Green Chemistry

RSC Publishing

PAPER

View Article Online
View Journal | View Issue

Cite this: *Green Chem.*, 2013, **15**, 2740

A new generation of aprotic yet Brønsted acidic imidazolium salts: low toxicity, high recyclability and greatly improved activity†

Lauren Myles,[a] Rohitkumar G. Gore,[b] Nicholas Gathergood*[b] and Stephen J. Connon*[a]

Received 28th May 2013,
Accepted 24th July 2013

DOI: 10.1039/c3gc40975a

www.rsc.org/greenchem

Catalysts which have low antimicrobial toxicity and are aprotic, yet which can act as Brønsted acidic catalysts in the presence of protic additives have been developed. The catalysts are recyclable, considerably more active (*i.e.* can be used at 10–50 times lower loadings) and of broader scope than their antecedent generation.

Since Forbes and Davis reported the design of a class of phosphonium- and imidazolium ion-based ionic liquids (*e.g.* **1**, Fig. 1A) equipped with a pendant acidic sulfonic acid moiety, interest in Brønsted acidic ionic liquids (BAILs) has gathered considerable pace.[1,2] These materials afford the practitioner the flexibility of a system which combines strong acidity with the traditional advantages[3] associated with the use of non-volatile ionic liquids.

Subsequently two other strategies for the design of acidic imidazolium-ion based ionic liquids (ILs) were reported: the protonated imidazole conjugate acids[3o,4] (*i.e.* **2**) and traditional imidazolium-ion based ILs which incorporate acidic counter-anions (*i.e.* **3**).[5] While these systems have found application in a wide-range of acid-catalysed reactions, the potential uncertainties from an environmental standpoint (to the best of our knowledge the toxicity and biodegradation profiles of these materials have yet to be established) and potential storage difficulties associated with the fact that these materials are strongly Brønsted acidic, remain.

We therefore became interested in the design of aprotic salts which could serve as acidic catalysts *only when used in conjunction with an additive*. These materials hold promise as catalysts which can be designed to be readily storable and of minimal toxicity/environmental impact, the catalytically useful acidity of which could be controlled in an 'on–off' fashion. In short, these catalysts would be acidic only when required.

Our inspiration for this work came from the serendipitous discovery that *N*-alkyl pyridinium ions could catalyse the acetalisation of benzaldehyde in the absence of any discernible acidic species in solution.[6,7] It was later demonstrated that this phenomenon also occurred in the case of *N*-alkyl imidazolium ions, which allowed the design of a suite of demonstrably low antimicrobial toxicity salts (of which **4**, Fig. 1A, proved the most active) capable of promoting the acetalisation of aldehydes (*inter alia*) at low catalyst loadings (*e.g.* 5–10 mol%, Fig. 1B).[8a] Along the same lines, we recently demonstrated that triazolium ion-based species could act in a similar fashion at loadings of 1–2 mol%.[8b] It was proposed that the low resonance stabilisation energy of the imidazolium ion would allow

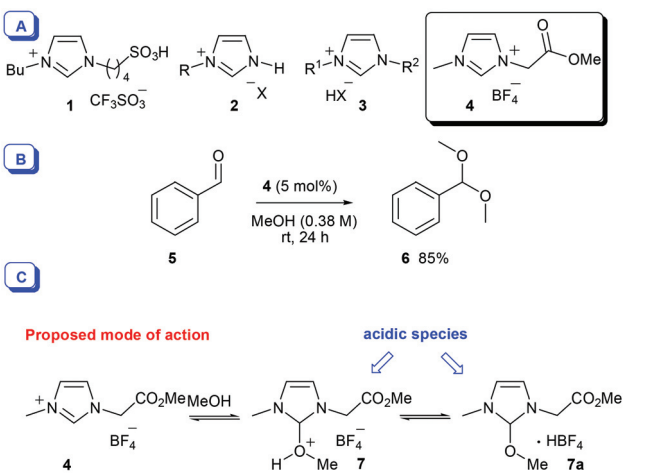


Fig. 1 Catalytically competent imidazolium ion-based acidic ionic liquids and the proposed mode of action of catalyst **4**.

[a]*School of Chemistry, Centre for Synthesis and Chemical Biology, Trinity Biomedical Sciences Institute, University of Dublin, Trinity College, Dublin 2, Ireland. E-mail: connons@tcd.ie; Fax: +353 16712826*

[b]*School of Chemical Sciences and National Institute for Cellular Biotechnology, Dublin City University, Glasnevin, Dublin 9, Ireland. E-mail: Nick.Gathergood@dcu.ie; Fax: +353 17005503*

†Electronic supplementary information (ESI) available: Synthesis of all catalysts not detailed in the Experimental section, general procedures, characterisation data and NMR spectra for all catalysts and products. See DOI: 10.1039/c3gc40975a

the addition of methanol to **4**, leading to the presence of low concentrations of **7**/**7a** in methanolic solution (Fig. 1C). These species could then serve as the Brønsted acidic agent responsible for the observed catalysis. While it should be noted that **7**/**7a** have not been directly observed experimentally, this hypothesis can account all of the data obtained thus far.[6–8]

While **4** was shown to be catalytically active and completely non-toxic to 20 sample microorganisms (8 bacteria and 12 fungi),[8] we were nevertheless aware that the utility and potential environmental impact of these systems could be significantly improved if: (a) catalytic activity could be increased significantly (so that less of the material would be required for use in synthetic applications) and (b) the tetrafluoroborate counteranion[9–13] (which is a *sine qua non* for high activity in catalysts such as **4**) could be replaced with a less hydrolytically unstable[14] substitute.

