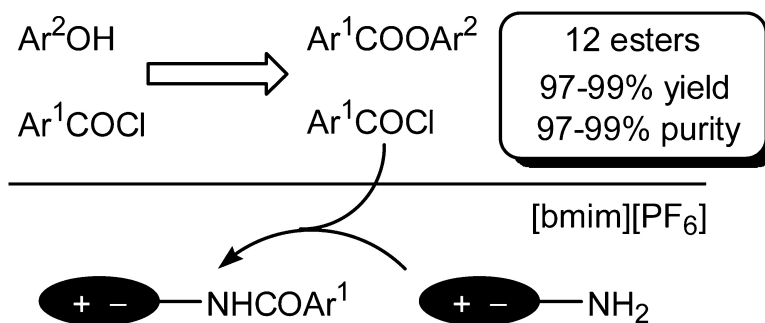


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Amino-Functionalized Ionic Liquid as A Nucleophilic Scavenger in Solution Phase Combinatorial Synthesis

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A new functionalized ionic liquid, 1-aminoethyl-3-methylimidazolium hexafluorophosphate was synthesized from 1-methylimidazole and 2-bromoethylamine hydrobromide. This ionic liquid was found to be an efficient scavenger for removing excess electrophiles, such as benzoyl chloride, *p*-toluenesulfochloride, phenyl isothiocyanate, and *p*-chlorophenyl isocyanate, in a solution-phase parallel synthesis. The resulting ionic liquid derivatives can be separated directly from the reaction mixture. Desired products were obtained with high purity. Only 1.5–2.0 equiv of this scavenger was needed with a sequestration time of less than 35 min. In addition, the used ionic liquid can be regenerated and recycled several times without significant loss of activity.

Introduction

In recent years, solution-phase chemistry has become a leading discovery and optimization tool for library generation in drug discovery.¹ It offers many advantages over solid-phase approaches, such as unlimited scale-up potential, easy manipulation, and reduction in validation time. However, in solution-phase syntheses, rapid purification or isolation of desired compounds from a reaction mixture is often a challenge. The application of scavengers can significantly accelerate such a purification or isolation process in a multistep sequence.² Polymer-supported scavengers are reactive species associated with polymeric supports that can selectively quench or sequester reaction byproducts or remove excess or unreacted starting materials. They can be removed simply by filtration after scavenging. However, these resin-bound scavengers have several limitations. First, overall reaction rates are low. This is mainly due to hindered access to functional groups within the resin core, especially in high-loading resins, and the biphasic nature of the reaction systems that contain polymer-bound entities. Second, solvent selection for both the synthetic and scavenging steps is dictated by the swelling requirements of the resin matrix that typically require a large volume of solvent. Third, a significant amount of excess polymer-supported scavenger is required, and reactions are not readily scaleable for the resynthesis of active compounds. These limitations prevented wide adaptation of such resin-based scavengers in medicinal chemistry. To address these limitations, a variety of new scavengers were developed in recent years. These include fluorine-phase³ and aqueous-phase⁴ scavengers as well as polyaromatic⁵ and PEG-supported scavenger reagents.⁶ These newer scavengers, however, have their own drawbacks, such

as costliness, relatively low loading, and the need for large amounts of solvents.

The use of ionic liquids has recently received more and more attention as eco-friendly reaction media in organic synthesis. These ionic liquids pose several unique properties, such as negligible vapor pressure, no miscibility with nonpolar solvents, reasonable thermal and chemical stability, and excellent electrical conductivity.⁷ Owing to these unique properties, the ionic liquids are being used as attractive alternatives to traditional solvents and liquid–liquid extractions. Recently, more attention has been focused on the synthesis of new ionic liquids with functional groups, so-called “task-specific” ionic liquids, and their applications in chemical research.⁸

In this paper, we hope to contribute to the field of combinatorial chemistry by combining, for the first time, the ease of removal feature of polymeric scavengers with the immiscibility (with nonpolar organic solvents) feature of ionic liquids in solution-phase combinatorial synthesis. In particular, we will describe the synthesis of a functionalized ionic liquid, 1-(2-aminoethyl)-3-methylimidazolium hexafluorophosphate [2-aemim][PF₆], and its application in scavenging excess electrophiles (Figure 1), such as benzoyl chloride, *p*-toluenesulfochloride, phenyl isothiocyanate and *p*-chlorophenyl isocyanate, in solution-phase synthesis.

