the same research group<sup>[71]</sup> and dealt with the hydrogenation of

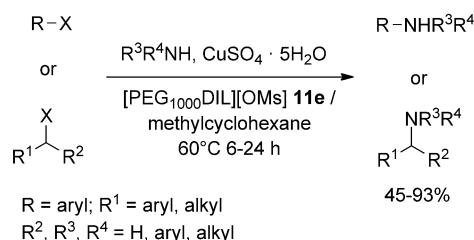
alkenes. Rhodium was again used as the catalyst, but in the absence of a ligand such as TPPTS in this case, with the expectation that the reduction of the starting salt ( $\text{RhCl}_3 \cdot \text{H}_2\text{O}$ ) would provide rhodium NPs that could catalyze the reaction.  $\text{RhCl}_3 \cdot \text{H}_2\text{O}$  was stirred in **3c** at 70 °C under hydrogen (4 MPa) for 2 h. This process generated NPs with an average particle size of 2 nm in diameter, as shown by TEM analysis. Then the reactor was filled with the olefin, the organic solvents (toluene and *n*-heptane), and hydrogen. The mixture of solvents used in this case provided a thermoregulated phase-transition process with a miscibility temperature of 60 °C. Starting from cyclohexene, 100% conversion

into cyclohexane was obtained at 60 °C for 1 h under 1 MPa of hydrogen. The turnover frequency (TOF) in this case was very similar to the one obtained by using  $[\text{BMIm}][\text{BF}_4]$  as a solvent. Other olefins (styrene, 1-octene, 1-dodecene) were also quantitatively hydrogenated. The product was recovered by separating the organic phase. The catalytic system could be used nine times without any loss in activity. Rhodium leaching in the organic phase was measured by inductively coupled plasma mass spectrometry (ICP-MS) and was inferior to the minimum detectable amount ( $0.005 \mu\text{g mL}^{-1}$ ).

As assumed by the authors, this could be attributed to the supplementary stabilization provided by the PEG chains of the PEG IL.

#### 4.1.3. Reactions with copper

Two types of copper-catalyzed reactions were developed by using IL-PEGs, namely, the amination of halides and the Huisgen cycloaddition. In 2010, Lu et al. described the possibility of aminating organic halides in a temperature-dependent biphasic system that consisted of IL-PEG and methylcyclohexane (Scheme 10).<sup>[72]</sup> As described in the reactions with rhodium (see Section 4.1.2), the use of **11** (Scheme 4) provided methyl-

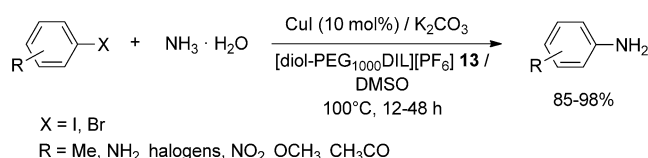


**Scheme 10.** Amination of organic halides.



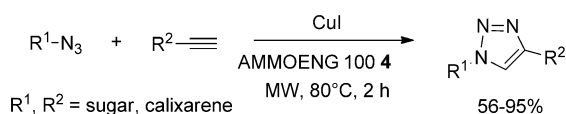
cyclohexane in a thermoregulated system. Various sizes of PEG were investigated (400, 600, 800, 1000) in the reaction of chlorobenzene with aqueous ammonia in the presence of copper salts: [PEG<sub>1000</sub>-DIL][MsO] (**11e**) provided the best results. Various copper salts were also screened. CuSO<sub>4</sub> was the most suitable and yielded 93% aniline, which was easily isolated by decantation of the reaction mixture and recovery of the organic phase. The aqueous phase was concentrated in vacuo, and the IL<sub>PEG</sub> containing the copper catalyst was recovered and used in an additional run. Up to eight reactions could be performed without loss of catalytic activity. The scope of the reaction was delineated, and substituted chloro- and bromoarenes gave rise to excellent yields of substituted anilines. This reaction was also extended to other halides (benzyl, allyl, alkyl halides) and various amines (primary, secondary) to give rise to the corresponding amine derivatives in good yield.

Amination reactions of a series of substituted aryl iodides and bromides with aqueous ammonia were reported by Luo et al.,<sup>[47]</sup> who used a diol-functionalized PEG-bridged dicationic IL [diol-PEG<sub>1000</sub>-DIL][PF<sub>6</sub>] (**13**) with CuI (10 mol%) as the catalyst and DMSO as the cosolvent (Scheme 11).



**Scheme 11.** Amination reaction with ammonia and [diol-PEG<sub>1000</sub>-DIL][PF<sub>6</sub>] (**13**).

The other application of copper dealt with the catalysis of the Huisgen reaction and was developed by the group of Marra and Dondoni.<sup>[73]</sup> The cycloaddition of various azides and alkynes was performed by using the commercially available IL AMMOENG 100, known also as ECOENG 500 (**4**), in the presence of CuI and under microwave irradiation (Scheme 12).



**Scheme 12.** Copper(I)-catalyzed azide–alkyne cycloadditions.

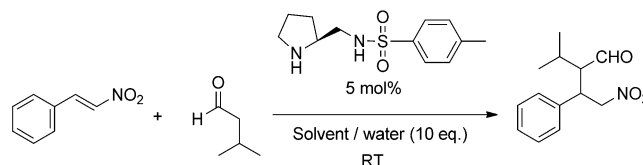
As little as 0.025 equivalents of CuI could be used in this reaction, which did not require the presence of a nitrogen-containing ligand, as usually described. The reaction product was recovered in good yield by extraction with organic solvents (diethyl ether, ethyl acetate). Unfortunately, CuI was also recovered in the organic layer and fresh catalyst had to be added in the next run. However, the IL **4** could be reused in several cycles.

#### 4.1.4. Reactions with tungsten

In 2010, Hou et al. prepared new Venturello catalysts by combining tungsten-based poly-oxometalates and a bis-Im PEG-IL (**11a**; Scheme 4).<sup>[42]</sup> This catalytic mixture was used in the epoxidation of alkenes with H<sub>2</sub>O<sub>2</sub> as the oxidant. The reaction was tested on cyclooctene as a substrate in the absence of an organic solvent and provided good results at room temperature despite long reaction times, which could be shortened by heating at 60 °C. The reaction product was recovered by cyclohexane extraction, and the IL<sub>PEG</sub>/catalyst system could be used in four more runs without significant loss of activity. Epoxidation of styrene or cyclohexene led to a known partial acidic hydrolysis of the epoxide. This side reaction could be limited by adding an extra organic solvent, of which ethyl acetate is the best compromise between environmental considerations and efficiency. The more hydrophobic [C<sub>12</sub>PEG<sub>300</sub>Im][POM] produced the best results, probably because it participated more efficiently in the necessary transfer of the peroxo species into the organic phase. Adding cyclohexane at the end of the reaction allowed better recovery of the reaction product.