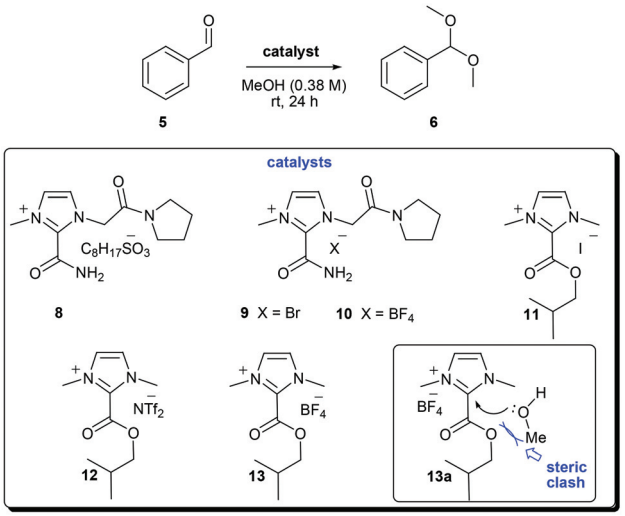
If the mechanistic hypothesis outlined in Fig. 1C accurately captures the mode of action of **4**, then it should be possible to bias the equilibrium between **4** and **7**/**7a** towards the latter through the installation of electron withdrawing substituents on the imidazolium ion, which would further reduce delocalisation and favour nucleophilic attack by the protic additive on the heterocycle. Since Gathergood and Scammells[15] had previously shown that the incorporation of hydrolytically susceptible moieties into the *N*-alkyl substituents of imidazolium salts improved biodegradability, we were also interested in determining the (hitherto unknown) influence that equipping the imidazolium ring with ester and amide substituents would have on both the toxicity and the biodegradability of the candidate catalyst structures.

Herein we describe the contribution that these substituents make to catalytic efficacy; their effect on toxicity and biodegradability is discussed in the next paper in this issue.

We began with the synthesis of a library of imidazolium salts **8–13** incorporating an electron withdrawing group at C-2. These materials were synthesised from the corresponding available imidazole carboxylic acids and then sequentially alkylated (full details in the ESI†). We also included structures with and without pendant ester/amide functionality in the *N*-alkyl substituent. These materials were evaluated as promoters of the room temperature acetalisation of benzaldehyde in methanol (Table 1).

The data associated with the prototype catalyst **4** is included for comparison (entry 1). We were pleased to find that the C-2 amide-substituted imidazolium ion **8** promoted (at 1 mol% loading) the formation of **6** from **5** in similar yield to that obtained using **4** at 5 mol% levels (entry 2). Exchange of the counterion from octylsulfate to bromide and tetrafluoroborate (*i.e.* catalysts **9** and **10**) led to a further (marginal) improvement in catalytic activity (entries 3 and 4). The C-2 substituted esters **11–13** also proved capable of promoting the reaction with considerably improved efficacy relative to **4** (entries 5–7). It appears that hydrogen-bonding to the C-2 substituent does not play a significant role in catalysis – as can be deduced from the similar performance of amides **8** and **9** to that of esters **10–12** (entries 2–3 and 4–6). It is also noteworthy that

Table 1 Aprotic C-2 substituted imidazolium ions: catalyst evaluation



Entry	Catalyst	Loading (mol%)	Yield[a] (%)
1	**4**	5	85
2	**8**	1	80
3	**9**	1	83
4	**10**	1	86
5	**11**	1	86
6	**12**	1	85
7	**13**	1	91
8	**13**	0.1	72

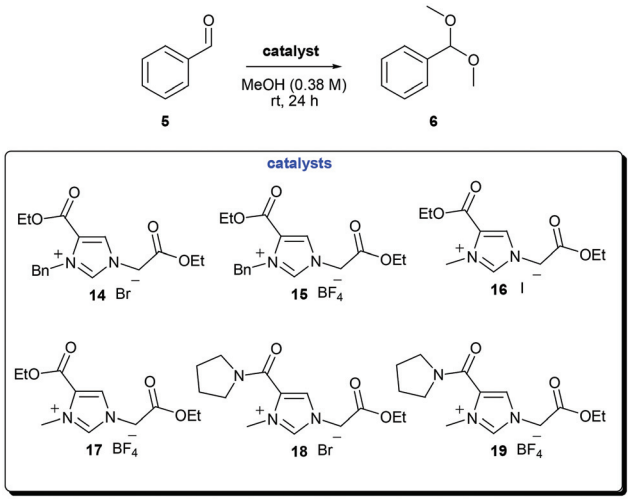
[a] Determined by ^{1}H NMR spectroscopy using an internal standard.

the influence of the anion on catalyst performance is considerably less significant in this library that was the case with catalysts devoid of ring-substitution (such as **4**);[8a] we would interpret this as strongly indicating that the more electrophilic imidazolium ion units are making a greater contribution to catalysis in this library. As before, we did observe more efficient catalysis when the imidazolium ion incorporates a tetrafluoroborate counterion (*i.e.* catalyst **13**), which allows the synthesis of the acetal **6** in 91% yield at 1 mol% catalyst loading (entry 7). At loadings lower than 1 mol% product yields diminish considerably (entry 8).