The basic idea here is to replace the polymeric core of the scavenger reagents by a functionalized ionic liquid. In comparison with the polymer-assisted scavenging, this “beadless” approach has several outstanding advantages, including a high active site/material ratio (high loading), time saving, easy monitoring with GC or HPLC, minimal solvent requirement and waste generation, and unlimited scale-up potential. It is also worth noting that the used ionic liquids could be regenerated and recycled at least three times without significant loss of activity.

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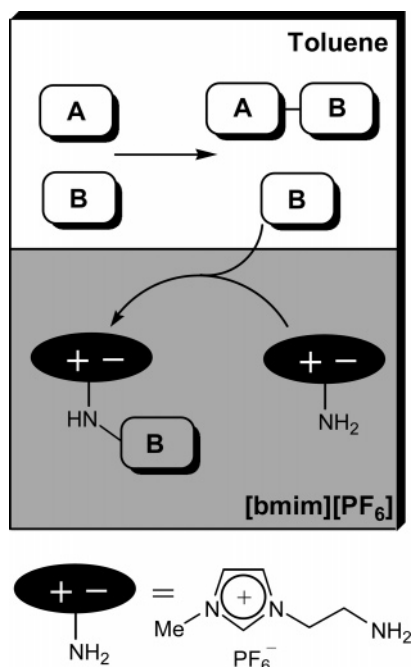
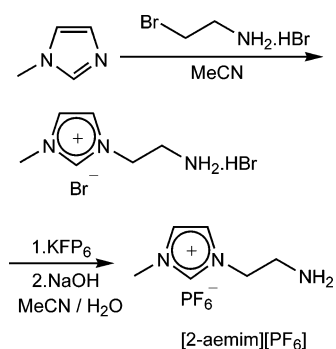


Figure 1.

Scheme 1



Results and Discussion

A novel amino-functionalized ionic liquid [2-aemim][PF₆] was synthesized from commercially available 1-methylimidazole and 2-bromoethylamine hydrobromide, followed by recrystallization, anion exchange with KPF₆, and a neutralization step (Scheme 1).

After filtration of the salts, the solvents were removed under vacuum, and the residue was washed by chloroform and ethyl ether. The product (67% yield) was verified by IR and ¹H NMR. Some physical data of [2-aemim][PF₆], such as miscibility and the interfacial tensions between [2-aemim][PF₆] and several organic solvents, are listed in Table 1. The relatively large difference in special gravity and high interfacial tension between [2-aemim][PF₆] and organic solutions will tend to promote phase separation after scavenging.

To demonstrate the utility of [2-aemim][PF₆] in scavenging electrophiles, we began with a solution of *p*-toluenesulfochloride (0.10 g, 0.53 mmol) in toluene (5 mL) as a model. Unfortunately, the ionic liquid became very viscous during scavenging, leading to a relatively long purification time. For instance, up to 9 h was required to sequester *p*-TsCl (0.10 g, 0.53 mmol) with 2.0 equiv of [2-aemim][PF₆] at room temperature (monitored by GC). Interestingly, we found

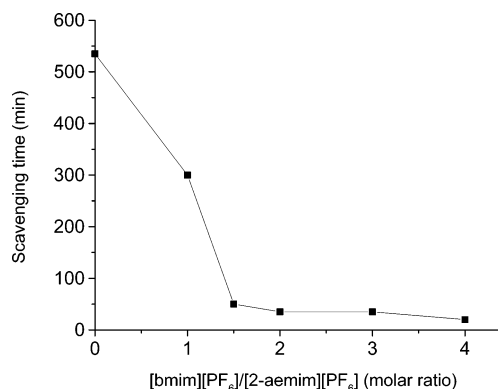


Figure 2. Influence of the molar ratio of [bmim][PF₆]/[2-aemim][PF₆] on scavenging time.

