Nitrogen Containing Ionic Liquids: Biodegradation Studies and Utility in Base Mediated Reactions

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Several ILs were prepared in order to study the susceptibility of various cores and substituents to biodegradability using the “CO₂ headspace” test (ISO 14593). Several of the ILs contained tertiary amine substituents and were tested as solvents and reagents for several base mediated processes including Suzuki-Miyaura, Sonogashira, Knoevenagel and Morita-Baylis-Hilman reactions. It was found that although these ILs contain basic functionality, they do not promote base mediated reactions. Density functional theory molecular calculations confirmed that the protonation of these ILs is energetically unfavorable.

Introduction

Ionic liquids (ILs) have become a ubiquitous tool in synthetic,^[1] industrial^[2] and materials chemistry.^{[3],[4]} The ability to easily alter both the organic cation and (in)organic anion provide the opportunity to tailor the solvent to a specific need. Our interest,^[5-8] in addition to others,^[9-11] in the biodegradation of ILs stems from concerns regarding the long term impact of the increasing utility of these species in both industrial and academic settings.

Aerobic biodegradation of carbon containing molecules by activated sludge represents a key component of wastewater treatment, and is responsible for removing the majority of organic contaminants.^[12] Depending on a variety of both physical and chemical properties, including aqueous solubility, volatility and lipophilicity, many organic residues may be physically removed in varying degrees from the bulk sewage during primary treatment. However ILs, due to their extremely low volatility and high stability, are likely to accumulate in the biosphere. It is therefore of great interest to design ILs susceptible to complete biodegradation.

Further to our recent studies probing the biodegradability of pyridinium ILs,^[13] we report herein the synthesis of a number of ILs and a study of their susceptibility to biodegradation. In addition to several pyridinium ILs, other cyclic and acyclic alkyl ammonium ILs were prepared (Fig. 1). Several of these ILs contain tertiary amines, whose basicity we hoped to exploit for synthetic purposes, by using the IL as both solvent and reagent/catalyst. The synthesis and use of basic ILs is well known.^[14,15] Basic ILs have been utilized for several diverse reactions including Heck coupling,^[16] copper free Sonogashira coupling,^[16] Knoevenagel condensation,^[17] condensation reactions to generate heterocycles,^[18-20] transesterification^[21-23] and bromination of alkenes.^[24]

Figure 1.

Results and Discussion

Ionic Liquid Synthesis

The majority of ILs utilized in this study were synthesized using a two-step procedure starting with alkylation at nitrogen using the required alkyl halide followed by anion metathesis using known methodology.^[1] The anion of choice for the majority of the ILs reported herein was the bis(trifluoromethane)sulfonimide (i.e. bistriflimide) anion, as ILs containing this anion tend to have low viscosity, low melting point, high thermal stability, and low water solubility/miscibility,^[1] which are often useful features for organic reactions. A dicyanamide IL was also prepared to probe the effect of increased water miscibility. Though the synthetic sequences were all somewhat straightforward, it was found that each substrate required distinct conditions for optimal alkylation outcomes as described in the experimental section.

The general method for anion metathesis, converting the halide salt to the bistriflimide, was performed by treating the alkyl halide with commercially available lithium bistriflimide in distilled water, followed by extracting the organic soluble IL into dichloromethane. The absence of halide impurities was confirmed using the AgNO_3 precipitate test. The dicyanimide IL was prepared by treatment of the halide salt with silver(I) dicyanamide, prepared from commercially available sodium dicyanamide upon treatment with silver(I) nitrate in water.

Scheme 1.

The pyridinium ILs **1** and **2** have been prepared previously,^[25] however nothing has been reported regarding their biodegradation. We wished to determine the effect of an unsaturated nitrogen substituent on biodegradation, by comparison with other *N*-substituted ILs that have previously shown good biodegradation.^[13] The alkylation of pyridine with both allyl bromide and benzyl bromide was carried out by addition of the alkyl halide at low temperature, as a strong exothermic reaction occurred at room temperature leading to discoloration of the IL product. Following metathesis to the desired bistriflimide salt, both ILs were synthesized in good overall yields. ILs **4** - **6** were synthesized to compare the effect of differing functional groups on a similar core (i.e. basic, neutral and acidic).

IL **3**, containing a *N,N*-diisopropyl substituent on the pendant nitrogen was also prepared as the moiety containing a *N,N*-dimethylamino side chain was prone to nucleophilic displacement of the tertiary amino group on the beta carbon releasing pyridine and led to isolation of dimethylaziridinium chloride after concentration *in vacuo* (Scheme 2). Presence of the *N,N*-

dimethylaziridinium chloride byproduct was confirmed by ^1H NMR spectroscopy (δ 3.44 ppm, s, 6H and δ 4.02 ppm, s, 4H in D_2O). No decomposition was observed in the case of IL bearing the more sterically hindered *N,N*-diisopropyl groups.

Scheme 2.

IL **4** was synthesized from picolyl chloride hydrochloride upon treatment with diethylamine in anhydrous acetonitrile at $-10\text{ }^{\circ}\text{C}$. This reaction afforded a cleaner product when acetonitrile was employed as the reaction solvent (rather than dichloromethane or diethyl ether), with isolation of pure 3-(aminomethyl)pyridine after a simple aqueous workup. Alkylation at the nitrogen in the pyridine ring occurred smoothly using 1-bromobutane. Reaction in this position, rather than the tertiary amine, was confirmed by the characteristic ^1H NMR spectrum shift of the pyridinium ring protons in addition to lack of shift of the benzylic-type methylene signal.

ILs based on other non-aromatic amine-based cores, specifically 1,4-dimethylpiperazine and 1,4-diazabicyclo[2.2.2]octane (DABCO), in addition to simple alkyl ammonium ILs were also synthesized. We did not expect these cores to be very susceptible to biodegradability based on previous studies;^[26] however, it was anticipated that they may be useful in base promoted reactions. Furthermore, alkyl ammonium ILs are becoming widely used in industry particularly as lubricants.^[27] Despite many alkyl ammonium bistriflimide ILs having desirable physical properties, they have been shown to be poorly biodegradable.^{[28],[29]} Hence, we hypothesized that more water miscible alkyl ammonium bistriflimides may be more susceptible to biodegradability in an aqueous environment and therefore prepared ILs **7**, **8** and **9** having increasingly polar substituents for enhanced water solubility.