While it was clear that **8–13** represented a considerable step forward in terms of catalytic activity, we were aware that the designs were not optimal. One particular cause for concern was the location of the electron-withdrawing substituent: while installing this at C-2 allows the maximum amount of both inductive and mesomeric forms of electron withdrawal to be exerted by the amide/ester moiety at the proposed site of nucleophilic attack by methanol, it also introduces a degree of counterproductive steric crowding (*i.e.* **13a**), which would be expected to limit catalyst performance.

It therefore seemed prudent to design a library of catalysts characterised by the location of the electron withdrawing group at a further remove from C-2. The C-4 substituted analogues **14–19** were therefore duly prepared from the corresponding available imidazole carboxylic acids and evaluated

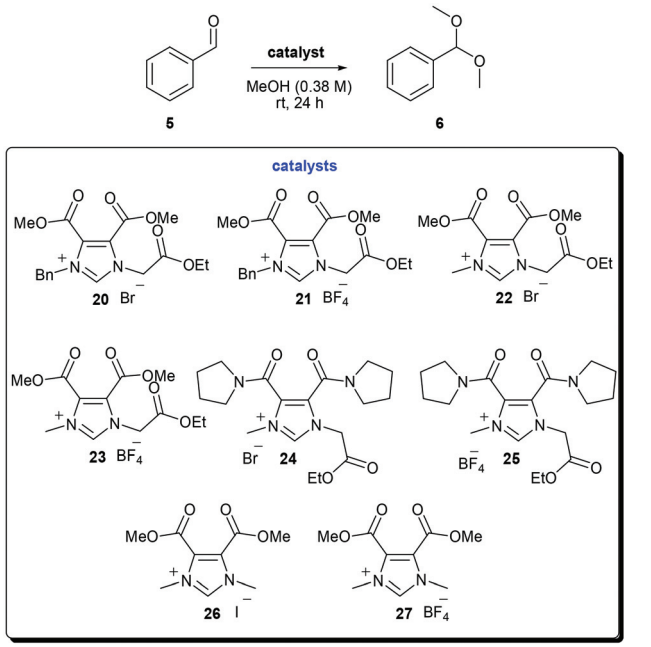
Table 2 Aprotic C-4 substituted imidazolium ions: catalyst evaluation



Entry	Catalyst	Loading (mol%)	Yield[a] (%)
1	**14**	1	>98
2	**15**	1	>98
3	**16**	1	>98
4	**17**	1	>98
5	**18**	1	95
6	**19**	1	>98
7	**14**	0.1	81
8	**15**	0.1	88
9	**16**	0.1	78
11	**17**	0.1	86
12	**19**	0.1	85

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

Table 3 Aprotic disubstituted imidazolium ions: catalyst evaluation



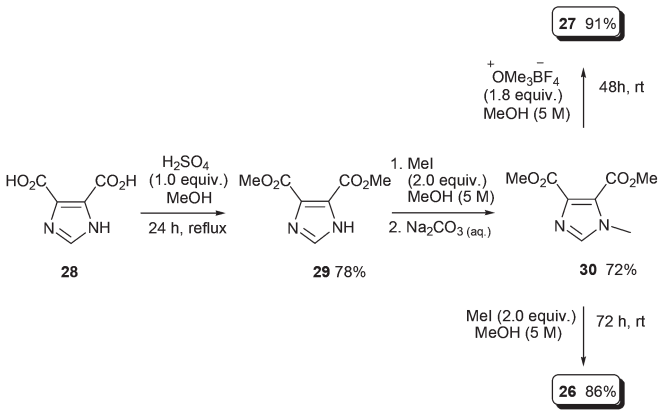
Entry	Catalyst	Loading (mol%)	Yield[a] (%)
1	**20**	1	>98
2	**21**	1	>98
3	**22**	1	>98
4	**23**	1	>98
5	**24**	1	>98
6	**25**	1	>98
7	**26**	1	98
8	**27**	1	>98
9	**20**	0.1	89
10	**21**	0.1	94
11	**22**	0.1	86
12	**23**	0.1	92
13	**24**	0.1	82
14	**25**	0.1	91
15	**27**	0.1	92

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

under identical conditions (Table 2). This strategy was successful – when utilised at 1 mol% loading, catalysts **14–17** and **19** promoted the reaction in essentially quantitative yield (entries 1–4 and 6). Imidazolium ion **18** (which incorporates an iodide counteranion) is also an excellent catalyst (the product is formed in 95% yield) yet is perceptibly less active than the other members of the library (entry 5). Since the ranking of **14–17** and **19** on the basis of activity could not be determined at 1 mol% loading, these materials were then re-evaluated at 0.1 mol% levels under otherwise identical conditions. Product yields remained high (entries 7–12), however none of the catalysts was capable of promoting the reaction to >90% yield inside 24 h. The nature of the anion-, activating substituent (*i.e.* ester *vs.* amide) and *N*-alkyl moiety appears to have little impact on efficacy in these systems.