Table 1. Some Physical Data of As-Synthesized Ionic Liquid (25 °C)

viscosity (N·m ⁻² ·s)	195.3
density (g·cm ⁻³)	1.56
surface tension (dyn·cm ⁻¹)	52.9
interfacial tension (dyn·cm ⁻¹)	
toluene	31.9
EtOAc	30.9
EtOH	18.2
miscibility	
H ₂ O	miscible
DMF	miscible
MeOH	miscible
MeCN	partially miscible
EtOH	partially miscible
CHCl ₃	immiscible
EtOAc	immiscible
toluene	immiscible

that the addition of a conventional ionic liquid, [bmim][PF₆] (1-butyl-3-methylimidazolium hexafluorophosphate), into the reaction mixture caused a dramatic enhancement in the sequestration.

Figure 2 shows that the scavenging time decreased sharply with an increase in the molar ratio of [bmim][PF₆] to [2-aemim][PF₆] until it reached 1.5, beyond which the scavenging time became nearly constant. As such, a molar ratio of 2 was chosen in subsequent investigations from the point of view of efficiency and economy. At that ratio, it only took 35 min to sequester all of the *p*-TsCl in toluene in the model system. The addition of [bmim]PF₆ probably benefited the scavenging process in two ways by increasing the solubility of electrophile in ionic phase and decreasing the viscosity of the ionic phase, thereby enhancing the mass transfer across the interface.

Two of the drawbacks of resin-supported scavengers are their high cost and the need for a large excess amount in order to clean up a typical reaction product, even in small-scale reactions. In our protocol, the optimal molar ratio of [2-aemim][PF₆]/excess reagent in scavenging was also investigated. In a model study, phenyl isothiocyanate (0.10 g, 0.75 mmol) in toluene (5 mL) was sequestered with different amounts of [2-aemim][PF₆]. In all cases, 2-fold [bmim][PF₆] was added to dilute [2-aemim][PF₆] as described above. As shown in Figure 3, only 1.5 equiv of [2-aemim][PF₆] provided a sufficiently short sequestration duration.

In addition, ionic liquid scavengers do not suffer from the

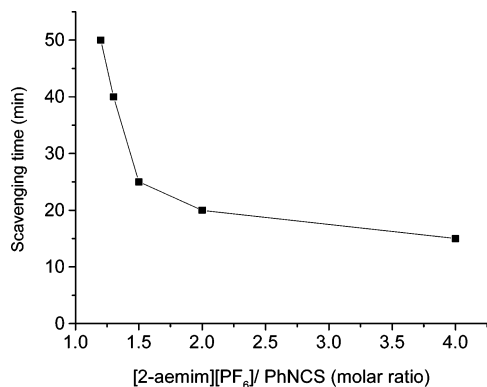
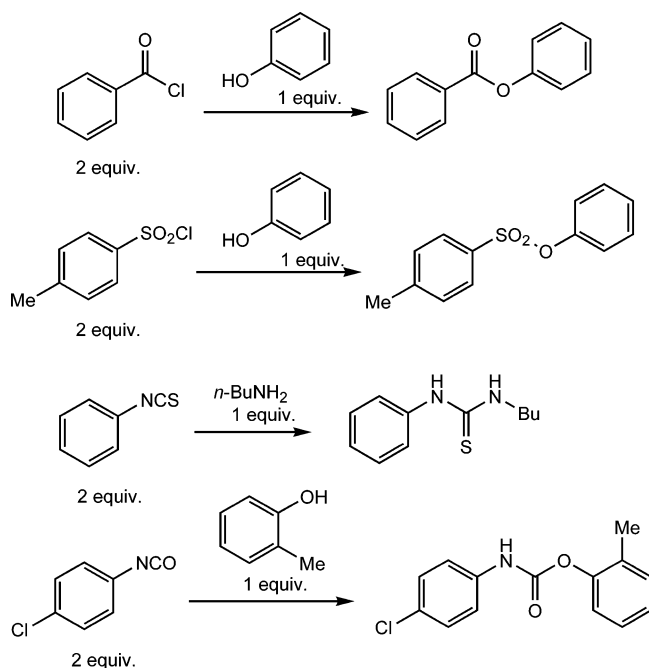


Figure 3. Influence of the molar ratio of [2-aemim][PF₆]/phenyl isothiocyanate on scavenging time.