Mono-alkylation of DABCO proceeded in good yield using either an alkyl chloride at reflux, or by addition of an alkyl bromide at low temperature and stirring at room temperature overnight. Mono-alkylation of the *N,N*-dimethylpiperazine core required use of the less reactive chloroalkane under microwave irradiation conditions, while use of the more reactive iodo- and bromo-alkyl halide resulted in dialkylation of the piperazine ring. In both cases, the hexyl derivative was found to be extremely viscous at room temperature; indeed the IL **12** was solid at room temperature. Surprisingly, homologation by one carbon had a dramatic effect, lowering both the melting point and viscosity (both being liquids at ambient temperature).

Biodegradation Studies

To evaluate the biodegradability of the test ILs, the “CO₂ headspace” test (ISO 14593) was utilized. This method allows the evaluation of the ultimate aerobic biodegradability of an organic compound in an aqueous medium at a given concentration of microorganisms by analysis of inorganic carbon (IC). The test IL, the sole source of carbon (and energy), was added at a concentration of 20 mg C/L to a mineral salts buffer medium. These solutions were inoculated with activated sludge collected from an activated sludge treatment plant, washed and aerated prior to use and incubated in sealed vessels with a headspace of air.

Biodegradation (mineralization to carbon dioxide) was determined by measuring the IC produced in the test bottles in excess of that produced in blank vessels containing inoculated medium only. The carbon dioxide generated during the biodegradation process was determined by using a Total Organic Carbon (TOC) analyzer equipped with a Non-Dispersive Infrared (NDIR) detector. Sodium n-dodecyl sulfate (SDS) was used as the reference substance; the test ran for 28 days and 4 replicates were performed for each IL. The extent of biodegradation was expressed as a percentage of the theoretical amount of inorganic carbon (ThIC) based on the amount of test compound added initially.

Figure 2. Biodegradation data (CO₂ Headspace test) associated with the ionic liquids **1** - **14**. **Table 1.**

Compound number	Biodegradation ^a (%)
1	0±1.7
2	1±0.3
3	0±0.4
4	3±0.5
5	3±1.6
6	60±5.0
7	4±0.3
8	6±0.6
9	3±0.7
10	1±1.2
11	1±1.7
12	0±3.7
13	0±3.2
14	0±3.8

^aIL initial concentration= 20 mg C/L; 95% confidence limits calculated from 4 replicates

Unfortunately, almost all ILs tested showed no significant mineralization under the conditions used in ready biodegradation assessments (Fig. 2), the only exception being IL **6**. This result is consistent with previous studies showing ILs with an ester in the 3-position of the pyridine ring showed good mineralization.^[30] IL **5** has been reported previously to have low susceptibility to biodegradation by *Sphingomonas paucimobilis*.^[31] It is clear that pyridinium ILs containing unsaturated substituents are not susceptible to mineralization, and the increasing polarity of alkyl ammonium ILs had little effect on biodegradability, indeed dicyanamide IL **14**, being completely miscible with water, was not observed to mineralize.

Inhibition tests were performed in order to evaluate inhibition as possible cause or contributory factor to the negligible biodegradation observed for most of the ILs. To evaluate the toxicity of these ILs to the microorganisms responsible for aerobic biodegradation, solutions containing a mixture of the compound and a reference substance (SDS) were tested. Biodegradation percentages for the mixtures of ILs and SDS were calculated based on the theoretical IC yields anticipated from only the reference substance. For all ILs tested, a certain degree of inhibition of the inoculum activity was found (see Table **S5** - Supporting Information). However, the inhibition percentages were lower than the limit commonly accepted to consider inhibitory effects (25%). Although these compounds are slightly inhibitory at the concentration applied in the test, toxicity seems to play a minor role and the lack of degradation is attributable to non-amenability of the organic cations to microbial attack under the conditions of the test.

ILs as Reagents

Given the numerous literature reports describing the use of tertiary amine bases in the Suzuki-Miyaura reaction^[32-35] we envisaged utilizing ILs **3**, **4**, **7** and **13** (Fig. 3) as both solvents and reagents for the reaction.

Figure 3.

Attempts to perform Suzuki-Miyaura couplings in the basic ILs under standard conditions (1 eq. Ar-I, 1.1 eq. Ar-B(OH)₂, 0.1 eq. Pd(PPh₃)₂Cl₂, 5 eq. IL, 90 °C, 1.5 h), resulted in only trace formation of the desired coupled product (Table 1). This result was consistent across the ILs tested and led to concerns regarding the basicity of the pendant amine group. Indeed, addition of an aqueous base to the reaction mixture (2M aqueous Na₂CO₃) resulted in good conversion to the biaryl product (Table 1, Entries 2, 4 and 6). Repeating the reaction in the presence of water (Table 1, Entry 3) reinforced that base was required for the reaction to occur.

These results indicate that the tertiary amino groups present on the IL are insufficiently basic to promote the Suzuki-Miyaura reaction and, in this respect, offer no advantage over conventional solvents.

Table 1. Suzuki-Miyaura coupling reactions in ILs **3**, **4** and **13**.

$\text{Ar}-\text{I} + \text{Ar}'-\text{B}(\text{OH})_2 \xrightarrow[\text{IL}]{\text{cat. 10 mol\%}} \text{Ar}-\text{Ar}'$						
Entry	IL	Ar	Ar'	Cat. ^c	Base	Yield
1	3		Ph	A	no	0%
2	3		Ph	A	Na ₂ CO ₃ ^a	74%
3	4	Ph	Ph	A	no ^b	<5%
4	4	Ph	Ph	A	Na ₂ CO ₃	87%
5	13		Ph-	A	no	0%
6	13		Ph-	A	Na ₂ CO ₃	80%
7	4		MeO ₂ C-	B	no	0%
8	4		MeO ₂ C-	B	Na ₂ CO ₃	24%

^A 2M Na₂CO₃ (aq.) for all reactions indicated.

^B water added to reaction.

^C Method A – Pd(Ph₃P)₂Cl₂, method B – Pd(Ph₃P)₄

Similar results were also observed when performing Sonogashira couplings.^[36] When the reaction was performed in the presence of triethylamine the coupled product was isolated in excellent yield (method A), however no product was observed in its absence (method B).

Scheme 3.

Modifying the reaction conditions, utilizing sonication and also using an alternate catalyst, in an attempt to improve the yield, had little effect (Table 2). Moderate conversion was obtained by addition of copper (I) iodide, however several homo-coupled bis-alkyne and biphenyl by-products were also observed by ¹H NMR spectroscopy and could not be separated from the desired product using standard flash chromatography.

Table 2. Sonogashira coupling reactions in ILs **3** and **4**.