Given the dramatic effect of the introduction of one electron withdrawing group (especially when not located at C-2) on catalyst activity, the final step in our optimisation study involved the design of catalysts characterised by the presence of two such groups at C-4 and C-5 (Table 3). As expected, catalysts **20–27** all proved highly active at 1 mol% levels (entries 1–8), with only the iodide **26** failing to promote the reaction to completion (entry 7). At 0.1 mol% loading, product yields were attenuated, however using catalysts incorporating the tetrafluoroborate counteranion (*i.e.* entries **10**, **12**, **14** and **15**) yields remained over 90%.

In addition to the catalyst activity exhibited by the optimum structure identified by this study (*i.e.* **21**), the performance of the simple structures **26** and **27** was also particularly gratifying: these materials are readily prepared from the inexpensive 4,5-imidazole carboxylic acid in a relatively atom-economic fashion (see Scheme 1) and are capable of acting as synthetically useful catalysts at loadings 5–50 times lower than those previously necessary using the optimal first generation material **4**. Their activity is such that one is no longer dependant on the nature of the anion to ensure high product yields – the iodide **26** can promote the formation of **6** in >90% yield at just 1 mol% loading. We also note with interest that Fatemi and Izadiyan[13] have very recently suggested that IL-symmetry is linked to cytotoxicity to rat luekemia cell lines;



Scheme 1 Synthesis of **26** and **27** from the inexpensive diacid **28**.

with less symmetrical salts in general proving more cytotoxic than more symmetrical counterparts.

The general catalyst order of activity (*i.e.* C-2 substituted < C-4 substituted < C-4/C-5 disubstituted) and the diminished influence of the anion relative to the case with **4** is in line with what one would expect from the mechanistic hypothesis outlined in Fig. 1C, which provides further evidence supporting this most unusual proposed mode of action.

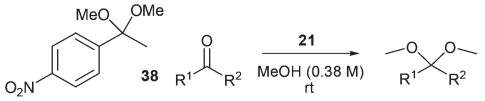
With an active and easily prepared catalyst in hand, our attention next turned to the question of substrate scope (Table 4). Catalyst **21** could catalyse the smooth acetalisation of activated- (*i.e.* **31–33**, entries 1–3), hindered- (*i.e.* **34**, entry 4) deactivated- (*i.e.* **35**, entry 5), heterocyclic- (*i.e.* **36**, entry 6) and α,β-unsaturated aldehydes (*i.e.* **37**, entry 7) with higher (excellent) isolated product yields *at 10–50 times lower catalyst loading* (in shorter reaction times) than those required for the synthesis of these acetals using catalyst **4**. We also found that **21** could promote the ketalisation of *p*-nitrobenzaldehyde to form **38** in good yield – a reaction which was completely beyond the scope of catalyst **4**.

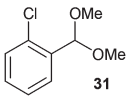
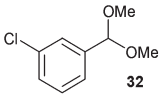
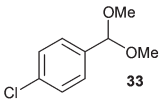
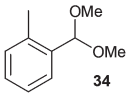
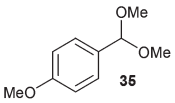
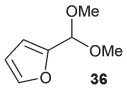
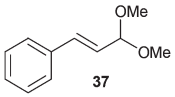
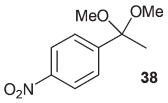
The synthetically useful dithiolane (a product usually formed under elevated temperatures) and dioxane derivatives **39** and **40** could also be formed from **5** in good–excellent yields at room temperature catalysed by **21** at low loading (Scheme 2).

According to the principle of microscopic reversibility, **21** should also serve as a useful catalyst for the hydrolysis of acetals/ketals. This proved to be the case: in an aqueous medium **21** (1 mol%) could mediate the conversion of acetal **6** back to benzaldehyde (**5**) under mild, ambient temperature conditions (Scheme 3).

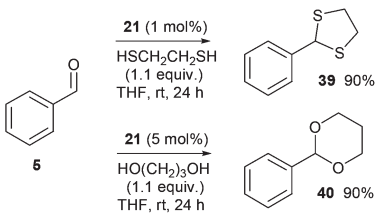
While at this juncture the superior activity and potential utility of **21** (relative to **4**) was beyond doubt, we were also interested in evaluating the recyclability of **21**. We carried out the protection of **5** as its dithiolane derivative **39** (Table 5). After 24 h, hexane was added to precipitate the catalyst and the solution containing the product was decanted and dried *in vacuo* to give **39** in excellent yield. The solid catalyst was dried *in vacuo* to remove the condensation water[16] and reused in 5 subsequent iterative cycles *without any loss of catalytic activity being observed*. The study was terminated at this point as the catalyst appeared to be beginning to show physical signs of decomposition. While **21** could not be recycled as

Table 4 Catalytic acetalisation/ketalisation: evaluation of substrate scope

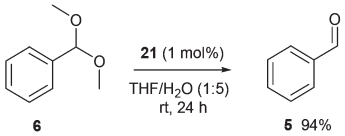


Entry	Product	Loading (mol%)	Time (h)	Yield[a] (%)
1	 **31**	0.1	24	95
2	 **32**	0.1	24	96
3	 **33**	0.1	24	98
4	 **34**	1	24	90
5	 **35**	1	24	92
6	 **36**	1	24	92
7	 **37**	1	24	90
8	 **38**	10	48	63[b]

[a] Isolated yield after chromatography. [b] Reaction at 35 °C.

