Highly recyclable, imidazolium derived ionic liquids of low antimicrobial and antifungal toxicity: A new strategy for acid catalysis†

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Imidazolium derived ionic liquid catalysts have been developed which are aprotic and of low antimicrobial and antifungal toxicity, yet which can act as efficient Brønsted acidic catalysts in the presence of protic additives. The catalysts can be utilised at low loadings and can be recycled 15 times without any discernible loss of activity.

Over the last decade Ionic Liquids (ILs) have been extensively investigated as potential replacements for volatile organic compounds for use as (*inter alia*) both tunable reaction media and catalytic solvents.[1] Much of this interest has been focussed on the development of ionic liquids as alternative, 'green' materials with applications as diverse as ionic compressors, the BASIL™ process and electroplating.[1q] Immense interest in the environmental impact of ILs[2] has led to a plethora of papers dealing with a) their toxicity[3] (for example antibacterial and antifungal),[4] b) the importance of biodegradation studies[5] (something only recognised since 2002),[6] and recently c) bioaccumulation and metabolite identification studies.[7]

The design of a 'green' compound, whether the role is as a solvent,[1] reagent or catalyst[8] should ideally address issues such as low toxicity and ready biodegradability without the generation of toxic, persistent metabolites. Of equal importance is the functional performance of the environmentally benign material. The decision to replace a 'toxic' chemical with a 'green' replacement is easier if a performance benefit is also attained. The role of a green chemist is to make this decision as easy as possible and avoid the 'gray area' where environmental protection comes at a performance cost.

By utilising the toxicity and ecotoxicity data available for ionic liquids, in particular imidazolium and pyridinium salts, and the similarity in structure to analogous heterocyclic reagents and catalysts we aim to design and prepare effective green compounds.

In 2002, Forbes and Davis[9] introduced imidazolium and phosphonium ILs equipped with covalently bound strongly Brønsted-acidic sulfonic acid functionality (**1**, Fig. 1). These materials represented a successful (from both catalytic and operational perspectives) marriage of the excellent solvent properties and non-volatility of ILs with the convenience and activity of traditional solid acids such as (for instance) *p*-TSA. This seminal report spawned considerable interest in the design of similarly devised Brønsted acidic based imidazolium-based IL catalysts and catalytic solvents.[10] Two other general strategies have emerged for the design of organic imidazolium ion based acidic ILs: the use of protonated imidazolium ion ILs (*i.e.* **2**, Fig. 1)[11] and the installation of an acidic counteranion (**3**, Fig. 1).[12–14] While these materials can - when appropriately designed - exhibit excellent catalytic activity and reduce some of the risks (both practical and environmental) associated with the use of more volatile liquid acids, they remain in effect (particularly in the cases of **1** and **3**) strong Brønsted acids and their environmental impact and toxicity have not yet, to the best of our knowledge, been unambiguously established.

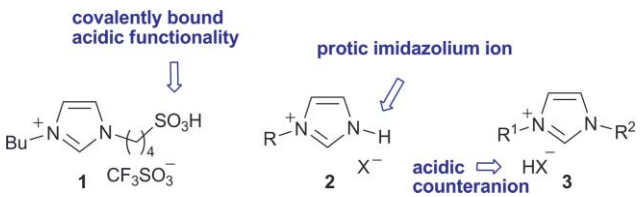

Fig. 1 Imidazolium ion-based acidic ILs: current strategies.

Recently, the somewhat unexpected observation that appropriately substituted pyridinium ions were capable of acting as Brønsted acid catalysts in the presence of protic additives has been reported.[15] It was postulated that the addition of nucleophiles to these aprotic materials generated catalytically active Brønsted acidic species *in situ* (*i.e.* **5–6**, Fig. 2). Later it was found that the catalytic efficiency of these compounds was influenced not only by the electronic structure of the cation but also by the counteranion employed.[16] We reasoned that this general strategy could also be applicable to the design of catalysts based on imidazolium ions - with potential advantage - as:

a) these species would in all likelihood possess less resonance stabilisation energy than the corresponding pyridinium ions,[17] thus the addition of protic nucleophiles to the heterocyclic core (leading to increased catalyst efficacy) would be predicted to be facilitated,

b) the presence of the twin nitrogen heteroatoms provides one with considerably enhanced opportunities (through the straightforward variation of the substituents at these positions) to fine tune not only the melting point of the material but

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† Electronic Supplementary Information (ESI) available: Synthesis of all catalysts, general procedures and toxicity screening methods. See DOI:10.1039/c003301d