#### 4.2. Organocatalysis

IL<sub>PEG</sub>s were also used in organocatalyzed reactions, such as Michael addition or Knoevenagel condensation. In 2007, Mečiarová et al. reported the catalytic activity of *N*-toluenesulfonyl-L-proline amide in the Michael addition of carbonyl compounds on (*E*)-β-nitrostyrene.<sup>[74]</sup> This reaction was comparatively tested in IL media. Among these solvents, one was based on a PEG backbone [ECOENG 500 (**4**); Scheme 13]. *N*-Toluenesulfonyl-L-



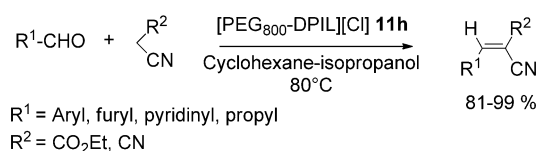
**Scheme 13.** Stereoselective Michael addition.

proline amide was chosen as a tunable surrogate of proline, which is an efficient organocatalyst in many reactions, with several attractive properties (nontoxic, inexpensive). The reaction was first tested at room temperature in [BMIm][EtSO<sub>3</sub>], but it was slow (40% yield) and the enantiomeric excess (*ee*) was poor (32% *ee*). Heating did not improve these results. Adding 10 equivalents of water provided 83% yield, but a poor *ee* value (24% *ee*). Various ILs were tested. Because their influence as acids/bases could have some significance in the reaction, the pH value of a 10 wt % solution of IL in water was evaluated. The results showed that **4** had a neutral pH value and ensured an excellent conversion (95%) of the starting material, albeit with a poor *ee* value (28% *ee*). The best IL was [BMIm][BF<sub>4</sub>] with a conversion of 98% and 70% *ee*.

Another organocatalytic transformation performed with IL<sub>PEG</sub>s was described in 2012 by Luo et al.<sup>[46]</sup> They designed and



synthesized the tertiary amine IL<sub>PEG</sub> [PEG<sub>800</sub>-DPIL][Cl] (**11h**), which could be active in a Knoevenagel condensation and could provide a thermoregulated biphasic reaction medium with organic solvents. IL **11h** is insoluble in less polar solvents, but does not form a thermoresponsive mixture with any of them. Fortunately, a 3:1 (v/v) ratio of cyclohexane and isopropanol provided the expected system with a critical miscibility temperature of 80 °C. This system was tested in a Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate. The reaction proceeded smoothly, and the product was recovered after decantation and separation of the organic solvents and extraction of the IL phase. [PEG<sub>800</sub>-DPIL][Cl] (**11h**) could be used in other runs, but its catalytic activity slowly decreased, probably because of the oxidation of nitrogen during the recovery of the product. The scope of the reaction (various aldehydes reacting with ethyl cyanoacetate or malononitrile) was explored (Scheme 14) and proved to be general (yields ranged from 81 to 99%). Only aliphatic aldehydes did not react with ethyl cyanoacetate.



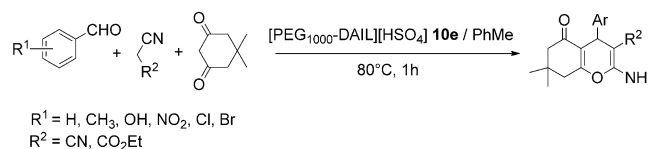
**Scheme 14.** Knoevenagel condensation in a thermoregulated biphasic system.

### 4.3. Multicomponent reactions (MCRs)

Another area of organic synthesis in which IL<sub>PEG</sub>s have proven their efficiency deals with MCRs. This approach is very efficient in the synthesis of heterocycles and complex structures in a single operation and may also be atom-economic. It provides a straightforward preparation of very diverse molecules. Pioneering work in this area was performed by Bazureau et al.,<sup>[75]</sup> who used IL<sub>PEG</sub> as a support for one of the reaction components. This support brings the advantages of high loading of the material, facile access to the active sites, and the capacity of absorbing microwaves. A family of ILs, [PEG<sub>n</sub>-Melm][X] ( $n = 1, 2$ , and  $3$ ;  $\text{X} = \text{BF}_4, \text{PF}_6$ ), were first derivatized as acrylates by an esterification reaction followed by the Michael addition of an amine to produce a  $\beta$ -amino ester in high yield (94–98%). The next step was the reaction with isothiocyanate to yield the supported thiourea derivatives (67–85% yield). Diethylamine triggered the cyclization/cleavage performed under microwave irradiation in solvent-free conditions to yield 2-thioxo tetrahydropyrimidin-4-*1H*-ones, releasing the IL<sub>PEG</sub>, which could be reused after extraction of the product with solvent.

Luo et al. reported a new PEG 1000 dicationic acidic IL, [PEG<sub>1000</sub>-DAIL][X] [e.g.,  $\text{X} = \text{HSO}_4$  (**10e**)], that could form a temperature-controlled (80 °C) bi-

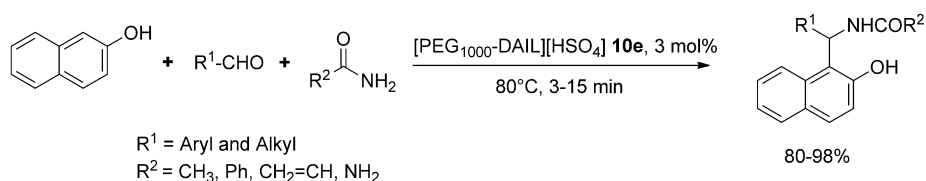
phasic system with toluene.<sup>[38]</sup> The application of this Brønsted acid in a three-component reaction for the formation of benzopyrans was described. The PEG<sub>1000</sub>-DAIL/toluene system was particularly efficient in the reaction of malononitrile, 5,5-dimethyl-1,3-cyclohexanedione, and 4-nitrobenzaldehyde, providing a 93% yield of the benzopyran derivative (Scheme 15).