Scheme 2



extensive mechanical degradation experienced by polymer-supported scavengers after operating at high agitation rates.

After demonstrating the feasibility of our protocol for removal of electrophiles in the model systems, we decided to apply [2-aemim][PF₆] to capture excessive electrophiles from reaction mixtures in practical solution-phase synthesis. Four “proof of concept” reaction systems, benzyl chloride (2.0 equiv)/phenol, *p*-toluenesulfochloride (2.0 equiv)/phenol, phenyl isothiocyanate (2.0 equiv)/*n*-butylamine, and *p*-chlorophenyl isocyanate (2.0 equiv)/*o*-cresol, were selected as representative examples (Scheme 2).

The results are listed in Table 2, which shows good yields (97%) and excellent purity (98%) of the desired products. In the cases of benzyl chloride or *p*-toluenesulfochloride

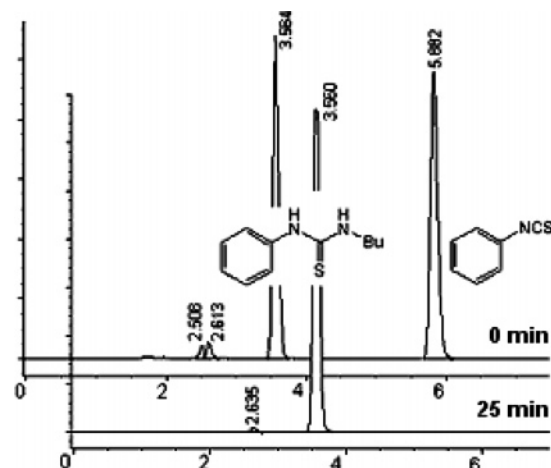


Figure 4. HPLC analysis of reaction mixture before and after scavenging.

(Table 2, entries 1 and 2), 2.0 equiv of [2-aemim][PF₆] to the remaining reagents to be scavenged was employed due to the release of hydrogen chloride in the reactions, although only 1.5 equiv of [2-aemim][PF₆] was required to achieve satisfactory scavenging efficiency in reactions with excessive isothiocyanate or isocyanate (Table 2, entries 3 and 4). The ionic liquid phase was removed by decantation, followed by extraction three times. The organic solvents used in extraction were found to influence the yield of the final product to a certain extent. Among the screened solvents, including toluene, diethyl ether, hexane, cyclohexane, tetrachloromethane, and others, a mixture of CH₂Cl₂ and Et₂O at a volume ratio of 1:2 (CH₂Cl₂/Et₂O) produced the highest yield. No ionic liquids were detected in the combined organic phase by HPLC. As an example, phenyl isothiocyanate (2.00 mmol) was allowed to react with *n*-butylamine (1.00 mmol) in 5 mL of toluene at room temperature. At the completion of the reaction, as monitored by HPLC for the depletion of amine, the reaction mixture was treated with [2-aemim][PF₆] (1.50 mmol) in [bmim][PF₆] (3.00 mmol) at ambient temperature for 25 min (Table 2, entry 3). The isothiocyanate was no longer detectable in the mixture by HPLC (Figure 4). After decantation and further extraction with CH₂Cl₂/Et₂O (1:2 v/v), the combined organic phase was distilled under vacuum, leading to a product in 97% yield and 99% purity (HPLC). The product was characterized by ¹H NMR. In contrast, the yield of the target product was only 91% when the ionic liquid phase after scavenging was extracted with toluene. The difference in yield was due to the different partition of the product between the ionic liquid phase and various organic solvents.

To further demonstrate the applicability of a ionic liquid-type scavenger in solution-phase parallel synthesis, a 12-member model library of aromatic esters was constructed.