Entry	IL	Catalyst	Time (h)	Temp (°C)	Yield
1	3	Pd(PPh ₃) ₂ Cl ₂	6	25	0% ^A
2	4	Pd(PPh ₃) ₂ Cl ₂	6	25	17% ^A
3	4	Pd(PPh ₃) ₂ Cl ₂	18	40	19%
4	4	PdCl ₂	10	60	0%

5	4	Pd(PPh ₃) ₂ Cl ₂	12	70	27%
6	4	Pd(PPh ₃) ₂ Cl ₂	20	55	70% ^{B,C}

^A Mixture was sonicated at ambient temperature.
^B CuI (5 mol%) added.
^C crude product

Once again the basic ILs showed no advantage over using conventional solvents.

Scheme 4.

The use of basic ionic liquids to mediate Knoevenagel condensations is known.^[37] Screening of several of our basic ILs showed that they were indeed able to facilitate condensation between benzaldehyde and ethyl cyanonitrile to give methyl-2-cyano-3-phenylacrylate. Stirring both the aldehyde and cyanoester in the IL at ambient temperature overnight, followed by extraction of the product with a mixture of hexane : Et₂O (4:1) gave the desired product. The results are summarised in Table 3.

ILs **4** and **7** gave the best yields; it is possible that these species act as organocatalysts (reacting with benzaldehyde due to their lower steric hindrance) during the condensation, a mechanism which has been reported previously.^[38] In addition, **7** is very similar to ILs reported by Hardacre^[37] used to catalyse the Knoevenagel condensation.

Table 3.

Solvent	Co-solvent	Yield

DBU	n/a	47% ^A
7	n/a	not observed ^B
TMEDA	n/a	not observed ^B
13	MeOH	< 5% ^b
TMEDA	MeOH	not observed ^B
4	n/a	not observed ^B
4	MeOH	not observed ^B

^A isolated yield

^B yield determined by LC/MS

In light of the results of the Knoevenagel condensation we turned to the Morita-Baylis-Hillman (MBH) reaction, predicting that similar results would be observed. Disappointingly, none of the ILs tested were able to catalyse the MBH reaction between benzaldehyde and methyl acrylate (Table 4). Methanol (added as a co-solvent) has been reported to aid other ILs in the MBH reaction, but unfortunately had no effect.^[39] This suggests that the pendant amines have significantly reduced nucleophilicity, most likely due to steric bulk. However, the lack of reactivity of DABCO-based IL **13** is surprising, given the known utility of DABCO in the MBH reaction.

Interestingly Cheng et al.^[39] have reported an IL that does catalyse the Morita-Baylis-Hillman reaction (Fig. 4). When the reaction is carried out in common imidazolium IL solvents, a dramatic decrease in yield is observed. This could be due to the reaction with the imidazolium core *via* removal of the acidic C2-proton under basic conditions.

Figure 4.

Modeling Studies

Density functional theory (DFT) calculations were undertaken to rationalize the low basicity observed for DABCO-based ILs. We hypothesized that the positive charge on one nitrogen atom of the bicyclic diamine reduces the basicity of the second amine functionality, as protonation would

result in a high-energy dicationic species. The protonation energetics of DABCO and simplified model ILs (Fig. 5) by hydronium were calculated at the B3LYP/6-311++G** level.

Figure 5.

The experimentally determined pK_a values of doubly protonated DABCO (DABCOH_2^{2+}) are $pK_{a1} = 2.97$ (H_2O and DMSO), and $pK_{a2} = 8.82$ (H_2O),^[40] 8.93 (DMSO).^[41] This data shows that the first protonation of DABCO is quite favourable while the second is much less so and are in agreement with our experimental determination of the reduced basicity of DABCO based ILs. B3LYP/6-311++G** DFT calculations for DABCO protonation qualitatively agree with the experimental pK_a values: $\Delta G_1 = -65.0$ kcal/mol, and $\Delta G_2 = 37.4$ kcal/mol, suggesting that theoretical results will qualitatively mirror experiment. The calculated protonation Gibbs energy change for bicyclic model IL **15** is 34.6 kcal/mol. While this ΔG value is large and likely not representative of the actual protonation equilibrium, the qualitative agreement with experiment is very good; calculations indicate that formation of a doubly cationic species through simple protonation is a significantly endergonic process and unlikely to occur to a significant extent. The high energy barrier to formation of dications with DABCO and DABCO-based IL **13** is likely due to electrostatic repulsion between the two positive nitrogens held close in space by the constraints of the bicyclic ring system. Such a rationale also partially explains why DABCO-based IL **13** is not reactive as a nucleophile in MBH reactions, despite the lack of steric bulk. The constraints of a bicyclic system reducing both basicity and nucleophilicity are supported by DFT calculations for the protonation of model ILs **16** and **17**, where such constraints are not present. The Gibbs energy changes for model ILs **16** and **17** are 5.1 and 2.7 kcal/mol respectively. While these barriers are significantly lower

than those calculated for DABCO and DABCO-based IL model **15**, protonation is still thermodynamically uphill, which is in good agreement with the good to moderate levels of reactivity observed in the Knoevenagel condensation (Scheme 4).

Conclusion

A series of ILs with cores including pyridine, 1,4-dimethylpiperazine, 1,4-diazabicyclo[2.2.2]octane (DABCO) and several simple alkyl ammonium ILs were synthesized and their biodegradability determined using the “CO₂ headspace” test (ISO 14593). All ILs showed poor biodegradability apart from IL **6**, which showed a high extent of ultimate biodegradation, consistent with previous studies. ILs **3**, **4**, **7** and **13** were utilized for several base mediated reactions and were found to have surprisingly low basicity/nucleophilicity; it is very likely that the formation of the requisite organic dication is thermodynamically uphill and unfavourable. This proposal was supported by DFT calculations and comparison to previously reported p*K*_a data.

Experimental

General

Commercially available reagents and solvents were used without further purification, apart from benzaldehyde, which was freshly distilled before use. The ¹H and ¹³C NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer at 400 and 100 MHz, respectively. High resolution mass spectra were obtained using a Waters LCT Premier XE time-of-flight mass spectrometer fitted with an electrospray (ESI) ion source and controlled with MassLynx software version 4.5. Low resolution mass spectra using electrospray ionisation (ES-MS) were obtained using a Micromass PlatformII instrument. Unless otherwise stated, cone voltage was 20 eV. LC/MS was performed on an Agilent 6100 Series Single Quadrupole LC/MS/Agilent 1200 Series Reverse Phase HPLC, column: Luna C8(2) 5u 50X 4.6mm 100A. All products were obtained in greater than 95% purity as determined by LC, unless otherwise indicated. ¹H NMR data for all known compounds matched

literature data and can be found in the supporting information. All computations were conducted with the Spartan'10 and Gaussian 09 (Revision C.01) computational software packages.^[42] Initial stationary point searches were carried out with the semiempirical AM1 method.^[43] The lowest energy conformers of **16**, **16-H⁺**, **17**, and **17-H⁺** were located via an AM1 conformational search. These AM1 optimized structures were then used as starting points for geometry optimization at the B3LYP/6-31G* level.^[44-46] These DFT optimized structures were then used as starting points for further geometry optimization at the B3LYP/6-311G* level, followed by the B3LYP/6-311++G** level. Vibrational analyses were carried out to confirm the nature of all stationary points and to calculate the thermal corrections (enthalpy and entropy) for 298 K, 1 atm, gas phase. The low basicity counterions were omitted. An archive of atomic coordinates in the .pdb file format and tables of thermodynamic parameters are provided as Supporting Information.