**Scheme 15.** Synthesis of benzopyrans.

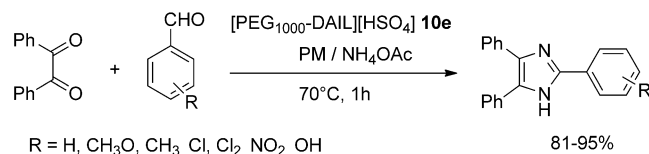
In toluene, only traces of product were detected, whereas in [PEG<sub>1000</sub>-DAIL][HSO<sub>4</sub>] (**10e**) a yield of 78% could be reached. The use of the biphasic system is a useful technique for catalyst recycling: the catalyst could be reused successively ten times without loss of activity. By varying the aldehyde and nitrile derivative, various substituted benzofurans could be obtained in good yield.

[PEG<sub>1000</sub>-DAIL][HSO<sub>4</sub>] (**10e**) was also used by the same group of investigators for the synthesis of substituted naphthols by MCRs.<sup>[41]</sup> In this case, **10e** was used as both the reaction medium and Brønsted acid catalyst to provide multiacidic sites to activate aldehydes efficiently, thus facilitating the reaction. The model reaction was the condensation of 3-nitrobenzaldehyde, 2-naphthol, and acetamide at 80 °C under solvent-free conditions (Scheme 16). With 3 mol% catalyst, a yield of 95% of the corresponding amidonaphthol was obtained within 5 min. The catalyst displayed improved activity relative to those of catalysts usually used in this reaction. Shorter reaction times and milder conditions could also be achieved with **10e**. Moreover, **10e** could be used if classical methods fail in the presence of aliphatic aldehydes or are not good enough because of long reaction times and relatively large amounts of catalyst. Increasing the amount of catalyst to 5 mol% did not improve the yield. Workup consisted of extracting the product with ethyl acetate after the addition of water to the reaction mixture. [PEG<sub>1000</sub>-DAIL][HSO<sub>4</sub>] (**10e**) could be recovered by removal of water and drying. Its activity in further cycles decreased slowly in combination with a slight loss in weight. The power of this reaction was illustrated by the quick and efficient formation of more than 20 substituted naphthols with yields ranging from 80 to 98% by varying the starting aldehydes and amides.



**Scheme 16.** Synthesis of 1-amidoalkyl-2-naphthols.

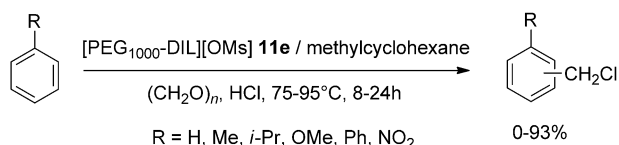
The group of Fang used **10e** as a component in a thermo-regulated biphasic medium to prepare trisubstituted imidazoles by MCRs.<sup>[40]</sup> In this case, a safer secondary solvent, propyleneglycol monomethyl ether (PM), was suggested. Mixing benzil, an aldehyde, and ammonium acetate, followed by stirring at 70 °C, resulted in the formation of the corresponding imidazole, which could be recovered from the PM layer after decantation. Again, the presence of the organic solvent increased the yield relative to that obtained for the reaction performed in the IL<sub>PEG</sub> alone. Recycling of the reaction medium was very effective. Varying the aldehyde provided diversely substituted 2,4,5-trisubstituted imidazoles (Scheme 17).



Scheme 17. Synthesis of imidazole derivatives.

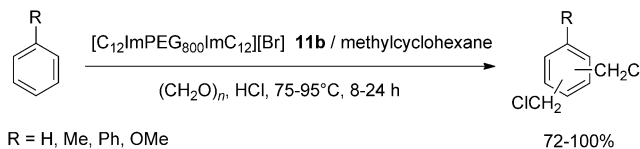
#### 4.4. Aromatic substitution

The group of Lu recently reported investigations concerning aromatic substitutions in IL<sub>PEG</sub>.<sup>[36,43,44]</sup> Because of their significance as synthetic intermediates with many applications, the synthesis of chloromethyl-substituted aromatic compounds is still investigated. The most important method for their preparation involves the reaction of formaldehyde and HCl in the presence of a catalyst. A promising approach is to use an IL, which could serve as a catalyst, as reported by Lu et al.<sup>[44]</sup> For this purpose, [PEG<sub>1000</sub>-DIL][MsO] (**11e**) was used to form a thermoregulated biphasic system with methylcyclohexane. The test reaction was the chloromethylation of ethyl benzene performed at 75 °C in a mixture containing **11e**, methylcyclohexane, and concentrated HCl by bubbling gaseous HCl through the reaction mixture. Optimum conditions consisted of a reaction time of 8 h with 0.6 equivalents of **11e**. The corresponding chloromethylated product was obtained with a conversion of 83% and 82% yield of the *para* isomer (1% for the *ortho* isomer). After recovery of the product in the methylcyclohexane layer, the reaction system could be reused. These results were extended to other aromatic compounds, including toluene, cumene, xylene, mesitylene, benzene, nitrobenzene, anisole, and biphenyl; the corresponding substituted compounds were obtained in good yields ranging from 75 to 91%, except for anisole (2%) and nitrobenzene (no reaction) (Scheme 18).



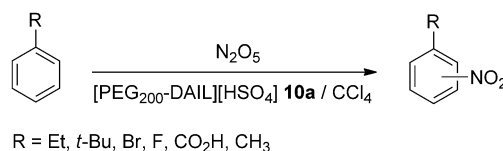
Scheme 18. Mono-chloromethylation of arenes.

A similar procedure was developed by the same authors to perform bis-monochloromethylation of aromatic hydrocarbons.<sup>[43]</sup> In this case, [C<sub>12</sub>ImPEG<sub>800</sub>ImC<sub>12</sub>][Br] (**11b**) was used as the IL and an excess of formaldehyde (6 equiv) was required. Bis-monochloromethylated products were obtained in 72–100% yield (Scheme 19).



Scheme 19. Bis-chloromethylation of arenes.

A final application of this type of system, with [PEG<sub>200</sub>-DAIL][HSO<sub>4</sub>] (**10a**), is the regioselective nitration of aromatic compounds by reaction with N<sub>2</sub>O<sub>5</sub>. The best results, in term of selectivity, were obtained with the use of a biphasic system together with CCl<sub>4</sub> as a solvent, especially for substituted substrates (Scheme 20). [PEG<sub>200</sub>-DAIL][HSO<sub>4</sub>] (**10a**) could be recycled six times with a reduced weight loss (5%).