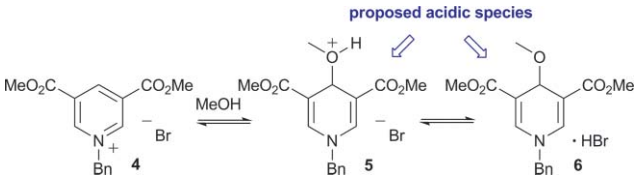


Fig. 2 Proposed mode of action of catalytic aprotic pyridinium ions.

also its steric, electronic, toxicity and stability to acid catalysed hydrolysis and biodegradability (*vide supra*) characteristics and,

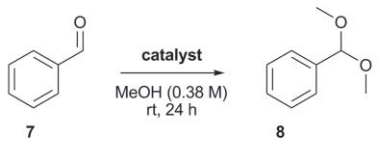
c) as our understanding of the structural factors which influence the environmental impact of imidazolium and pyridinium-based ILs deepens,[4] it should be possible to combine the practical advantages derived from the physical properties of acidic ILs (*i.e.* **1–3**, Fig. 1) with both the additive-controlled acidity associated with electrophilic pyridinium ions (Fig. 2) and the inclusion of the relatively environmentally benign nature of ester or amide[4,18] substituted imidazolium ions (*vide supra*) *in a catalytically active aprotic imidazolium ion-based IL specifically designed to be non-toxic and* (*preferably*) *biodegradable*, *the acidity of which would be controllable in an 'on-off' fashion using specific protic additives.*

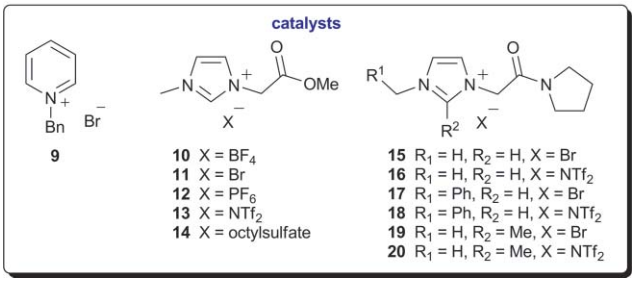
It would be our hope that such a compound could potentially serve as a catalytic material/solvent when required, yet which would be a safely storable, non-acidic, non-toxic material.

In order to test this hypothesis we synthesised a small, targeted library of imidazolium-ion based ILs assembled to allow the contributions of steric hindrance, the biodegradable side chain and the counterion on catalyst performance.[19] In preliminary experiments we evaluated these catalysts in the acetalisation of benzaldehyde in methanol (Table 1). In the absence of catalyst no acetal is detected after 24 hours. We were pleased to find that each of the imidazolium ions tested (all of which are equipped with either ester (which we have shown to greatly facilitate biodegradation),[4] or pyrrolidinamide substituents, (biodegradation studies of amide examples on-going)) promoted the transformation under conditions under which the pyridinium species (**9**) is inactive, which underlines the inherent superiority of imidazolium over pyridinium ions as catalysts in these reactions.

It is clear that neither the ester (**10–14**, entries 2–6) nor the pyrrolidinamide (**15–20**, entries 7–12) substituent designed to facilitate biodegradation influence catalytic activity to any significant degree. The nature of the alkyl groups at either of the imidazolium nitrogen atoms (*i.e.* methyl *vs.* benzyl) also seems to be of marginal importance (entries 7–8 *vs.* 9–10). This is consistent with a mode of action analogous to that outlined in Fig. 2 where methanol attacks the catalyst at the C-2 carbon. A key parameter influencing catalyst efficacy in these systems proved to be the counteranion–tetrafluoroborate salt **10** (entry 2) and NTf_2 salts **13**, **16**, **18** and **20** (entries 5, 8, 10 and 12 respectively) are clearly superior to the other materials evaluated in this study. This is both expected (as the strength of the putative acid intermediate in these reactions will be influenced by the counterion) and fortunate, as the counterion plays a very significant role in determining the melting point of imidazolium ions–in particular the NTf_2 anion is known to endow imidazolium ions with significantly lower melting points than many other common counterions. The high activity conferred by the tetrafluoroborate anion is consistent

Table 1 Aprotic imidazolium ions: preliminary catalyst evaluation





Entry	Catalyst	Yield (%)[a]
1	**9**	0
2	**10**	85
3	**11**	11
4	**12**	33
5	**13**	51
6	**14**	12
7	**15**	13
8	**16**	23
9	**17**	9
10	**18**	29
11	**19**	11
12	**20**	27

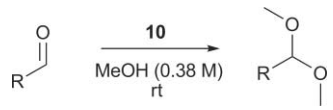
[a] Average of two experiments determined by ^{1}H NMR spectroscopy using an internal standard.