General method for anion metathesis (NTf₂)

The quaternary salt (1.0 eq.) was dissolved in distilled water to which LiNTf₂ (1.1 eq.) in minimal distilled water was added. The resulting solution was stirred at room temperature for 30 min. CH₂Cl₂ was added and the separated aqueous layer washed twice more with CH₂Cl₂. The combined organic layers were washed with cold distilled water until negative to a AgNO₃ precipitate test, dried (Na₂SO₄), filtered and concentrated *in vacuo* before drying overnight under high vacuum (0.1 mmHg at 60 °C).

*1-Allylpyridinium triflimide (**1**)^[25]*

To 1 mL anhydrous pyridine (12.4 mmol) in anhydrous toluene (2 mL) in an ice bath was added allyl bromide (0.95 mL, 11.0 mmol) dropwise with stirring. The solution was allowed to warm slowly to room temperature and stirred overnight. The solid residue, which formed, was dissolved in anhydrous MeCN and the desired product was isolated by precipitation through

addition of Et₂O followed by rapid filtration under a stream of nitrogen. The resulting product (0.9 g, 4.50 mmol, 41%) treated under general conditions to give the triflimide as a clear oil (1.72 g, 96%). ¹H NMR (400 MHz, DMSO-d₆) δ 9.03 (dd, J = 6.8, 1.3 Hz, 2H), 8.64 (tt, J = 7.6, 1.3 Hz, 1H), 8.19 (dd, J = 7.6, 6.8 Hz, 2H), 6.17 (ddt, J = 17.0, 10.3, 6.3 Hz, 1H), 5.45 (dq, J = 10.3, 1.2 Hz, 1H), 5.39 (dq, J = 17.0, 1.2 Hz, 1H), 5.27 (d, J = 6.3 Hz, 2H). ¹³C NMR (100 MHz, DMSO-d₆) δ 145.89, 144.81, 131.68, 128.25, 121.83, 119.47 (q, J_{C-F} = 319.9 Hz), 62.44. HRMS ⁺ve calc for C₈H₁₀N⁺ 120.0808 found 120.0803; HRMS ⁻ve calc for C₂F₆NO₄S₂⁻ 279.9178 found 279.9165.

1-Benzylpyridinium triflimide (2)^[25]

To 0.5 mL anhydrous pyridine (6.2 mmol) in anhydrous toluene (1 mL) in an ice bath was added benzyl bromide (0.95 mL, 11.0 mmol) dropwise with stirring. The solution was allowed to warm slowly to room temperature and stirred overnight. The solid residue, which formed, was dissolved in anhydrous MeCN and the desired product was isolated by precipitation through addition of Et₂O followed by rapid filtration under a stream of nitrogen. The resulting orange solid (281 mg, 1.1 mmol) was treated under general conditions to give the triflimide as a clear oil (0.5 g, 98%). ¹H NMR (400 MHz, DMSO-d₆) δ 9.21 – 9.18 (m, 2H), 8.63 (tt, J = 7.8, 1.3 Hz, 1H), 8.20 – 8.16 (m, 2H), 7.53 – 7.51 (m, 2H) 7.48 – 7.43 (m, 3H), 5.85 (s, 2H). ¹³C NMR (100 MHz, DMSO-d₆) δ 146.00, 144.82, 134.25, 129.39, 129.25, 128.74, 128.49, 119.47 (q, J_{C-F} = 319.8 Hz), 63.35. HRMS ⁺ve calc for C₁₂H₁₂N⁺ 170.0964 found 170.0969; HRMS ⁻ve calc for C₂F₆NO₄S₂⁻ 279.9178 found 279.9177.

1-(2-(Diisopropylamino)ethyl)pyridinium triflimide (3)

To 2-diisopropylaminoethyl chloride hydrochloride (3.17 g, 1.6 mmol) in 8 mL distilled water at 0 – 5 °C was added conc. NH₄OH (aq.) dropwise until pH 8-9 was reached. The aqueous solution was extracted with Et₂O (3 x 20 mL), dried (Na₂SO₄), filtered concentrated *in vacuo* (at room

temperature) to give 2.63 g of a yellow oil. The oil was transferred to a sealed tube, dissolved in 2 mL anhydrous toluene (2 mL) and pyridine (1.1 eq.) was added at 0 °C. The resulting solution was stirred at room temperature for 5 mins, allowed to reach rt then heated at 100 °C for 3 days. The crude salt was treated under general conditions to give the triflimide, as a bright yellow liquid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.90-8.92 (m, 2H), 8.57 (tt, J = 7.8, 1.3 Hz, 1H), 8.12-8.17 (m, 2H), 4.55 (t, J = 5.4 Hz, 2H), 2.97 (sept, J = 6.6 Hz, 2H), 2.89 (t, J = 5.4 Hz, 2H), 0.74 (d, J = 6.6 Hz, 12H). ¹³C NMR (100 MHz, DMSO-d₆) δ 145.25, 127.20, 119.49 (q, J_{C-F} = 320.1 Hz), 59.78, 46.50, 45.30, 20.23. HRMS ⁺ve calc for C₁₃H₂₃N₂⁺ 207.1856 found 207.1857; HRMS ⁻ve calc for C₂F₆NO₄S₂⁻ 279.9178 found 279.9180.

1-Butyl-3-((diethylamino)methyl)pyridinium triflimide (4)

Picolyl chloride HCl salt (10.0 g, 61.0 mmol) was suspended in anhydrous acetonitrile, the suspension was cooled in an ice/brine bath (-10 °C to 0 °C) and Et₂NH (40 mL, 387 mmol) was added in 2 x 20 mL portions slowly. The mixture was allowed to reach room temperature and stirred for 4 days. The resulting mixture was filtered, the precipitate was washed with small portions of anhydrous MeCN (3 mL). The filtrate was concentrated *in vacuo* to give a residue, which was dissolved in 100 mL 2M NaOH and extracted with 3 x 100 mL diethyl ether, the combined organics were dried (Na₂SO₄), filtered and concentrated *in vacuo* to give 9.7 g (97%) of an orange oil. ¹H NMR (CDCl₃, 400 MHz) 8.54 (dd, J = 2.4, 0.4 Hz, 1H), 8.49 (dd, J = 4.8, 1.2 Hz, 1H), 7.74 (b, 1H), 7.25 (dd, J = 7.6, 4.6 Hz, 1H), 3.61 (s, 2H), 2.55 (q, J = 6.8 Hz, 4H), 1.07 (t, J = 6.8 Hz, 6H).