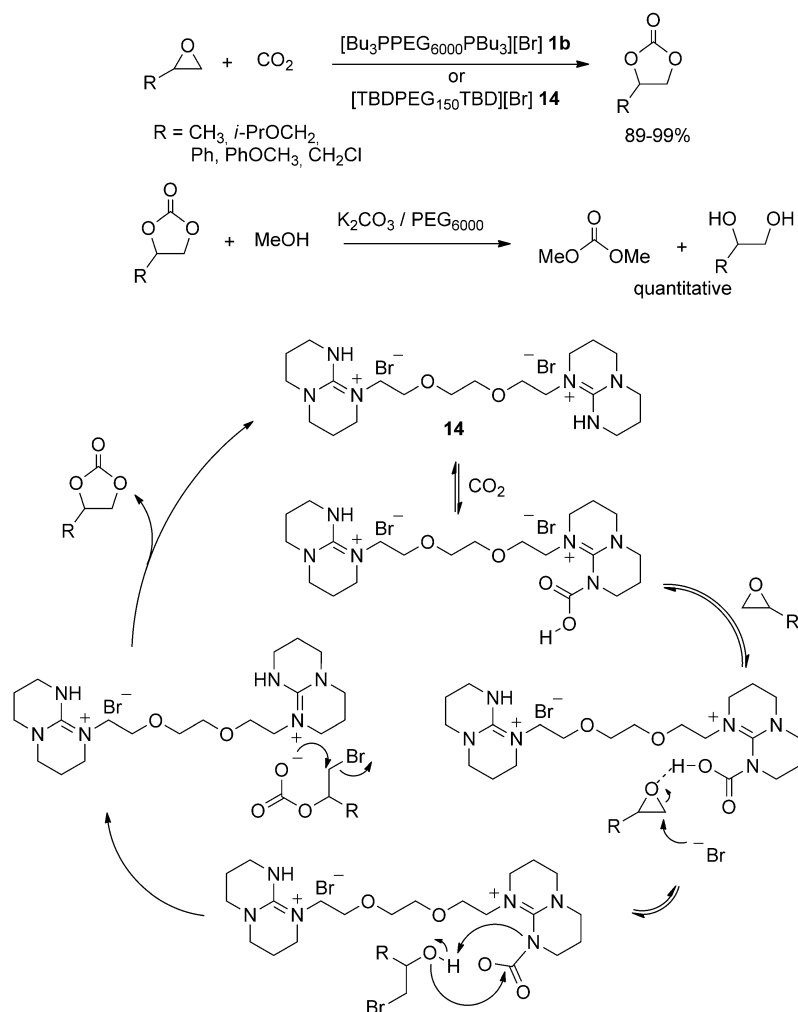


Scheme 20. Nitration of aromatic compounds.

#### 4.5. Reactions of CO<sub>2</sub>

The recovery and use of CO<sub>2</sub> in chemistry has become an innovative, important approach to find solutions for sustainable development. CO<sub>2</sub> can be transformed chemically to prepare new organic molecules that are useful as solvents or intermediates for organic synthesis. The group of He has reported several applications of the transformation of CO<sub>2</sub> involving an IL<sub>PEG</sub>.<sup>[18,19,76]</sup> Originally, He et al. investigated the IL<sub>PEG</sub>-CO<sub>2</sub>-catalyzed reaction with propylene oxide to form propylene carbonate to further produce dimethylcarbonate (DMC) and propylene glycol after reaction with methanol.<sup>[76]</sup> The two transformations were investigated separately (Scheme 21).

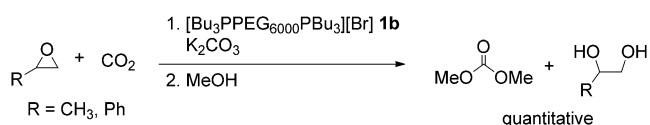
PEG-supported phosphonium, [Bu<sub>3</sub>PPEG<sub>6000</sub>PBu<sub>3</sub>][Br] (**1b**), gave rise to the best results, especially when compared with PEG or phosphonium alone. The initial conditions involved high temperature (393 K) and pressure (8 MPa). However, the pressure could be decreased to 0.2 MPa. This was probably attributable to the high solubility of CO<sub>2</sub> in the IL<sub>PEG</sub>, which reduced problems of mass transfer and diffusion. A quantitative yield and excellent selectivity were obtained. The recyclability of the catalyst was evaluated. At the end of the reaction, the catalyst was solidified by adding diethyl ether and recovered by filtration. No leaching was observed, and the activity remained after five runs; the desired compound was obtained



**Scheme 21.** Synthesis of DMC and glycol derivatives from CO<sub>2</sub> and the proposed mechanism for the cycloaddition of CO<sub>2</sub> with epoxides by using [TBDPEG<sub>150</sub>TBD][Br] (**14**) as a catalyst.

with high purity without further purification. The scope of the reaction was studied by varying the terminal epoxide, and the reaction proceeded again with good to excellent yields. The next step, methanolysis of the cyclic carbonate in DMC, was performed with PEG-supported K<sub>2</sub>CO<sub>3</sub>. A combination of K<sub>2</sub>CO<sub>3</sub> in **1b** catalyzed both transformations in one pot. Excellent yields of DMC and the corresponding glycols were obtained (Scheme 22).

This work was further developed by studying the same reaction, but with a larger family of ILs, such as **11i** and **14**.<sup>[18]</sup> The most efficient and recyclable catalyst was [TBDPEG<sub>150</sub>-TBD][Br] (**14**, *m* = 2, A = NH, X = Br), which enabled the reaction to occur at room temperature, probably through activation of the epox-