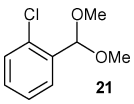
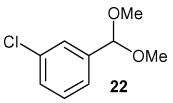
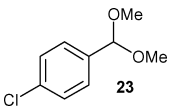
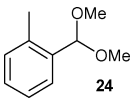
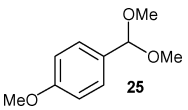
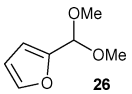
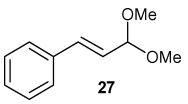
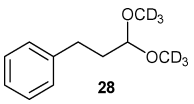
with previous studies on the strength of added acids in IL media,[20,21] investigations into the effect of the counterion on the acidity/catalytic activity of both sulfonic acid-substituted pyridinium ions[22] and protic imidazolium ions,[10a] in addition to correlating with our own experience concerning the catalytic activity of aprotic pyridinium ions in acetalisation reactions.[15]

With an active catalyst in hand we next wished to evaluate its general utility in the acetalisation of other substrates. Gratifyingly, it was found that **10** could promote the efficient, *room temperature* protection of aromatic aldehydes of variable steric and electronic characteristics at low catalyst loadings of 5–10% (Table 2). Activated (irrespective of the substitution pattern, *i.e.* acetals **21–23**, entries 1–3), hindered (*i.e.* **24**, entry 4) and electron rich deactivated (*i.e.* **25**, entry 5) benzaldehydes could all be transformed into their corresponding acetals with good-excellent isolated product yields. Aldehydes incorporating highly useful (from a synthetic standpoint) heterocyclic and α,β-unsaturated moieties were also compatible with the methodology (**26** and **27** respectively, entries 6 and 7), while the saturated aldehyde **28** underwent near quantitative acetalisation at just 1 mol% catalyst loading inside 1 min reaction time (entry 8).

As expected, the utility of this catalytic strategy is not confined to methanolysis. The employment of dithiol and diol nucleophiles **29–31** in only slight excess resulted in the formation of the synthetically useful dithiolane (a product usually formed under elevated temperatures), dithiane and dioxane derivatives

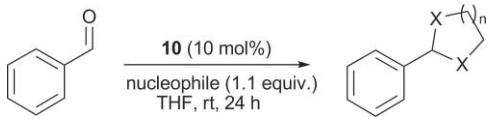
Table 2 Catalytic acetalisation of aldehydes: evaluation of substrate scope

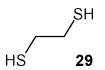
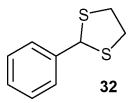
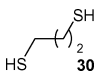
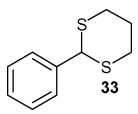
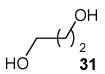
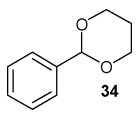


Entry	Product	Loading (mol%)	Time/h	Yield (%)[a]
1	 **21**	5	24	96
2	 **22**	5	24	93
3	 **23**	5	24	95
4	 **24**	10	24	87
5	 **25**	10	24	87
6	 **26**	10	24	89
7	 **27**	10	24	83
8	 **28**	1	1 min	97[b]

[a] Isolated yield after chromatography. [b] Determined by ^{1}H NMR spectroscopy using an internal standard due to product decomposition on chromatography.

Table 3 Catalysed dithiolane, dithiane and dioxane syntheses



Entry	Nucleophile	Product	Yield (%)[a]
1	 **29**	 **32**	92
2	 **30**	 **33**	65
3	 **31**	 **34**	86

[a] Isolated yield after chromatography.

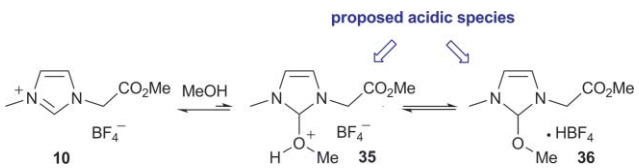


Fig. 3 Proposed mode of action of catalytic aprotic imidazolium ions.

32–34 in good-excellent yields at room temperature (Table 3, entries 1–3).