To crude material from above (1.22 g, 7.4 mmol) in 3 mL anhydrous toluene was added 1-bromobutane (0.79 mL, 7.3 mmol), the resulting solution was stirred at room temperature for 1 h before being heated to 80 °C overnight. The resulting solution was cooled to room temperature, 25 mL distilled water was added, the aqueous solution was extracted with 3 x 20 mL Et₂O. The crude

salt was treated under general conditions to give the triflimide (3.55g, 97%) as a red oil. ^1H NMR (400 MHz; DMSO- d_6) δ 8.96-8.99 (m, 2H), 8.50-8.52 (m, 1H), 8.08-8.11 (m, 1H), 4.60 (t, J = 7.3 Hz, 2H), 3.74 (s, 2H), 2.51 (q, J = 7.3 Hz, 4H), 1.89 (q, J = 7.5, 2H), 1.29 (sex, J = 7.5 Hz, 3H), 0.99 (t, J = 7.1 Hz, 6H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz; CDCl_3) δ 144.83, 143.85, 142.99, 142.38, 127.81, 119.60 (q, $J_{\text{C-F}}$ = 319.4Hz), 61.92, 53.73, 33.12, 18.98, 12.94, 11.60. HRMS $^{+ve}$ calc for $\text{C}_{14}\text{H}_{25}\text{N}_2^{+}$ 221.2012 found 221.2018; HRMS $^{-ve}$ calc for $\text{C}_2\text{F}_6\text{NO}_4\text{S}_2^{-}$ 279.9178 found 279.9180.

1-Butyl-3-methylpyridinium triflimide (5)^[47]

3-Picoline (1 mL, 10.3 mmol) was dissolved in 10 mL anhydrous toluene, 1-bromobutane (1.2 mL, 11.3 mmol) was added and the resulting mixture stirred at room temperature for 3 h, before being refluxed for 14 h. The top layer of the biphasic mixture was decanted carefully and the bottom (ionic liquid) layer was shaken with 3 x 10 mL Et_2O decanting the organic layer each time. The resulting material was carefully placed under vacuum. The resulting residue was treated under general conditions to give the triflimide as a clear oil (4.03 g, 91% over 2 steps). ^1H NMR (400 MHz; DMSO- d_6) δ 8.99 (s, 1H), 8.90-8.91 (m, 1H), 8.44 (d, J = 7.9Hz, 1H), 8.05 (dd, J 7.9, 6.2 Hz, 1H), 4.54 (t, J = 7.4 Hz, 2H), 2.50 (s, 3H), 1.90 (quin, J = 7.4, 2H), 1.29 (sex, J = 7.4 Hz, 2H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz; DMSO- d_6) δ 145.69, 144.18, 141.93, 141.92, 138.82, 127.30, 119.47 (q, $J_{\text{C-F}}$ = 319.9 Hz), 60.46, 32.55, 18.74, 17.78, 13.20. HRMS $^{+ve}$ calcd 150.1277 found 150.1280; $^{-ve}$ calcd 279.9178 found 279.9178.

1-Butyl-3-carboxypyridinium triflimide (6)

Nicotinic acid (1.23 g, 10.0 mmol) was suspended in 10 mL anhydrous MeCN in a sealed tube, 1-iodobutane (1.2 mL, 10.5 mmol) was added and the resulting mixture was stirred at room temperature for 1h. The mixture was heated at 100°C overnight and concentrated *in vacuo*. The

resulting residue was taken up in 20 mL distilled water washed with CH₂Cl₂ (3 x 15 mL), the aqueous solution was concentrated *in vacuo* to give 1.14 g of a 10:1 mixture of the alkylated product and nicotinic acid. The residue was dissolved in 15 mL distilled water and treated with LiNTf₂ (1.09 g, 3.8 mmol) in minimal distilled water. The resulting cloudy mixture (which cleared) was stirred for 30 mins at room temperature. The mixture was diluted with 25 mL (4:1 CH₂Cl₂:EtOAc) and the aqueous solution was washed with a further 2 x 25 mL (4:1 CH₂Cl₂:EtOAc) the combined organic layers were washed with ice cold 5mL portions of distilled water until negative to a AgNO₃ precipitate test. The organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo* and placed under high vacuum, then dried overnight under high vacuum (0.1 mmHg at 60 °C) to give to the desired triflimide (2.58 g, 56%). ¹H NMR (400 MHz; DMSO-d₆) δ 11.10 (br, 1H), 8.99 (s, 1H), 8.90-8.91 (m, 1H), 8.44 (d, *J* = 7.9Hz, 1H), 8.05 (dd, *J* 7.9, 6.2 Hz, 1H), 4.54 (t, *J* = 7.4 Hz, 2H), 2.50 (s, 3H), 1.90 (quin, *J* = 7.4, 2H), 1.29 (sex, *J* = 7.4 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (100 MHz; DMSO-d₆) δ 163.20, 147.39, 146.11, 145.24, 131.86, 128.29, 119.59 (q, *J*_{C-F} = 319.9 Hz), 61.09, 32.91, 18.87, 13.26. HRMS +ve calcd for 180.1019 found 180.1022; -ve calcd 279.9178 found 279.9182.

***N*-(2-(Dimethylamino)ethyl)-*N,N*-dimethylhexylammonium triflimide (7)**

N,N'-tetramethylethylene diamine (1.5 mL, 10.0 mmol) was dissolved in anhydrous toluene (2 mL), 1-chlorohexane (1.35 mL, 10.0 mmol) was added and the resulting solution was microwaved at 100 °C for 1 h, then concentrated *in vacuo* to give a white solid. The crude salt was treated under general conditions to give the triflimide as a light yellow oil (4.24g, 89% over steps). ¹H NMR (400 MHz; DMSO-d₆) δ 3.36 (t, *J* = 6.2 Hz, 2H), 3.25-3.29 (m, 2H), 3.04 (s, 6H), 2.61 (t, *J* = 6.2 Hz, 2H), 2.19 (s, 6H), 1.61-1.69 (m, 2H), 1.25-1.32 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H). ¹³C NMR (100 MHz; DMSO-d₆) δ 119.46 (q, *J*_{C-F} = 320.0 Hz), 63.67, 59.82, 52.30, 50.35, 44.98, 30.60, 25.39, 21.80, 21.67, 13.75. HRMS +ve calcd 201.2325 found 201.2321; -ve calcd 279.9178 found 279.9169.