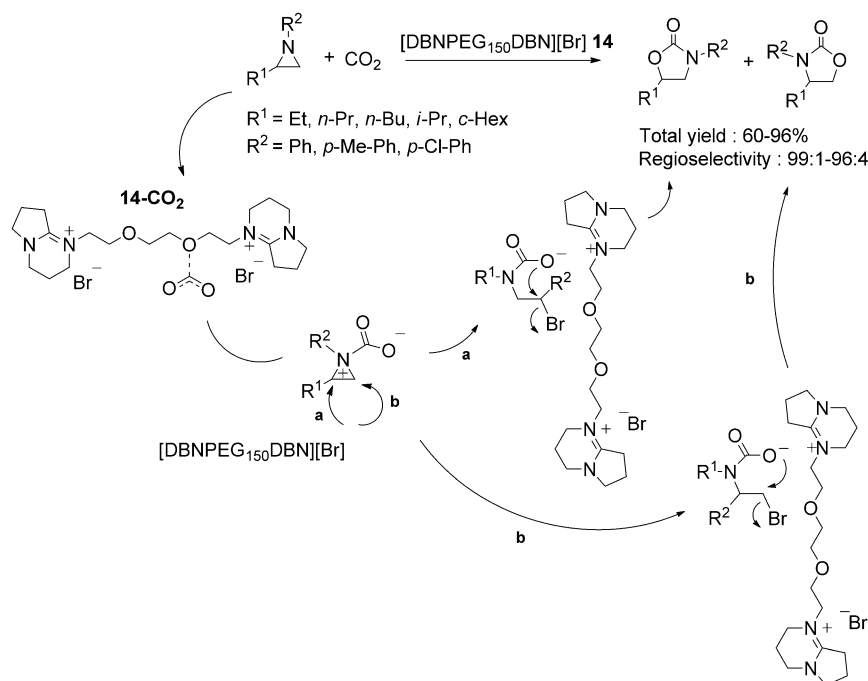


**Scheme 22.** One-pot preparation of DMC and glycol derivatives.

ide by the secondary amine of the IL<sub>PEG</sub>, as demonstrated by FTIR experiments. The proposed reaction mechanism for the cycloaddition of CO<sub>2</sub> with epoxides by using **14** as a catalyst is outlined in Scheme 21. In this case, PEG can be considered as a CO<sub>2</sub>-philic material: the “CO<sub>2</sub>-expansion of PEG”<sup>[18]</sup> effect is responsible for the physical changes in the physical properties of the liquid-phase mixture—the viscosity is reduced and the gas/liquid diffusion rates are increased to facilitate the conversion of CO<sub>2</sub>. Compared with [Bu<sub>3</sub>PPEG<sub>6000</sub>PBu<sub>3</sub>][Br] (**1b**) used in the previous study, catalyst [TBDPEG<sub>150</sub>-TBD][Br] (**14**) was sufficiently basic to catalyze the transesterification reaction without need for a supplementary base, such as K<sub>2</sub>CO<sub>3</sub>. Nevertheless, this reaction was not as efficient as with a supplementary base because of the reversible nature of the transesterification. The one-pot reaction gave rise to DMC in 83% yield.

In the last application, CO<sub>2</sub> was reacted with aziridines to provide nitrogen-containing heterocycles<sup>[19]</sup> (Scheme 23). In this case, the use of the same IL<sub>PEG</sub> as that previously described,

[DBNPEG<sub>150</sub>-DBN][Br] (**14**, *m* = 1, A = NH, X = Br), provided the best results because its structure resulted in the best balance between basicity and steric hindrance. Temperature, pressure, and reaction time did not have any significant influence on the reaction selectivity. For full conversion and good yield, a temperature of 120 °C was optimum. When the pressure of CO<sub>2</sub> was too high, a lower yield was obtained, probably because of a dilution effect. Consequently, a pressure of 3 MPa was preferred. Again, the catalyst could be reused in five successive cycles without loss of activity. Various aziridines were obtained in good to excellent yields. Selectivity towards formation of the less hindered product was always observed. When a larger substituent was present on the nitrogen atom, longer reaction times were needed, with nearly no influence of the substituent on the carbon atoms. When the reaction was tested with unfunctionalized PEG-150 as a catalyst, the conversion was low (52%) and the 5-substituted-2-oxazolidinone was obtained in low yield (16%). This result proved that the presence of the cation was of particular importance for the success of the reaction, as suggested by the reaction mechanism illustrated in Scheme 23. A comparative study with [DBN(CH<sub>2</sub>)<sub>4</sub>DBN][Br] (*m* =



**Scheme 23.** Reaction of aziridines with  $\text{CO}_2$  and the corresponding mechanism, which shows the role of IL<sub>PEG</sub> **14**.

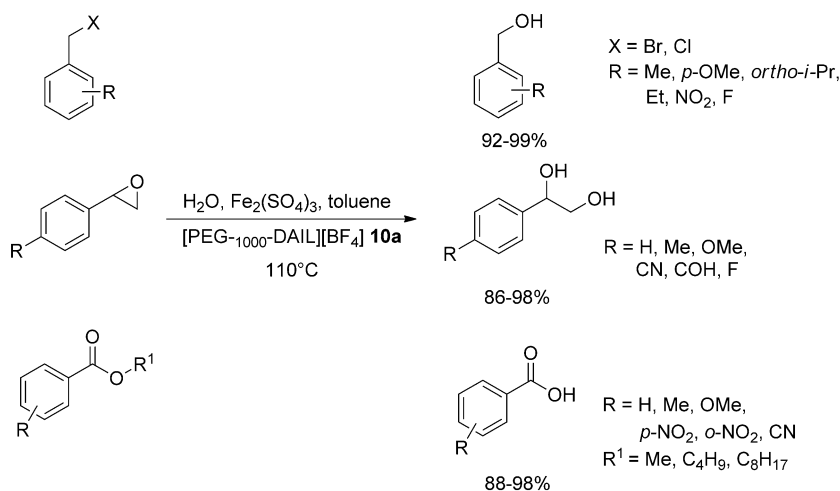
1, A = NH, X = Br), with an alkyl group instead of PEG, revealed a much lower activity and thus showed the importance of the polyether linkage for the complexation of  $\text{CO}_2$ . The catalytic cycle (Scheme 23) involved three steps. Compound [DBN-( $\text{CH}_2$ )<sub>4</sub>DBN][Br] (**14**) played the role of the catalyst in activating the molecule of  $\text{CO}_2$ , as demonstrated by in situ FTIR experiments. However, a zwitterionic carboxyaziridine could also be formed through coordination with  $\text{CO}_2$ . This intermediate underwent nucleophilic attack of the bromide anion coming from [DBN( $\text{CH}_2$ )<sub>4</sub>DBN][Br] (**14**) and led to ring opening according to two different pathways (a and b in Scheme 23). Here, the [DBN( $\text{CH}_2$ )<sub>4</sub>DBN] cation played the role of stabilizer of the carbamate intermediates. Finally, the oxazolidinones were formed through intramolecular nucleophilic attack to regenerate catalyst **14**.

#### 4.6. Additional reactions

The use of [PEG-<sub>1000</sub>-DAIL][BF<sub>4</sub>] (**10a**) together with ferric sulfate has been reported for hydrolysis reactions.<sup>[39]</sup> Various starting materials were used, including halides, epoxides, and esters. The reaction conditions were tested for the hydrolysis of 1-(chloromethyl)-4-methoxybenzene with water in a thermoregulated system composed of [DBN-

the leaving group of an organic molecule, as shown in Scheme 25. This reaction was also observed in the case of a base-sensitive substrate. This is an important process in medicinal chemistry in the area of  $^{18}\text{F}$  radiopharmaceutical research involved in positron emission tomography (PET).