An analysis of the data in Tables 1-3 leads us to propose that these catalysts operate *via* an analogous mechanism to that suggested in Fig. 2. The protic additive (*e.g.* MeOH) adds to the C-2 position of the imidazolium ion to generate the acidic species **35** and **36** *in situ* (Fig. 3).[23]

Preliminary screening of the toxicity of 3 ionic liquids was performed to establish the influence of the ester or amide group and counter-ion. **10**, **11** and **15** were selected as a sample set based on structure and catalytic activity. A broad spectrum of organisms was chosen with results relevant to environmental and medicinal applications of interest.

In vitro antifungal activities (Table 5) of **10**, **11** and **15** were evaluated on a panel of four ATCC strains (*Candida albicans* ATCC 44859, *Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258) and eight clinical isolates of yeasts (*Candida krusei* E28, *Candida tropicalis* 156, *Candida glabrata* 20/I, *Candida lusitaniae* 2446/I, *Trichosporon beigelii* 1188) and filamentous fungi (*Aspergillus fumigatus* 231, *Absidia corymbifera* 272, *Trichophyton mentagrophytes* 445). Antifungal activity was not observed for either **10**, **11** and **15** at the highest concentration screened (2.0 mM). Antimicrobial activity of imidazolium and pyridinium ionic liquids has been reported previously, with increasing toxicity observed across a series of alkyl (C6-C14) substituted methylimidazolium chlorides.[4, 24]

In vitro antibacterial activities (Table 5) of the compounds were evaluated on a panel of three ATCC strains (*Staphylococcus aureus* ATCC 6538, *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027) and five clinical isolates (*Staphylococcus aureus* MRSA HK5996/08, *Staphylococcus epidermidis* HK6966/08, *Enterococcus* sp. HK14365/08, *Klebsiella pneumoniae* HK11750/08, *Klebsiella pneumoniae* ESBL HK14368/08). Antimicrobial activity was not observed for **10**, **11** and **15** at the highest concentration screened (2.0 mM).

Gilmore *et al.*[4c] recently tested 1-hexyl-3-methylimidazolium chloride for antimicrobial activity against a number of pathogens (cocci, rods and fungi) with MIC values of >1.644 mM observed. The data from the screening of **10**, **11** and **15** in Tables 4 and 5 are comparable to Gilmore's results, although it

Table 4 Antifungal activity of **10**, **11**, **15** (MIC [mmol L^{-1}])

Organisms	Time/h	**10**	**11**	**15**
Candida albicans	24	>2.0	>2.0	>2.0
ATCC 44859	48	>2.0	>2.0	>2.0
Candida albicans	24	>2.0	>2.0	>2.0
ATCC 90028	48	>2.0	>2.0	>2.0
Candida parapsilosis	24	>2.0	>2.0	>2.0
ATCC 22019	48	>2.0	>2.0	>2.0
Candida krusei	24	>2.0	>2.0	>2.0
ATCC 6258	48	>2.0	>2.0	>2.0
Candida krusei	24	>2.0	>2.0	>2.0
E28	48	>2.0	>2.0	>2.0
Candida tropicalis	24	>2.0	>2.0	>2.0
156	48	>2.0	>2.0	>2.0
Candida glabrata	24	>2.0	>2.0	>2.0
20/I	48	>2.0	>2.0	>2.0
Candida lusitaniae	24	>2.0	>2.0	>2.0
2446/I	48	>2.0	>2.0	>2.0
Trichosporon beigelii	24	>2.0	>2.0	>2.0
1188	48	>2.0	>2.0	>2.0
Aspergillus fumigatus	24	>2.0	>2.0	>2.0
231	48	>2.0	>2.0	>2.0
Absidia corymbifera	24	>2.0	>2.0	>2.0
72	48	>2.0	>2.0	>2.0
Trichophyton mentagrophytes	72	>2.0	>2.0	>2.0
445	120	>2.0	>2.0	>2.0

Table 5 Antibacterial activity of **10**, **11**, **15** (MIC [mmol L^{-1}])

Organisms	Time/h	**10**	**11**	**15**
S. aureus	24	>2.0	>2.0	>2.0
CCM 4516/08	48	>2.0	>2.0	>2.0
S. aureus	24	>2.0	>2.0	>2.0
H 5996/08	48	>2.0	>2.0	>2.0
S. epidermidis	24	>2.0	>2.0	>2.0
H 6966/08	48	>2.0	>2.0	>2.0
Enterococcus sp.	24	>2.0	>2.0	>2.0
J 14365/08	48	>2.0	>2.0	>2.0
E. coli	24	>2.0	>2.0	>2.0
CCM4517	48	>2.0	>2.0	>2.0
Klebsiella pneumoniae	24	>2.0	>2.0	>2.0
D 11750/08	48	>2.0	>2.0	>2.0
Klebsiella pneumoniae	24	>2.0	>2.0	>2.0
J 14368/08	48	>2.0	>2.0	>2.0
Pseudomonas aeruginosa	24	>2.0	>2.0	>2.0
CCM 1961	48	>2.0	>2.0	>2.0

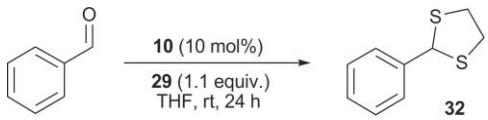
is noted that different strains of organisms are investigated in the two studies.