N,N-Diethyl-N-(2-hydroxyethyl)hexylammonium triflimide (8)

2-(Diethylamino)ethanol (1.17 g, 10.0 mmol) was dissolved in 2 mL anhydrous toluene, 1-bromohexane (1.4 mL, 10.0 mmol) was added at room temperature, resulted solution was stirred at room temperature for 1 h then heated to 80 °C for 48 h, the resulting solution was concentrated *in vacuo*. The resulting residue was treated under general conditions to give the triflimide (4.53 g, 94% over steps) as a pale yellow oil. ¹H NMR (400 MHz; DMSO-d₆) δ 5.24 (t, *J* = 5.0 Hz, 1H), 3.76-3.77 (m, 2H), 3.29 (dd, *J* = 9.0 and 3.9 Hz, 4H), 3.17-3.22 (m, 2H), 1.55-1.63 (m, 2H), 1.29 (m, 6H), 1.18 (t, *J* = 7.1 Hz, 6H), 0.87 (t, *J* = 6.9 Hz, 3H). ¹³C NMR (100 MHz; DMSO-d₆) δ 119.46 (q, *J*_{C-F} = 320.0 Hz), 58.26, 57.33, 54.50, 53.23, 30.62, 25.40, 21.87, 20.94, 13.77, 7.25. HRMS +ve calcd 202.2165 found 202.2166; -ve calcd 279.9178 found 279.9173.

N-Butyl-N,N-bis(2-hydroxyethyl)pentylammonium triflimide (9)

To a suspension of diethanolamine (924 mg, 8.8 mmol) and potassium carbonate (1.27 g, 9.2 mmol) in anhydrous MeCN (11 mL), was added 1-bromobutane (1.0 mL, 9.2 mmol) dropwise, with stirring, at 0 °C. After 5 min the ice bath was removed and the solution was allowed to reach room temperature and stirred for 24 h. The solution was filtered, concentrated *in vacuo*, the resulting residue was purified by silica plug (DCM) to yield 1.15 g clear oil (81%). ¹H NMR (400 MHz; CDCl₃) δ 3.62 (t, *J* = 5.4 Hz, 4H), 2.86 (s, 2H), 2.66 (t, *J* = 5.4 Hz, 4H), 2.55-2.52 (m, 2H), 1.45 (pent, *J* = 7.5 Hz, 2H), 1.30 (sex, *J* = 7.5 Hz, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). To a portion of the clear oil (553 mg, 3.4 mmol) in anhydrous toluene (2 mL) was added 1-iodobutane (0.45 mL, 3.9 mmol). The resulting mixture was heated in a sealed tube at 120°C for 6h, then cooled to room temperature. The solution was diluted with 25 mL distilled water, and the aqueous layer was washed consecutively with 3 x 10 mL portions of Et₂O. The aqueous solution was then treated under general conditions to give the triflimide as a colourless oil (1.3 g, 75%). ¹H NMR (400 MHz; DMSO-d₆) δ

5.22 (t, $J = 5.1$ Hz, 2H), 3.78-3.79 (m, 4H), 3.40 (t, $J = 5.1$ Hz, 4H), 3.29 (t, $J = 4.2$ Hz, 4H), 1.57-1.68 (m, 4H), 1.22-1.36 (m, 6H), 0.92 (t, $J = 7.2$ Hz, 3H), 0.87 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz; DMSO- d_6) δ 119.46 (q, $J_{\text{C-F}} = 319.9$ Hz), 59.98, 59.24, 59.01, 56.63, 54.57, 27.86, 23.17, 21.60, 20.86, 19.11, 13.72, 13.46. HRMS +ve calcd 232.2271 found 232.2281; -ve calcd 279.9178 found 279.9177.

1-Hexyl-1,4-dimethylpiperazinium triflimide (10)

1,4-Dimethylpiperazine (500 μL , 3.7 mmol) and 1-chlorohexane (462 μL , 3.4 mmol) were microwaved at 110 $^{\circ}\text{C}$ in 2 mL anhydrous MeCN for 1.5 h. The resulting mixture was concentrated *in vacuo* to give 242 mg (1.0 mmol) crude product. The crude salt was treated under general conditions to give the triflimide as a clear oil (483 mg, 30% over two steps). ^1H NMR (400 MHz, DMSO- d_6) δ 3.36 (dd, $J = 8.0, 3.7$ Hz, 4H), 3.30 (s, 2H), 3.00 (s, 3H), 2.56-2.73 (m, 4H), 2.27 (s, 3H), 1.62-1.70 (m, 2H), 1.28-1.30 (m, 6H), 0.86-0.90 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 119.51, (q, $J_{\text{C-F}} = 319.9$ Hz) 59.23, 47.52, 44.45, 30.71, 25.47, 21.90, 20.86, 13.82. HRMS ^{+}ve calc for $\text{C}_{12}\text{H}_{27}\text{N}_2^{+}$ 199.2169 found 199.2167. HRMS ^{-}ve calc for $\text{C}_2\text{F}_6\text{NO}_4\text{S}_2^{-}$ 279.9178 found 279.9170.

1-Heptyl-1,4-dimethylpiperazinium triflimide (11)

1,4-Dimethylpiperazine (410 μL , 3.0 mmol) and 1-chloroheptane (385 μL , 2.5 mmol) were microwaved at 150 $^{\circ}\text{C}$ in 2 mL anhydrous MeCN for 1 h. The resulting mixture was concentrated *in vacuo* to give 397 mg (1.6 mmol) crude product which was diluted in 15 mL distilled water (15 mL) and washed with Et_2O (3 x 5 mL). The crude salt was treated under general conditions to give the triflimide as a clear oil (681 mg, 55% over two steps). ^1H NMR (400 MHz, DMSO- d_6) δ 3.36 (dd, $J = 8.4, 4.2$ Hz, 4H), 3.31 (d, $J = 4.6$ Hz, 2H), 3.00 (s, 3H), 2.70 (d, $J = 13.7$ Hz, 2H), 2.58-2.63 (m, 2H), 2.27 (s, 3H), 1.62-1.70 (m, 2H), 1.24-1.34 (m, 8H), 0.87 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100

MHz, DMSO- d_6) δ 119.50 (q, J_{C-F} = 319.9 Hz), 59.20, 47.49, 44.40, 39.52, 31.01, 28.18, 25.75, 21.98, 20.89, 13.85. HRMS $^{+ve}$ calc for $C_{13}H_{29}N_2^+$ 213.2325 found 213.2327. HRMS $^{-ve}$ calc for $C_2F_6NO_4S_2^-$ 279.9178 found 279.9169.