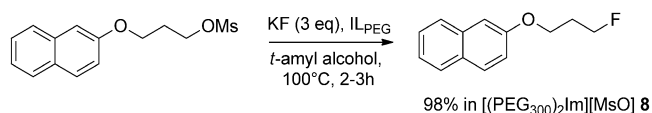
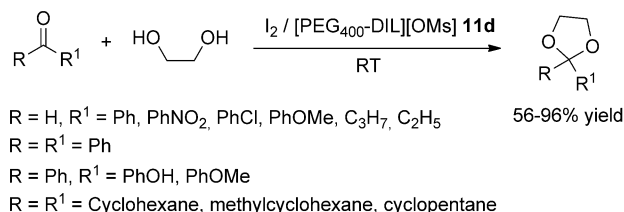
Another application concerns the development of a method for the protection of carbonyl compounds catalyzed by iodine in a similar IL, as described by Cai and Ren (Scheme 26).<sup>[45]</sup> This reaction was performed in a thermoregulated biphasic system composed of [PEG-<sub>400</sub>-DIL][OMs] (**11d**)/toluene. The temperature-dependent biphasic system was used for the iodine-catalyzed protection of carbonyl compounds. The reaction of ben-



**Scheme 24.** Hydrolysis reactions in [PEG<sub>1000</sub>-DAIL][BF<sub>4</sub>] (**10a**).

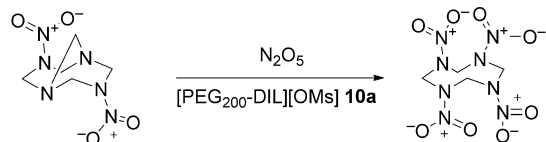
( $\text{CH}_2$ )<sub>4</sub>DBN] (**10a**) and toluene at 100 °C. Various metallic salts were tested (copper, zinc, manganese, cadmium, and iron). Ferric sulfate produced the best results with a quantitative yield of hydrolyzed products. Catalyst **10a** could be recovered and used again in further cycles. This reaction was then extended to epoxides and esters (Scheme 24).

In 2011, Kim et al. described a nucleophilic fluorination reaction performed in IL<sub>PEG</sub>.<sup>[34]</sup> These ILs favored the reaction because the Im salt core could have phase-transfer catalyst-like activity: the PEG moiety acted as a Lewis base toward the metal cations, making the fluoride “free” and active. Indeed, dihexaethylene glycol imidazole [(PEG<sub>300</sub>)<sub>2</sub>Im][MsO] (**8**) was efficient in catalyzing the reaction of a fluoride salt to substitute

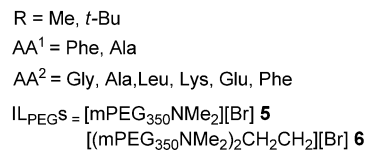
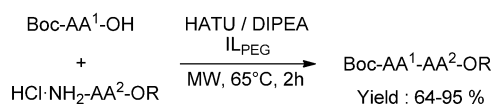
**Scheme 25.** Fluorination reaction.**Scheme 26.** Protection of carbonyl compounds.

zaldehyde and ethylene glycol was also examined with other IL<sub>PEGs</sub>: [PEG<sub>200</sub>-DIL][OMs] (**11a**; 80% yield), [PEG<sub>400</sub>-DIL][OMs] (**11d**; 83% yield), [PEG<sub>1000</sub>-DIL][OMs] (**11e**; 79% yield), [PEG<sub>2000</sub>-DIL][OMs] (**11f**), and [PEG<sub>4000</sub>-DIL][OMs] (**11g**). PEGs with higher molecular weights, such as PEG<sub>2000</sub> and PEG<sub>4000</sub>, remained in the solid state at room temperature and required higher reaction temperatures to melt and higher stirring rates for efficient mass transport.

Zhi et al. reported the synthesis of the military explosive HMX, which has limited applications owing to its high cost.<sup>[37]</sup> The synthesis of HMX was performed with conventional reagents, but the results showed that a combination of [PEG<sub>200</sub>-DIL][OMs] (**10a**)/N<sub>2</sub>O<sub>5</sub> in HNO<sub>3</sub> allowed a 61% yield of the expected product to be achieved, as shown in Scheme 27.

**Scheme 27.** Synthesis of the explosive HMX.

Colacino et al. reported the use of IL<sub>PEGs</sub> to carry out peptide syntheses.<sup>[32]</sup> Alkylammonium monocationic [mPEG<sub>350</sub>-NMe<sub>2</sub>][Br] (**5**) and dicationic [(mPEG<sub>350</sub>-NMe<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>][Br] (**6**) were used as solvents in the synthesis of dipeptides under microwave irradiation. Different coupling reactions were performed in **5** at 65 °C, under microwave irradiation, for 2 h, with 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) as a coupling agent in the presence of diisopropylethylamine (DIPEA; 4 equiv). Moderate to good yields of dipeptides (64–95%) were obtained after simple workup (Scheme 28). The desired peptides were recovered by adding water and diethyl ether to the crude reaction mixture; this reduced the viscosity of the reaction mixture. Chromatographic purification of the dipeptides was not necessary and unreacted starting material and coupling agents were

**Scheme 28.** Synthesis of dipeptides in IL<sub>PEG</sub>.

retained in the IL<sub>PEG</sub> phase. Moreover, traces of diketopiperazine byproducts could not be detected in either the final product or the IL phase. The synthesis of Boc–Phe–Ala–OMe, which was obtained in 76% yield, was also conducted in dicationic **6**.

## 5. Comparison of IL<sub>PEGs</sub> with ILs

As described in previous sections, the structure, and consequently, some properties of IL<sub>PEGs</sub> are different from more “classical” ILs, including their use as solvents in organic synthesis. Nevertheless, it is difficult to provide a close comparison of results because, in most studies, when IL<sub>PEGs</sub> are used as solvents comparative data with classical ILs are not reported. In this section, we describe the important features displayed by IL<sub>PEGs</sub> and those that arise from the presence of the PEG skeleton in these molecules.