Table 2. Electrophile Trapping from Reaction Mixture

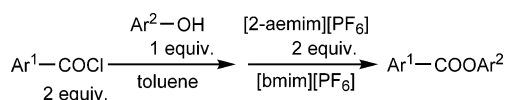
entry	substrate	electrophile (excess)	<i>t</i> (min)	yield (%)	purity (%)
1 ^a	C ₆ H ₅ OH	benzoyl chloride	25	97	99
2 ^a	C ₆ H ₅ OH	<i>p</i> -TsCl	35	99	99
3 ^b	NH ₂ (CH ₂) ₃ CH ₃	phenyl isothiocyanate	25	97	99
4 ^b	<i>o</i> -CH ₃ C ₆ H ₄ OH	4-chlorophenyl isocyanate	30	98	98

^a Purity was determined by GC. ^b Purity was determined by HPLC.

Table 3. Electrophile Trapping from Solution Phase Parallel Synthesis of Aromatic Esters

entry	electrophile (excess)	substrate	<i>t</i> (min)	yield (%)	purity ^a (%)
1	3,5-dinitrobenzoyl chloride	phenol	30	98	99
2	3,5-dinitrobenzoyl chloride	<i>o</i> -cresol	30	99	99
3	3,5-dinitrobenzoyl chloride	2,4-dichlorophenol	30	97	98
4	<i>o</i> -methylbenzoyl chloride	phenol	25	97	98
5	<i>o</i> -methylbenzoyl chloride	<i>o</i> -cresol	25	98	99
6	<i>o</i> -methylbenzoyl chloride	2,4-dichlorophenol	25	99	98
7	<i>o</i> -fluorobenzoyl chloride	phenol	25	98	99
8	<i>o</i> -fluorobenzoyl chloride	<i>m</i> -nitrophenol	25	97	99
9	<i>o</i> -fluorobenzoyl chloride	2,4-dichlorophenol	25	99	97
10	<i>p</i> -fluorobenzoyl chloride	phenol	25	98	99
11	<i>p</i> -fluorobenzoyl chloride	<i>m</i> -nitrophenol	25	97	97
12	<i>p</i> -fluorobenzoyl chloride	2,4-dichlorophenol	25	98	98

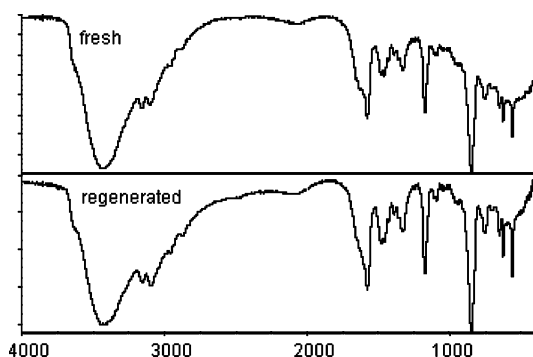
^a Purity was determined by GC.

Scheme 3

Four substituted benzoyl chlorides (2 equiv) were treated with three phenols (1 equiv) for 30 min, and the excess acyl chlorides were sequestered with [2-aemim][PF₆]. As shown in Table 3, high yields (97%) and purity (97%) of products were obtained. The success in the four “proof of concept” reaction systems and the 12-member model library of aromatic esters encourages us to believe that, in principle, the amino-functionalized ionic liquid can be a suitable scavenger for other kinds of electrophiles, as well.

Although recycling and reuse of the supporting materials in combinatorial chemistry is an important subject from the perspectives of economy and environment, little attention has been paid in this area. Marshall resin⁹ and Tentagel resin¹⁰ have been proved recyclable and reusable in solid-phase organic synthesis. Recently, Guinó and co-workers demonstrated the possibility of recycling and reusing a polymer-supported scavenger for amine sequestration.¹¹ In this study, we also investigated the reusability of an IL-based scavenger. Since the amino group on the ionic liquid is regenerated after hydrolysis, the used ionic liquid is expected to be functional again.