1-Hexyl-1,4-diazabicyclo[2.2.2]octanium triflimide (12)^[48]

To DABCO (2.28 g, 20.3 mmol) in 25 mL anhydrous MeCN at 0 °C, was added 1-bromoheptane (2.8 mL, 19.9 mmol) dropwise with stirring. The resulting solution was allowed to reach room temperature and stirred overnight. The resulting solution was concentrated *in vacuo*. 915 mg of the residue treated under general conditions to give the triflimide as a clear oil (1.5 g, 96%) which crystallized on standing. 1H NMR (400 MHz, DMSO- d_6) δ 3.24 (t, J = 7.5 Hz, 6H), 3.13-3.18 (m, 2H), 3.01 (t, J = 7.5 Hz, 6H), 1.60-1.68 (m, 2H), 1.25-1.33 (m, 6H), 0.88 (t, J = 7.0, 3H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 119.48 (q, J_{C-F} = 320.0 Hz), 63.26, 51.53, 44.68, 30.67, 25.50, 21.82, 20.94, 13.76. HRMS $^{+ve}$ calc for $C_{12}H_{25}N_2^+$ 197.2012 found 197.2022; HRMS $^{-ve}$ calc for $C_2F_6NO_4S_2^-$ 279.9178 found 279.9173.

1-Heptyl-1,4-diazabicyclo[2.2.2]octanium triflimide (13)^[48]

To DABCO (1.41 g, 12.5 mmol) in 25 mL anhydrous MeCN, was added 1-chloroheptane (1.9 mL, 12.4 mmol) dropwise with stirring. The resulting solution was gently refluxed overnight then concentrated *in vacuo*. The resulting residue was dissolved in 30 mL distilled water, washed with 3 x 15 mL Et₂O. The crude salt was treated under general conditions to give the triflimide as a clear oil (5.23 g, 86% over 2 steps). 1H NMR (400 MHz, DMSO- d_6) δ 3.24 (t, J = 7.5 Hz, 6H), 3.13-3.17 (m, 2H), 3.01 (t, J = 7.5 Hz, 6H), 1.60-1.68 (m, 2H), 1.23-1.35 (m, 8H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 119.51 (q, J_{C-F} = 319.9 Hz), 63.30, 51.56, 44.70, 30.99, 28.19, 25.82, 21.99, 21.02, 13.89. HRMS $^{+ve}$ calc for $C_{13}H_{27}N_2^+$ 211.2169 found 211.2175, HRMS $^{-ve}$ calc for $C_2F_6NO_4S_2^-$ 279.9178 found 279.9184.

1-(2-Hydroxyethyl)-1,4-diazabicyclo[2.2.2]octanium dicyanimide (14)

To DABCO (224 mg, 2.0 mmol) in 2.5 mL anhydrous MeCN was added 2-chloroethanol (134 μ L, 2.0 mmol) was microwaved at 80 °C for 40 min. The resulting solution was concentrated *in vacuo*, the remaining residue was dissolved in 10 mL distilled water and washed with 3 x 5 mL Et₂O. The aqueous solution was treated with AgN(CN)₂ (348 mg, 2 mmol) and stirred overnight at room temperature. The heterogenous mixture was filtered, the filtrate concentrated *in vacuo* then taken up in MeOH and placed in the freezer overnight, filtered then concentrated *in vacuo* and placed under high vacuum, then dried under high vacuum (0.1 mmHg at 60 °C) to give a clear brown oil (402 mg, 90% over 2 steps). ¹H NMR (400 MHz, DMSO-d₆) δ 5.29 (s, 1H), 3.85 (s, 2H), 3.36 (t, J = 7.5 Hz, 6H), 3.30 (t, J = 5.2, 2H), 3.02 (t, J = 7.5 Hz, 6H). ¹³C NMR (100 MHz, DMSO-d₆) δ 119.10, 65.37, 54.15, 52.48, 44.71. LRMS –ve 66, +ve 157.

ISO 14593 - CO₂ Headspace Test

To evaluate the biodegradability of the test ILs, the “CO₂ headspace” test (ISO 14593, OECD 310) was applied. This method allows the evaluation of the ultimate aerobic biodegradability of an organic compound in an aqueous medium at a given concentration of microorganisms by analysis of inorganic carbon (IC). The test IL, as the sole source of carbon and energy, was added at a concentration of 20 mgC/L to a buffer-mineral salts medium. These solutions were inoculated with activated sludge collected from an activated sludge treatment plant, washed and aerated prior to use and incubated in sealed vessels with a headspace of air. Biodegradation (mineralisation to carbon dioxide) was determined by measuring the IC produced in the test bottles in excess of that produced in blank vessels containing inoculated medium only. Sodium *n*-dodecyl sulfate (SDS) was used as reference substance. The test ran for 28 days. The extent of biodegradation was expressed as a percentage of the theoretical amount of inorganic carbon (ThIC) based on the amount of test

compound added initially. The reference substance, SDS, underwent $89 \pm 2\%$ biodegradation in this assay.

Accessory Publication

^1H and ^{13}C NMR and computational data are available from the journal's website.

Acknowledgements

The authors wish to thank the ARC Centre of Excellence for Free Radical Chemistry and Biotechnology Natural Science and Engineering Research Council of Canada (NSERC-DG to RDS). Computational facilities are provided by ACEnet, the regional high performance computing consortium for universities in Atlantic Canada. ACEnet is funded by the Canada Foundation for Innovation (CFI), the Atlantic Canada Opportunities Agency (ACOA), and the provinces of Newfoundland and Labrador, Nova Scotia, and New Brunswick. We also wish to thank Dr. Jason Dang for obtaining all HRMS data.

References

- [1] P. Wasserscheid, T. Welton, *Ionic Liquids in Synthesis*, John Wiley & Sons, **2008**.
- [2] N. V. Plechkova, K. R. Seddon, *Chem. Soc. Rev.* **2008**, 37, 123–150.
- [3] M. Antonietti, D. Kuang, B. Smarsly, Y. Zhou, *Angew. Chem. Int. Ed. Engl.* **2004**, 43, 4988–4992.
- [4] M. Galiński, A. Lewandowski, I. Stępnia, *Electrochimica Acta* **2006**, 51, 5567–5580.
- [5] N. Gathergood, P. J. Scammells, *Aus. J. Chem.* **2002**, 55, 557–560.
- [6] N. Gathergood, M. T. Garcia, P. J. Scammells, *Green Chem.* **2004**, 6, 166–175.
- [7] M. T. Garcia, N. Gathergood, P. J. Scammells, *Green Chem.* **2005**, 7, 9–14.
- [8] N. Gathergood, P. J. Scammells, M. T. Garcia, *Green Chem.* **2006**, 8, 156–160.