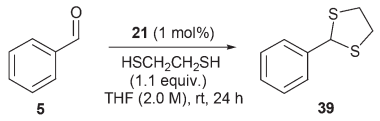


Scheme 2 Dithiolane/dioxane formation: stoichiometric nucleophiles.



Scheme 3 Acetal hydrolysis under mild conditions promoted by **21**.

Table 5 Catalyst recycling



Entry	Cycle	Yield[a] (%)
1	1	94
2	2	94
3	3	94
4	4	95
5	5	94

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

many times as **4** (which was recycled in our previous study 14 times),[8] **21** was employed at considerably lower loading in this study (1 mol% *vs.* 10 mol%), and as such can be considered more recyclable than **4** due to its significantly superior TON over the accumulated cycles.

Conclusions

In summary, we have designed a 3rd generation of aprotic salts capable of behaving as Brønsted acids in an 'on–off' fashion, controlled by the use of protic additives. These catalysts offer greatly improved catalytic efficacy (with the attendant reduced environmental impact) without compromising the low toxicity profile associated with the first generation series. Analysis of a previous study provided a measure of mechanistic insight, which suggested that the installation of electron withdrawing groups on the imidazolium ring would facilitate the formation of greater equilibrium concentrations of the putative acidic adduct with methanol, leading to faster catalysis. An initial library was prepared, the members of which possessed either an ester or an amide group at C-2. These catalysts proved considerably more active than either the optimum 1st generation benchmark material **4**[8a] or the 2nd generation triazolium ion-based systems.[8b] Removal of the activating group to C-4 led to further improvements in efficacy, while the installation of a second electron withdrawing moiety at C-5 resulted in a suite of catalysts capable of promoting the acetalisation of benzaldehyde by methanol at catalyst loadings 50 times lower than that required to produce the product using **4**.

The optimum catalyst systems are prepared in a straightforward manner from an inexpensive starting material and are characterised by a marked reduction in the relative contribution of the anion to catalysis, which gives the practitioner the flexibility to choose the anion based on environmental/toxicological/solubility/chemoselectivity considerations if required. In addition it removes the obligation to use the hydrolytically suspect tetrafluoroborate anion associated with the first generation catalyst series. The optimum catalyst in this study could promote ambient temperature acetalisation and thioacetalisation reactions of a range of aldehydes at catalyst loadings of 0.1–1 mol% and could catalyse both the reverse hydrolytic process and a ketalisation reaction which were beyond the scope of the first generation series.[17,18] After the reaction the catalyst can be recovered by simply adding hexane and decanting the product. The recycled catalyst can be reused in 5 iterative recycles (at 1 mol% loading) without any discernible loss of catalytic activity. Biodegradation, antibacterial and antifungal toxicity studies are reported in the following paper. We are grateful to the Environmental Protection Agency for their financial support of this work.

Experimental

General

Proton nuclear magnetic resonance spectra were recorded on 400 MHz and 600 MHz spectrometers in $CDCl_3$ referenced relative to residual $CHCl_3$ (δ = 7.26 ppm), DMSO-d_6 referenced relative to residual DMSO (H) (δ = 2.51 ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instruments (100 MHz and 150 MHz) with total proton decoupling. All melting points are uncorrected. Infrared spectra were obtained using neat samples on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. Flash chromatography was carried out using silica gel, particle size 0.04–0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualised by UV irradiation, $KMnO_4$ or anisaldehyde staining. All aldehydes were sourced commercially and either distilled under vacuum (if liquid) or dissolved in CH_2Cl_2 and washed with NaOH (if solid) prior to use. Methanol and THF were distilled from sodium and stored under argon best results were obtained using freshly distilled methanol. All reactions were carried out in oven-dried glassware with magnetic stirrers under an atmosphere of argon, unless specified. Careful drying of all catalysts is essential for best results a convenient procedure for this follows: the catalysts were dissolved in dry toluene under argon. The solvent was removed *in vacuo* and the procedure was repeated twice, taking care the compound was not exposed to air. The catalysts were then dried under high vacuum for 2 h and used in the reaction.

2-(Isobutoxycarbonyl)-1,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (13)

A round-bottomed flask was charged with isobutyl 1-methyl-1*H*-imidazole-2-carboxylate (0.200 g, 1.1 mmol) and dry diethyl ether (10 mL) under nitrogen. To this solution was added trimethyloxonium tetrafluoroborate (0.162 g, 1.1 mmol) quickly. The reaction mixture was stirred vigorously for 24 h. The product precipitated as a white solid, was filtered, and then washed with diethyl ether (2 × 10 mL). The product was dried *in vacuo* for 24 h to give **13** as a white solid (0.302 g, 97%). Mp 64–65 °C; δ_H (400 MHz, $CDCl_3$); 1.05 (d, J = 6.8 Hz, 6H), 2.14 (sept, J = 6.8, 6.4 Hz, 1H), 4.16 (s, 6H), 4.29 (d, J = 6.4 Hz, 2H), 7.65 (s, 2H); δ_C (100 MHz, $CDCl_3$); 19.1, 27.5, 39.3, 74.2,

126.7, 132.2, 153.9; *m*/*z* (ES) 197.1295 ($[M - BF_4^-]^+$. $C_{10}H_{17}N_2O_2^+$ requires 197.1285).