### 5.1. Complexation of the polymeric backbone/stabilization of NPs

It has long been known that the influence of PEG on the outcome and speed of many types of organic reactions is very strong and either promotes or slows reactions through solvent or complexation effects<sup>[5,6]</sup> because of the presence of the polyoxygenated backbone. Consequently, IL<sub>PEGs</sub> also modulate these effects because of the presence of PEG chains. This is considerably less the case with classical ILs, for which most of the modulation is attributable to the nature of the cation and/or the anion. One can cite, for example, the crown ether effect in which the ether oxygen atoms are able to chelate a cation or a proton and enhance or reduce their reactivities. For example, the copper-catalyzed Huisgen cycloaddition is described in Section 4.4.3 in which the use of IL<sub>PEGs</sub>, compared with classical ILs, provides a chelating medium and avoids the necessity for an additional nitrogen ligand and yields good results regarding the regioselectivity.<sup>[73]</sup> Another example, this time of Brønsted acidity, is presented in Section 4.6. Acid-catalyzed MCRs are described in this section. The IL<sub>PEGs</sub> contain a sulfonic acid, the acidity of which is increased because of the structure of the IL<sub>PEGs</sub>; this results in an enhancement of the reactivity and better efficiency of the reaction.<sup>[41]</sup>

Another difference of transition-metal-catalyzed reactions is the simple way through which PEG stabilizes metallic NPs, starting from metals or metallic salts in the presence of reduc-



ing agents. Although classical ILs may stabilize NPs, the presence of a polymer enhances this property through steric stabilization. This is all the more the case if PEG in the IL<sub>PEG</sub>s presents a free hydroxyl group. In this case, the NPs can be easily obtained during the course of the reaction and the redox process involves the simultaneous reduction of the metal precursor, suspended in the IL<sub>PEG</sub>s, and oxidation of the polyol backbone of the solvent. The IL<sub>PEG</sub>s act not only as the reaction solvent but also as a reducing agent and stabilizer to limit particle growth and prevent their agglomeration and sintering. Examples were provided in Section 4.4, in which metal-catalyzed transformations were described that generated metallic NPs in some cases. In Section 4.4.2, regarding rhodium chemistry, it is noteworthy that the use of IL<sub>PEG</sub>s not only provided a medium for the generation of NPs, but also avoided the leaching of the metal in the case of recycling by precipitation.

For organocatalysis, in one example (Section 4.5) the importance of the influence of the IL as an acid or a base was described. In this case, some IL<sub>PEG</sub>s presented a neutral pH and ensured a good conversion in the reaction but with poor *ee*. Finally, a more classical IL was preferred for this transformation.

## 5.2. Reaction processes

The presence of PEG in an IL may facilitate the process of a reaction, namely the recovery of the product. In a classical way, most IL<sub>PEG</sub>s are soluble in water and extraction of the product in an organic solvent after dilution with water can be considered. Another approach would consist of precipitating the IL<sub>PEG</sub>s if the PEG chains are long enough to impose their solubility properties and recovering the product in the filtrate after filtration.

A more original and practical way to process the reaction is to take advantage of the thermomorphic properties of some of the IL<sub>PEG</sub>s. As already discussed in the case of [PEG-DAIL][X] solvents **10**, in the presence of a suitable organic solvent, they form a temperature-dependent biphasic system with a miscibility temperature ( $T_m$ ) that strictly depends on the intrinsic characteristics of the selected [PEG-DAIL][X]. At room temperature ( $T < T_m$ ), the system is biphasic: IL<sub>PEG</sub> (containing the catalysts) is immiscible with the upper organic phase (*n*-heptane, toluene, PM, methylcyclohexane, cyclohexane/isopropanol) containing the substrate (Figure 3a). Upon heating ( $T > T_m$ ), the system becomes monophasic and the reaction can proceed homogeneously (Figure 3b). At the end of the reaction, upon cooling to room temperature ( $T < T_m$ ), the system switches back to two phases again (Figure 3c).

By simple phase separation, the IL<sub>PEG</sub> phase (containing the catalyst) can be separated from the organic phase containing the product and reused in subsequent reaction runs. This so-called "monophase reaction/two-phase separation" system incorporates high catalytic efficiency, improved product isolation, catalyst recovery, good recyclability, and operational simplicity.

As already detailed in the case of the cycloaddition of CO<sub>2</sub> with epoxides (Scheme 21) in the presence of aziridines (Scheme 23), the presence of a polyether chain in the IL structure allows solubilization of the gas in the reaction medium,

which is favored by the CO<sub>2</sub>-philicity of the polyether linkage. The cycloaddition of epoxides is commonly performed at high pressure, which is not suitable from an economical point of view and poses safety concerns. This problem is efficiently solved by using IL<sub>PEG</sub> to activate CO<sub>2</sub> to allow it to operate under mild conditions, at low pressure (preferably at 0.1 MPa), and without the need for additional solvents, co-catalyst supports, or metals.

## 6. Toxicity Studies

Since interest increased in ILs 15 years ago, they have been labeled as a "green and eco-friendly alternative" to traditional volatile organic solvents (VOSs) because of their less hazardous synthesis; negligible vapor pressure, which limits their diffusion into the atmosphere and does not contribute to air pollution; low flammability; ease of containment; and so forth, as well as their potentially lower (eco)toxicity. These assumptions, based on a very narrow view of what "green" really is, do not take into account the potential environmental hazards of ILs. Their biodegradability and their toxicity to aquatic and terrestrial ecosystems, owing to their solubility in water, and their possible dispersion into aquatic systems is a matter of concern.

Recent studies on different aquatic species<sup>[77]</sup> demonstrated that IL toxicity was directly related to their hydrophobicity/lipophilicity and their aromatic character. This suggests that, as for TSILs designed to achieve specific properties for special applications, it is also possible to extend this concept to design inherently environmentally safer ILs by manipulating their chemical structures in a "case-to-case study". However, all studies reported nowadays in the field<sup>[77,78]</sup> that are related to their toxicity at different levels of biological complexity (enzymes, bacteria, algae, rat and human cell lines, duckweed, and invertebrates) refer to ILs without polyether (PEG) chains in the structure and only spread data are available for IL<sub>PEG</sub>s. For this reason, it is not possible, on the basis of actual knowledge, to unambiguously draw conclusions on their toxicity and biodegradability profiles. However, while waiting for future studies devoted to clarifying these aspects and broadening their scopes, the examples already reported can be useful in opening up a new perspective for further studies.

In an interesting study,<sup>[79]</sup> some alkyl Im, pyridinium, and Pyr ILs and some ammonium polyether ILs were evaluated for their acute toxicity and histological damage towards zebra fish (*Denio rerio*). Their lethal effect was evaluated after 96 h exposure at a concentration limit of 100 mg L<sup>-1</sup>. Although **19** and **20** were not toxic, mortality was observed for **4** [lethal concentration (LC<sub>50</sub>) of 5.9 mg L<sup>-1</sup>; Figure 4]. This value is remarkably low compared with those obtained with other solvents, such as methanol (up to 29400 mg L<sup>-1</sup>), dichloromethane, acetonitrile (> 100 mg L<sup>-1</sup>), and aniline (up to 100 mg L<sup>-1</sup>), and indicates the high toxicity of **4**. Moreover, the histological alterations induced by **4** at the level of secondary gill lamellae are, as expected, attributable to its action on biological membranes as a cationic surfactant,<sup>[80,81]</sup> increasing membrane permeability to external ions and modifying the properties of the lipid bilayer.