- [9] E. Liwarska-Bizukojc, D. Gendaszewska, *J. Biosci. Bioeng.* **2012**, *115*, 71–75.
- [10] Y. Y. Deng, P. P. Besse-Hoggan, M. M. Sancelme, A.-M. A. Delort, P. P. Husson, M. F. M. C. Gomes, *J. Hazard. Mater.* **2011**, *198*, 10–10.
- [11] D. Coleman, N. Gathergood, *Chem. Soc. Rev.* **2010**, *39*, 600–637.
- [12] S. J. Khan, J. E. Ongerth, *Chemosphere* **2004**, *54*, 355–367.
- [13] L. Ford, J. R. Harjani, F. Atefi, M. T. Garcia, R. D. Singer, P. J. Scammells, *Green Chem.* **2010**, *12*, 1783–1789.
- [14] A. R. Hajipour, F. Rafiee, *JICS* **2009**, *6*, 647–678.
- [15] C. Chiappe, B. Melai, A. Sanzone, G. Valentini, *Pure Appl. Chem.* **2009**, *81*, 2035–2043.
- [16] Martyn John Earle, Stewart Forsyth, Ute Frohlich, Nimal Gunaratne, Suhas Katdare, Kenneth Richard Seddon, The Queen's University Of Belfast, *Ionic Liquids with a Cation Comprising a Basic Moiety*, **2006**, WO2006072775A3.
- [17] C. Ye, J. C. Xiao, B. Twamley, A. D. LaLonde, M. Grant Norton, J. M. Shreeve, *Eur. J. Org. Chem.* **2007**, *2007*, 5095–5100.
- [18] H. R. Shaterian, K. Azizi, *J. Mol. Liq.* **2013**, *8*–13.
- [19] H. R. Shaterian, M. Mohammadnia, *J. Mol. Liq.* **2012**, *173*, 55–61.
- [20] I. Yavari, E. Kowsari, *Mol. Divers.* **2009**, *13*, 519–528.
- [21] Y. Zhang, Q. Jiao, B. Zhen, Q. Wu, H. Li, *Applied Catalysis A: General* **2013**, *453*, 327–333.
- [22] M. Fan, J. Yang, P. Jiang, P. Zhang, S. Li, *R. Soc. Chem. Adv.* **2013**.
- [23] S. Zhou, L. Liu, B. Wang, F. Xu, R. C. Sun, *Chin. Chem. Lett.* **2012**, *23*, 379–382.
- [24] P. Primerano, M. Cordaro, A. Scala, *Tetrahedron Lett.* **2013**, *54*, 4061–4063.
- [25] X. Wang, C. A. Ohlin, Q. Lu, Z. Fei, J. Hu, P. J. Dyson, *Green Chem.* **2007**, *9*, 1191–1197.
- [26] C. C. Pretti, M. M. Renzi, S. E. S. Focardi, A. A. Giovani, G. G. Monni, B. B. Melai, S. S. Rajamani, C. C. Chiappe, *Ecotoxicol. Environ. Saf.* **2011**, *74*, 748–753.
- [27] J. Qu, J. J. Truhan, S. Dai, H. Luo, P. J. Blau, *Tribol. Lett.* **2006**, *22*, 207–214.

- [28] S. Stolte, S. Steudte, O. Areitioaurtena, F. Pagano, J. Thöming, P. Stepnowski, A. Igartua, *Chemosphere* **2012**, 89, 1135–1141.
- [29] A. S. Wells, V. T. Coombe, *Org. Process Res. Dev.* **2006**, 10, 794–798.
- [30] J. R. Harjani, R. D. Singer, M. T. Garcia, P. J. Scammells, *Green Chem.* **2008**, 10, 436–438.
- [31] C. Abrusci, J. Palomar, J. L. Pablos, F. Rodriguez, F. Catalina, *Green Chem.* **2011**, 13, 709–717.
- [32] I. Greiner, E. Hohmann, L. Vida, G. Keglevich, *Open Organic Chemistry Journal* **2008**, 2, 65–67.
- [33] B. H. Lipshutz, T. B. Petersen, A. R. Abela, *Org. Lett.* **2008**, 10, 1333–1336.
- [34] F. Chanthavong, N. E. Leadbeater, *Tetrahedron Lett.* **2006**, 47, 1909–1912.
- [35] N. Miyaara, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, 20, 3437–3440.
- [36] K. Sonogashira, *J. Organomet. Chem.* **2002**, 653, 46–49.
- [37] C. Paun, J. Barklie, P. Goodrich, H. Gunaratne, A. McKeown, V. I. Pârvulescu, C. Hardacre, *J. Mol. Catal. A Chem.* **2007**, 269, 64–71.
- [38] L. Albrecht, B. Richter, C. Vila, H. Krawczyk, K. A. Jørgensen, *Chemistry* **2009**, 15, 3093–3102.
- [39] X. Mi, S. Luo, J.-P. Cheng, *J. Org. Chem.* **2005**, 70, 2338–2341.
- [40] R. L. Benoit, D. Lefebvre, M. Fréchet, *Can. J. Chem.* **1987**, 65, 996–1001.
- [41] P. Paoletti, J. H. Stern, A. Vacca, *J. Phys. Chem.* **1965**, 69, 3759–3762.
- [42] (a) *Spartan '10*; Wavefunction, Inc.; Irvine, CA, 2011; <http://www.wavefun.com>. (b) M. J. Frisch *et al.* Gaussian, Inc., Wallingford CT, 2010.
- [43] E. G. Zoebisch, E. F. Healy, J. Stewart, *J. Am. Chem. Soc.* **1985**, 3902–3909.
- [44] C. Lee, W. Yang, R. Parr, *Phys. Rev., B Condens. Matter* **1988**, 37, 785–789.
- [45] A. D. Becke, *J. Chem. Phys.* **1993**, 98, 1372–1377.
- [46] A. D. Becke, *J. Chem. Phys.* **1993**, 98, 5648–5652.
- [47] C. A. Ohlin, P. J. Dyson, G. Laurenczy, *Chem. Commun. (Camb.)* **2004**, 1070–1071.

- [48] A. Wykes, S. L. MacNeil, *Synlett* **2007**, 2007, 107–110.