3-Benzyl-1,5-bis(ethoxycarbonyl)-1*H*-imidazol-3-ium tetrafluoroborate (15)

To a 50 mL round bottomed flask fitted with a magnetic stirring bar, **14** (150 mg, 0.38 mmol) was added. To this $NaBF_4$ (75 mg, 0.68 mmol) and acetone (10 mL) were added and the mixture was placed under an argon atmosphere. The resulting suspension was stirred at room temperature for 4 days, after which time a white precipitate was formed. This precipitate was filtered using a Buchner funnel under vacuum and washed with dry acetone (2 × 5 mL). The combined filtrate and washings were then concentrated *in vacuo* giving the pure product **15** as a pale yellow solid (146 mg, 96%). δ_H (400 MHz, DMSO-d_6); 1.32 (t, J = 6.8 Hz, 6H), 3.56 (q, J = 6.8 Hz, 4H), 4.69 (s, 1H), 5.95 (s, 1H), 7.26–7.48 (m, 5H), 7.86 (s, 1H), 8.95 (s, 1H); δ_C (100 MHz, DMSO-d_6); 15.1, 15.2, 49.5, 58.1, 62.1, 62.5, 126.7, 128.9, 129.7, 130.1, 134.4, 137.5, 146.2, 161.2, 169.0; *m*/*z* (ES) 317.1423 ($[M - BF_4^-]^+$. $C_{17}H_{21}N_2O_4^+$ requires 317.1422).

3-Benzyl-1-(2-ethoxy-2-oxoethyl)-4,5-bis(methoxycarbonyl)-1*H*-imidazol-3-ium tetrafluoroborate (21)

To a 50 mL round bottomed flask fitted with a magnetic stirring bar, **20** (250 mg, 0.57 mmol) was added. To this $NaBF_4$ (74.8 mg, 0.68 mmol) and acetone (10 mL) were added and the mixture was placed under an argon atmosphere. The resulting suspension was stirred at room temperature for 4 days. After which time a white precipitate was formed. This precipitate was filtered and washed with dry acetone (2 × 5 mL). The combined filtrate and washings were then concentrated *in vacuo* to give the pure catalyst **21** as a pale yellow oil (249 mg, 98%). δ_H (400 MHz, DMSO-d_6); 1.23–1.26 (m, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 4.22 (q, J = 7.1 Hz, 2H), 5.39 (s, 2H), 5.62 (s, 2H), 7.26 (s, 1H), 7.43 (d, J = 7.2 Hz, 2H), 7.64 (t, J = 7.2 Hz, 2H), 9.89 (s, 1H); δ_C (100 MHz, DMSO-d_6); 14.2, 47.9, 50.4, 51.5, 53.9, 62.1, 123.7, 128.9, 129.6, 133.2, 138.7, 157.8, 159.7, 164.2, 166.9, 168.2; *m*/*z* (ES) 361.1392 ($[M - BF_4^-]^+$. $C_{18}H_{21}N_2O_6^+$ requires 361.1394).

4,5-Bis(methoxycarbonyl)-1,3-dimethyl-1*H*-imidazol-3-ium iodide (26)

A 25 mL round-bottomed flask, fitted with a magnetic stirring bar, was charged with **22a** (250 mg, 1.26 mmol) in acetonitrile (2 mL). Methyl iodide (79 μL, 1.26 mmol) was added and the resulting solution was stirred at room temperature for 3 days. Upon completion of the reaction, the solvent was removed *in vacuo* giving the pale yellow oil **26** (368 mg, 86%). δ_H (400 MHz, DMSO-d_6); 3.91–4.02 (m, 12H), 9.40 (s, 1H); δ_C (100 MHz, DMSO-d_6); 36.2, 53.8, 126.6, 141.2, 157.3; *m*/*z* (ES) 213.0877 ($[M - I^-]^+$. $C_9H_{13}N_2O_4^+$ requires 213.0875).

4,5-Bis(methoxycarbonyl)-1,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (27)

A 25 mL round-bottomed flask, fitted with a magnetic stirring bar, was charged with **22a** (250 mg, 1.62 mmol) in acetonitrile (2 mL). Trimethyloxonium tetrafluoroborate (240 mg, 1.62 mmol) was added and the reaction mixture was stirred at room temperature for 3 days. Upon completion of the reaction, the solvent was removed *in vacuo* giving the pale yellow solid **27** (344 mg, 91%). δ_H (400 MHz, DMSO-d_6); 3.95 (br.s, 12H), 9.42 (s, 1H); δ_C (100 MHz, DMSO-d_6); 38.1, 53.8, 126.7, 141.2, 157.3; *m*/*z* (ES) 213.0873 ($[M - BF_4^-]^+$. $C_9H_{13}N_2O_4^+$ requires 213.0875).