The regeneration of the ionic liquid [2-aemim][PF₆] used in *p*-TsCl/PhOH system (Table 2, entry 2) was selected to demonstrate the reusability concept. No significant difference was observed after comparing the FTIR (Figure 5) and ¹H NMR spectra of the regenerated ionic liquid with that of the freshly prepared. To illustrate the reusability of the ionic

**Figure 5.** IR spectra of fresh and regenerated scavenger.**Table 4.** Reusability of [2-aemim][PF₆] as Scavenger in the Reaction of *p*-Toluenesulfochloride and Phenol

run	<i>t</i> (min)	phenyl <i>p</i> -toluenesulfonate		recovery of [2-aemim][PF ₆] (%)
		yield (%)	purity (%)	
1	35	98	99	91
2	35	97	99	92
3	40	98	98	90

liquid scavenger, the regenerated [2-aemim][PF₆] (without addition of fresh scavenger) was reused three times with comparable activity (35 min, 90% recovery; 35 min, 91% recovery; 40 min, 90% recovery) in the demo reaction between *p*-toluenesulfochloride and phenol (Table 4). These examples demonstrate clearly that this new process delivered the desired product with comparable yields and purities and preserved the activity of the scavenger after the regeneration process.

Conclusion

In summary, the results described here illustrate a novel scavenging strategy for trapping electrophiles in a solution-phase reaction that utilizes an amino-functionalized ionic liquid. There are several advantages using this strategy, namely, favorable reaction kinetics, high load capacity, short sequestration duration, low dosage, reusability, ease of scale-up, broad solvent selection, and ease of monitoring the reaction progress. In addition, excellent chemical yields and purities are obtained. The method is nicely suited for robotic execution. Further development of functionalized ionic liquids as a synthetic tool is currently under investigation and will be reported in due course.

Experimental Section

General. IR spectra were obtained on a Nicolet Nexus 470 FT-IR instrument (KBr tablet). ¹H NMR spectra were recorded on a Bruker AM-500 (500 MHz) instrument with D₂O or CDCl₃ as solvent. Viscosity was measured using an Ubbelohde viscometer. Surface tension and interfacial tension were measured using DCA 315. GC analysis was performed on a Hewlett-Packard HP6890 plus instrument. HPLC analysis was performed on a Hewlett-Packard 1100 instrument. GC/MS was recorded on a HP 6890 apparatus with HP 5973 mass selective detector.

Synthesis of Ionic Liquid [2-aemim][PF₆]. A mixture of 1-methylimidazole (8.20 g, 0.10 mol) and 2-bromoethylamine hydrobromide (20.50 g, 0.10 mol) in 50 mL of acetonitrile was heated with stirring at 80 °C for 4 h. On completion, the solvent was removed by distillation, and the residue was recrystallized (ethanol) to afford the hydrobromide of [2-aemim][Br] as a white solid. The mixture of [2-aemim][Br]·HBr, KPF₆ (18.40 g, 0.10 mol), and 40 mL of CH₃CN/H₂O (1:1, v/v) was left for 24 h at room temperature and then NaOH (4.00 g, 0.10 mol) was added for neutralization. Solvents were evaporated under vacuum. This was followed by the addition of methanol (20 mL) and CHCl₃ (2 mL). The precipitated salts were filtered off, and the solvents were evaporated. The obtained yellow oil was washed successively with chloroform (10 mL × 3) and ether (10 mL × 3). After drying for 6 h under vacuum at 80 °C, the expected ionic liquid was obtained (18.16 g, 67%). IR (KBr): 3430, 3086, 2896, 1581, 1452, 1175, 847 cm⁻¹. ¹H NMR (D₂O, 500 MHz): δ_H 3.25 (m, 2H, NH₂-CH₂), 4.12 (s, 3H, CH₃), 4.49 (t, J₁ = 5.87 Hz, J₂ = 6.08 Hz, 1H, N-CH₂), 4.52 (t, J₁ = 6.07 Hz, J₂ = 6.23 Hz, 1H, N-CH₂), 7.68 (s, 1H, NCH), 7.75 (s, 1H, NCH), 8.63 (s, 2H, NH₂), 8.99 (s, 1H, N(H)CN).