By avoiding the introduction of long lipophilic alkyl chains into the ionic liquids structure we postulate that undesirable antimicrobial and antifungal toxicity has been limited. Our data is limited to ionic liquids **10**, **11** and **15** at present - further toxicity-screening studies are on-going.

Significant is the effect of the anion on antimicrobial and antifungal toxicity. Changing the bromide **11** to the BF_4 analogue **10** did not increase the toxicity of the ionic liquid with MIC values >2.0 mmol L^{-1} observed. While more lipophilic NTf_2 derivatives may have increased antimicrobial and antifungal toxicity,[2,3] examples **13**, **16**, **18** and **20** gave inferior results in the preliminary catalyst screening (Table 1). Notwithstanding, the toxicity of the NTf_2 examples herein will be published in due course.

Finally, the ability of catalysts to accelerate reactions and generally render them more efficient/selective under milder

Table 6 Catalyst recycling



Entry	Cycle	Yield (%)[a]
1	1	92
2	2	90
3	3	89
4	4	91
5	5	90
6	6	90
7	7	91
8	8	90
9	9	90
10	10	90
11	11	89
12	12	90
13	13	90
14	14	91
15	15	90

[a] Determined by ^{1}H NMR spectroscopy using an internal standard.

conditions than those required for the uncatalysed process is particularly attractive from a 'green' perspective, however, a second, often overlooked advantage is that by definition, catalysts should be unchanged at the end of the reaction and thus should in principle be recyclable (if they are sufficiently robust) indefinitely. To evaluate the recyclability of **10** we carried out the protection of benzaldehyde as its 1,3-dithiolane **32** catalysed by **10** (Table 6). After 24 h, hexane was added to precipitate the catalyst and the solution containing the product was decanted and dried *in vacuo* to give **32** in excellent yield. The solid catalyst was dried *in vacuo* to remove the condensation water[25] and reused in 14 subsequent iterative cycles *without any loss of catalytic activity being observed*. It is noteworthy that the recycling study was terminated at this stage only because *no attenuation* of catalyst activity was detected in the 15th cycle. It is significant that catalyst **10** incorporating the methyl ester group, susceptible to acid catalysed hydrolysis, gave efficient recycling and performance. To the best of our knowledge this represents the most recyclable Brønsted acidic IL catalyst reported to date.

Conclusions

In conclusion we have designed the first small library of aprotic ionic liquid catalysts with low antibacterial and antifungal toxicity - specifically designed to be of reduced environmental impact - which can behave as Brønsted acids in a controlled fashion. This allows these materials to act as acidic catalysts under controlled conditions, without requiring the precautions usually associated with the storage and use of strongly acidic substances. The systematic variation of the catalyst's steric and electronic characteristics (within the framework of using substituents designed to render these materials more environmentally benign than archetypal long alkyl chain substituted imidazolium ILs) revealed that the counterion makes a key contribution to overall catalyst efficacy. The most active catalyst developed

promotes acetalisation and thioacetalisation reactions of a range of aldehydes at room temperature and low catalyst loadings, and after the reaction the catalyst can be recovered by simply adding hexane and decanting the product. The recycled catalyst can be reused in 15 iterative recycles without any discernible loss of catalytic activity. Antifungal and antibacterial toxicity studies demonstrated that the three ionic liquids did not inhibit the growth of any organism screened at concentrations of >2.0 mM. The inclusion of either an ester or an amide group (as opposed to an alkyl chain) did not lead to an increase in toxicity. We were pleased to find that changing the bromide to the tetrafluoroborate anion also did not lead to significant increase in toxicity. The most active catalyst (*i.e.* **10**) was also non-toxic, within the scope of the screening performed. Further toxicity, ecotoxicity and biodegradation studies are in progress, to establish the environmental fate of the ionic liquid catalysts presented herein, and lead to a more informed decision of performance *vs.* environmental impact.

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