General procedure – acetalisation of aldehydes

A 20 mL reaction vessel was fitted with a magnetic stirring bar, charged with catalyst (0.08 mmol), fitted with a septum and flushed with argon. Benzaldehyde (170 μL, 1.67 mmol) was added followed by dry methanol (3.4 mL) *via* syringe. The solution was then stirred under argon at room temperature. When conversion was judged to be either complete or >95% conversion (by ^{1}H NMR spectroscopic analysis) the reaction was quenched with $PhNHNH_2$ and solvent was removed *in vacuo*. The crude product was either purified by flash-chromatography or the yield was calculated using an internal standard.

Notes and references

1 A. C. Cole, J. L. Jensen, I. Ntai, K. L. T. Tran, K. J. Weaver, D. C. Forbes and J. H. Davis, *J. Am. Chem. Soc.*, 2002, **124**, 5962.

2 For representative recent examples using this strategy see: (*a*) D. C. Forbes and K. J. Weaver, *J. Mol. Catal. A: Chem.*, 2004, **214**, 129; (*b*) H. Xing, T. Wang, Z. Zhou and Y. Dai, *Ind. Eng. Chem. Res.*, 2005, **44**, 4147; (*c*) J. Guia, H. Bana, X. Cong, X. Zhang, Z. Hu and Z. Sun, *J. Mol. Catal. A: Chem.*, 2005, **225**, 27; (*d*) D. Liu, J. Gui, X. Zhu, L. Song and Z. Sun, *Synth. Commun.*, 2007, **37**, 759; (*e*) A. Hubbard, T. Okazaki and K. K. Laali, *Aust. J. Chem.*, 2007, **60**, 923; (*f*) D.-Q. Xu, J. Wu, S.-P. Luo, J.-X. Zhang, J.-Y. Wu, X.-H. Du and Z.-Y. Xu, *Green Chem.*, 2009, **11**, 1239; (*g*) L. Yang, L.-W. Xu and C.-G. Xia, *Synthesis*, 2009, 1969; (*h*) J. Akbari and A. Heydari, *Tetrahedron Lett.*, 2009, **50**, 4236; (*i*) Y. W. Zhao, J. X. Long, F. G. Deng, X. F. Liu, Z. Li, C. G. Xia and J. J. Peng, *Catal. Commun.*, 2009, **10**, 732; (*j*) X. Liu, H. Ma, Y. Wu, C. Wang, M. Yang, P. Yana and U. Welz-Biermann, *Green Chem.*, 2011, **13**, 697; (*k*) A. K. Ressmann, P. Gaertner and K. Bica, *Green Chem.*, 2011, **13**, 1442.

3 Selected reviews: (*a*) T. Welton, *Chem. Rev.*, 1999, **99**, 2071; (*b*) P. Wasserchеid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772; (*c*) R. Sheldon, *Chem. Commun.*, 2001, 2399; (*d*) J. S. Wilkes, *Green Chem.*, 2002, **4**, 73; (*e*) J. H. Davis and P. Fox, *Chem. Commun.*, 2003, 1209; (*f*) R. A. Sheldon, *Green Chem.*, 2005, **7**, 267; (*g*) A. Riisager, R. Fehrmann, M. Haumann and P. Wasserscheid, *Eur. J. Inorg. Chem.*, 2006, 695; (*h*) C. Hardacre, J. D. Holbrey, M. Nieuwenhuyzen and T. G. A. Youngs, *Acc. Chem. Res.*, 2007, **40**, 1146; (*i*) A. A. H. Padua, M. F. Costa Gomes and J. N. A. Canongia Lopes, *Acc. Chem. Res.*, 2007, **40**, 1087;

(*j*) X. Han and D. W. Armstrong, *Acc. Chem. Res.*, 2007, **40**, 1079; (*k*) J. Ranke, S. Stolte, R. Störmann, J. Arning and B. Jastorff, *Chem. Rev.*, 2007, **107**, 2183; (*l*) F. van Rantwijk and R. A. Sheldon, *Chem. Rev.*, 2007, **107**, 2757; (*m*) M. Smiglak, A. Metlen and R. D. Rogers, *Acc. Chem. Res.*, 2007, **40**, 1182; (*n*) V. I. Pârvulescu and C. Hardacre, *Chem. Rev.*, 2007, **107**, 2615; (*o*) T. L. Greaves and C. J. Drummond, *Chem. Rev.*, 2008, **108**, 206; (*p*) M. A. P. Martins, C. P. Frizzo, D. N. Moreira, N. Zanatta and H. G. Bonacorso, *Chem. Rev.*, 2008, **108**, 2015; (*q*) Y. Gua and G. Li, *Adv. Synth. Catal.*, 2009, **351**, 817; (*r*) N. V. Plechkova and K. R. Seddon, *Chem. Soc. Rev.*, 2008, **37**, 123; (*s*) D. Chaturvedi, *Curr. Org. Synth.*, 2011, **8**, 438; (*t*) C. Chiappe and S. Rajamani, *Eur. J. Org. Chem.*, 2011, 5517.