The Use of [2-aemim][PF₆] as Scavenger. Purification in the PhNCS/*n*-BuNH₂ system (Table 2, entry 3) was chosen as a representative example. A solution of phenyl isothiocyanate (0.27 g, 2.00 mmol) and *n*-butylamine (0.07 g, 1.00 mmol) in 5 mL toluene was stirred at room temperature for 6 h (monitored by HPLC). Then a mixture of [2-aemim][PF₆] (0.54 g, 2.00 mmol) with [bmim][PF₆] (0.90 g, 4.0 mmol) was added and the biphasic mixture was stirred at ambient temperature for 25 min. The electrophile-free organic phase was separated from the ionic liquids by decanting, and the ionic phase was then extracted with CH₂Cl₂/Et₂O (1:2 v/v) (10 mL × 3). Distillation of the combined organic phase under vacuum gave the desired substituted thiourea in 97% yield (0.20 g, 99% purity). ¹H NMR (CDCl₃, 500 MHz): δ_H 0.83 (t, J = 7.3 Hz, 7.3 Hz, 3H, CH₃), 1.26 (m, 2H, CH₂-CH₃), 1.51 (m, 2H, CH₂-CH₂-CH₃), 3.58 (d, J = 5.5 Hz, 2H, HN-CH₂), 6.24 (s, 1H, NH-CH₂), 7.25–7.50 (m, 5H, -phenyl), 8.98 (s, 1H, NH-phenyl).

Construction of Model Library: Typical Procedure. A solution of phenol (0.09 g, 1.00 mmol) in 10 mL of toluene was cooled to 0 °C and dosed dropwise with 3,5-dinitrobenzyl chloride (0.46 g, 2.00 mmol). The mixture was stirred at room temperature. On completion as monitored by GC, a mixture of [2-aemim][PF₆] (0.54 g, 2.00 mmol) with [bmim][PF₆] (1.14 g, 4.0 mmol) was added; the biphasic mixture was stirred at ambient temperature for 30 min. The electrophile-free organic phase was separated from the ionic liquids by decanting. The ionic phase was extracted with CH₂Cl₂/Et₂O (1:2 v/v) (10 mL × 3), and the combined organic phase was distilled under vacuum to afford the desired product in 98% yield (0.28 g, 99% purity). MS (GC/MS): *m/z* 288 (M⁺), 195, 149, 103, 75.

Regeneration of [2-aemim][PF₆]. The regeneration of the ionic liquid [2-aemim][PF₆] used in the *p*-TsCl/PhOH system (Table 3, entry 2) was chosen as a representative example. In a typical procedure, used ionic liquid (9.24 g) was placed

in a flask equipped with a condenser, and 15 mL of concentrated hydrochloric acid (37%) and ethanol (20 mL) were added. After refluxed for 3 h, the precipitated hydrochloride of [2-aemim][PF₆] was collected by filtration, and the filtrate was distilled under vacuum. The residue was then added to 20 mL of ethanol; another portion of hydrochloride can also be obtained. Precipitates were combined and washed with ethanol (5 mL × 3), then neutralized with NaOH (0.40 g, 0.01 mol) in H₂O (2 mL). The solvents were distilled under vacuum, and 20 mL of THF was added to separate the ionic liquid from the residue. After removing THF under reduced pressure, 2.44 g (90% recovery) of [2-aemim][PF₆] was obtained. ¹H NMR (D₂O, 500 MHz): δ_H 3.25 (t, J₁ = 6.0 Hz, J₂ = 5.9 Hz, 2H, NH₂-CH₂), 4.08 (s, 3H, CH₃), 4.41 (t, J₁ = 6.0 Hz, J₂ = 5.9 Hz, 2H, N-CH₂), 7.63 (s, 1H, NCH), 7.67 (s, 1H, NCH), 8.63 (s, 2H, NH₂), 8.83 (s, 1H, N(H)CN).

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Supporting Information Available. ¹H NMR spectra of amino-functionalized ionic liquid and products, together with GC or HPLC before and after scavenging. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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