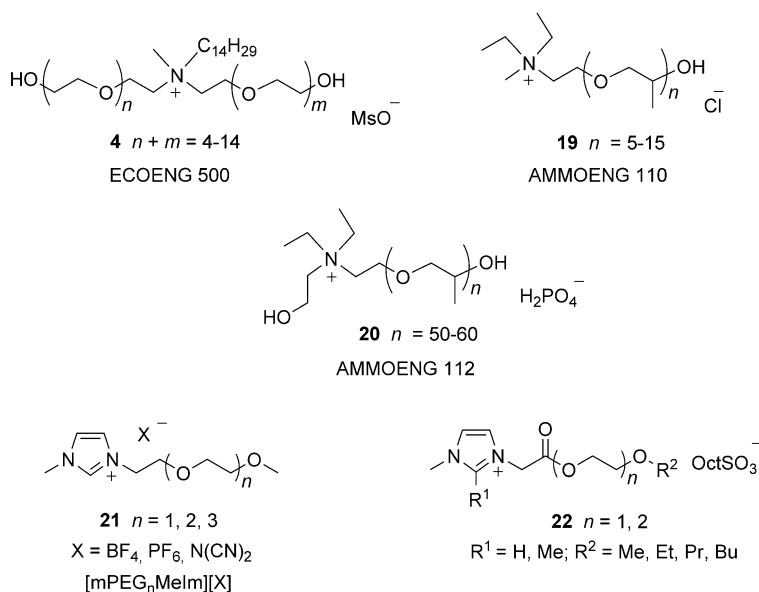


Figure 4. Polyether-based ILs.

Studies concerning PEG-based ILs clearly show that their effects are strictly related to their chemical structure. For example, the  $\text{LC}_{50}$  is  $> 100 \text{ mg L}^{-1}$  for alkyl Im, pyridinium, and Pyr ILs and they are not highly toxic for zebra fish. The ILs [mPEG<sub>100</sub>Melm][X] (**21**;  $n = 1$ ,  $X = \text{BF}_4, \text{PF}_6$ ) were also evaluated for their toxicity towards two colon carcinoma, HT-29 and CaCo-2, cell lines.<sup>[82]</sup> Different from their homologues with alkyl substituents on the Im cation, they proved to be nontoxic in the concentration range used. The toxicity of [mPEG<sub>n</sub>Melm][X] (**21**;  $n = 1, 2, 3$ ,  $X = \text{BF}_4, \text{N}(\text{CN})_2$ ) was also evaluated on the crustacean *Daphnia magna* and on the bacterium *Vibrio fischeri*. The inhibition of the activity of acetylcholine esterase (AChE) was studied because this enzyme is often a target for environmental contaminants. In the crustacean *D. magna*, salts with the  $[\text{BF}_4]$  anion were slightly, but consistently and significantly, more toxic than the corresponding  $\text{N}(\text{CN})_2$  salts, with a tenfold reduction in toxicity for longer polyether chains. The parent [BMIm][X] IL is markedly the most toxic ( $\text{EC}_{50} = 0.05 \text{ mM}$ ) relative to polyether cations **21**, which are not significantly different from each other ( $\text{EC}_{50} = 0.08\text{--}0.65 \text{ mM}$ ). The data show that the first oxygen atom introduced in the side chain of the cation is the major contributor to a reduction in toxicity. Increasing the number of oxygen atoms does not further reduce the toxicity. On the contrary, for the bacterium *V. fischeri*, the toxicity of [mPEG<sub>n</sub>Melm][X] (**21**;  $n = 1, 2, 3$ ,  $X = \text{BF}_4, \text{N}(\text{CN})_2$ ) increased with the size of the polyether chain; [mPEG<sub>150</sub>Melm][ $\text{N}(\text{CN})_2$ ] (**21**;  $n = 3$ ) was the most toxic ( $\text{EC}_{50} = 0.45 \text{ mM}$ ), even more than alkyl [BMIm][ $\text{N}(\text{CN})_2$ ] ( $1.3 \text{ mM}$ ). The bacterium *V. fischeri* is sensitive to chain elongation but not to anion species, which is opposite to what was observed in the crustacean *D. magna*. Oxygenated cation salts **21** do not inhibit the activity of AChE at a concentration  $1 \text{ mM}$  regardless of the anion and the number of oxyethylene units present in the side chains.

The different toxicity profiles displayed by **21** in bacterial cell lines (*V. fischeri*) and on the crustacean *D. magna* clearly in-

dicate that the evaluation of the environmental impact and greenness of ILs is not a trivial task and suggest a species-dependent mechanism of action. Seven strains of bacteria (Gram positive and Gram negative) were used to assess the antimicrobial activity of IL<sub>PEGs</sub> **22**.<sup>[83]</sup> Relative to Im salts with long alkyl chains, those with ether or polyether chains exhibited no toxicity, even at a concentration as high as  $20 \text{ mg mL}^{-1}$ . The biodegradability ( $\text{CO}_2$  headspace test) was also investigated. IL<sub>PEGs</sub> **22** with butoxy or propoxy terminal groups are readily biodegradable (at least 60% over 28 days), whereas those with methoxy or ethoxy terminal substitutions are less biodegradable (between 55 and 59%).

## 7. Summary and Outlook

In the last decade, ILs, including those containing polyether substituents, have very often been considered as a green alternative to VOSs, more particularly chlorinated hydrocarbons. Because of their unique properties (no vapor pressure, high thermal stability, nonflammability, high polarity, mechanical and electrochemical stability, electrical conductivity, high polarity, and ability to dissolve both organic and inorganic substrates), they have often been selected as alternative and valuable reaction media for various organic transformations. However, before their inclusion into the toolbox of the green chemist, eco-friendly syntheses for their preparation and their isolation need to be investigated and more extensive and deep studies should be addressed to determine general trends in their toxicity, biodegradability in living organisms, and environmental persistence. On the other hand, in the context of green credentials, the use of PEG-based IL (or ILs in general) is appropriate when leading to a cleaner and greener chemical process (large increase in reactivity and selectivity) or when the reactions have only been demonstrated to work in the IL<sub>PEG</sub> environment. However, in contrast to their parent compounds, ILs and PEGs, IL<sub>PEGs</sub> have been considerably less investigated and more research needs to be performed to shed light on their full potential and versatility in the field of organic syntheses and catalytic processes.

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