4 For representative recent examples using this strategy see: (*a*) H.-P. Zhu, F. Yang, J. Tang and M.-Y. He, *Green Chem.*, 2003, **5**, 38; (*b*) G. Zhao, T. Jiang, H. Gao, H. B. Han, J. Juang and D. Sun, *Green Chem.*, 2004, **6**, 75; (*c*) H.-H. Wu, F. Yang, P. Cui, J. Tang and M.-Y. He, *Tetrahedron Lett.*, 2004, **45**, 4963; (*d*) Y. Du and F. Tian, *Synth. Commun.*, 2005, **3**, 2703; (*e*) N. B. Darvatkar, A. R. Deorukhkar, S. V. Bhilare and M. M. Salunkhe, *Synth. Commun.*, 2006, **36**, 3043; (*f*) A. R. Hajipour, L. Khazdooz and A. E. Ruoho, *Catal. Commun.*, 2008, **1**, 9; (*g*) H. Li, Y. Qiao, L. Hua, Z. Hou, B. Feng, Z. Pan, Y. Hu, X. Wang, X. Zhao and Y. Yu, *ChemCatChem*, 2010, **2**, 1165.

5 For representative recent examples of this strategy see: (*a*) A. Arfan and J. P. Bazureau, *Org. Process Res. Dev.*, 2005, **9**, 743; (*b*) Z. Duan, Y. Gu and Y. Deng, *Synth. Commun.*, 2005, **35**, 1939; (*c*) D.-Q. Xu, W.-L. Yang, S.-P. Luo, B.-T. Wang, J. Wu and Z.-Y. Xu, *Eur. J. Org. Chem.*, 2007, 1007.

6 B. Procuranti and S. J. Connon, *Org. Lett.*, 2008, **10**, 4935.

7 B. Procuranti, L. Myles, N. Gathergood and S. J. Connon, *Synthesis*, 2009, 4082.

8 (*a*) L. Myles, R. Gore, N. Gathergood and S. J. Connon, *Green Chem.*, 2010, **12**, 1157; (*b*) L. Myles, N. Gathergood and S. J. Connon, *Chem. Commun.*, 2013, **49**, 5316.

9 While the tetrafluoroborate anion has not yet been found to unduly influence toxicity (see ref. 10–12), a recent report has suggested that limiting the number of fluorine atoms in the anion can reduce cytotoxicity (ref. 13). In addition, we were nevertheless concerned about its hydrolytic stability (see ref. 14), which could impede performance (*e.g.* scope) in certain processes, and at a minimum introduce a certain degree of uncertainty regarding the catalytically active species in solution.

10 B. Jastorff, R. Störmann, J. Ranke, K. Mölter, F. Stock, B. Oberheitmann, W. Hoffmann, J. Hoffmann, M. Nüchter, B. Ondruschkae and J. Filser, *Green Chem.*, 2003, **5**, 136.

11 M. Alvarez-Guerra and A. Irabien, *Green Chem.*, 2011, **13**, 1507.

12 S. Stolte, J. Arning, U. Bottin-Weber, M. Matzke, F. Stock, K. Thiele, M. Uerdingen, U. Welz-Biermann, B. Jastorff and J. Ranke, *Green Chem.*, 2006, **8**, 621.

13 M. H. Fatemi and P. Izadiyan, *Chemosphere*, 2011, **84**, 553.

14 For a recent study on the hydrolytic stability of imidazolium ion-based ILs incorporating tetrafluoroborate counteranions see: M. G. Freire, C. M. S. S. Neves, I. M. Marrucho, J. A. P. Coutinho and A. M. Fernandes, *J. Phys. Chem. A*, 2010, **114**, 3744.

15 (*a*) N. Gathergood and P. Scammells, *Aust. J. Chem.*, 2002, **55**, 557; (*b*) M. T. Garcia, N. Gathergood and P. J. Scammells, *Green Chem.*, 2004, **6**, 9; (*c*) N. Gathergood, P. J. Scammells and M. T. Garcia, *Green Chem.*, 2006, **8**, 156; (*d*) M. T. Garcia, N. Gathergood and P. J. Scammells, *Green Chem.*, 2005, **7**, 9; (*e*) S. Morrissey, B. Pegot, D. Coleman, M. T. Garcia, D. Ferguson, B. Quilty and N. Gathergood, *Green Chem.*, 2009, **11**, 475; (*f*) D. Coleman, M. Spulak, M. T. Garcia and N. Gathergood, *Green Chem.*, 2012, **14**, 1350–1356; (*g*) D. Coleman and N. Gathergood, *Chem. Soc. Rev.*, 2010, **39**, 600.

16 For a discussion of the role of water in recycling of IL catalysts for condensation reactions see ref. 2*a*.

17 I. Beadham, M. Gurbisz and N. Gathergood, in *Handbook of Green Chemistry, Chapter 6, Volume 9: Designing Safer Chemicals, First Edition*, Series editor Paul Anastas, ed. R Boethling and A Voutchkova, Wiley-VCH Verlag GmbH & Co. KGaA, 2012, pp. 137–158.

18 I. Beadham, M. Gurbisz and N. Gathergood, in *Handbook of Green Chemistry, Chapter 7, Volume 9: Designing Safer Chemicals, First Edition*, Series editor Paul Anastas, ed. R. Boethling and A. Voutchkova, Wiley-VCH Verlag GmbH & Co. KGaA, 2012, pp. 159–226.

