ChemComm

RSC Publishing

COMMUNICATION

View Article Online
View Journal

The catalytic versatility of low toxicity dialkyltriazolium salts: *in situ* modification facilitates diametrically opposed catalysis modes in one pot†

Cite this: DOI: 10.1039/c3cc41588k

Received 1st March 2013,
Accepted 24th April 2013

DOI: 10.1039/c3cc41588k

www.rsc.org/chemcomm

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

The ability of triazolium salts to serve as a precatalyst for both an acid and a powerful base/nucleophile (controlled by additives) has been exploited in a process characterised by a unique *in situ* catalyst modification strategy.

There has been considerable recent interest in the design of novel Brønsted Acidic Ionic Liquids (BAILS) as conveniently handled, non-volatile acidic materials for a variety of synthetic applications. Four general strategies have emerged (Fig. 1): **A**: the covalent attachment of an acidic moiety (*e.g.* **1**, Fig. 1A),[1,2] use of protic (acidic) imidazolium ions (*e.g.* **2**),[3] incorporation of an acidic counterion (*e.g.* **3**)[4] and non-protic ionic liquids, which become acidic only upon addition of a protic additive (*e.g.* **4**).[5] We began our studies into the latter class of catalysts with the goal of designing *low toxicity materials* which would serve as powerful acid catalysts only in the presence of a protic additive. These catalysts are not only non-volatile, they also do not have the safety and environmental hazards associated with their storage which are a characteristic of other strongly acidic materials. For instance, the non protic catalyst **4** could promote the conversion of **5** to the corresponding acetal (**6**) in good yield at room temperature (Fig. 1B)[5b] and was shown to be of low antimicrobial toxicity. The more electrophilic pyridinium ion **7** exhibited enhanced activity and can be recycled,[5a] however its synthesis is not ideal from an environmental standpoint, and on prolonged storage its activity diminishes. It was proposed that the activity of these aprotic catalysts derives from the formation of the active species **8**/**8a** (Fig. 1C) after reversible addition of the protic additive to **4**, and as such the acidity of these catalysts is controllable by the practitioner in an 'on–off' fashion.[5]

Since we had shown that the activity of **7** is related to the influence of the substituents at C-3 and C-5, we speculated that a 1,2,4-triazolium ion (*e.g.* **9**, Fig. 1D) – which incorporates an additional endocyclic, aromaticity-lowering heteroatom – could serve as a more active, highly accessible, non-toxic analogue of the imidazolium ion series of catalysts (*e.g.* **4**). Thus **9** could represent a compromise between the stability of **4** and the activity of **7**, while being easier to prepare (multigram scale) than either.

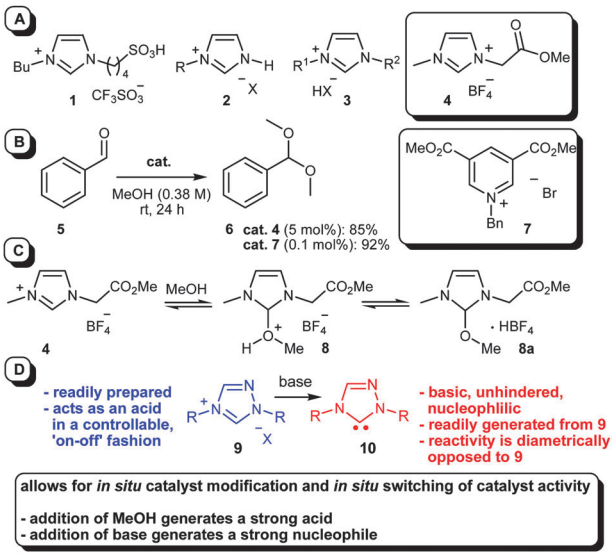


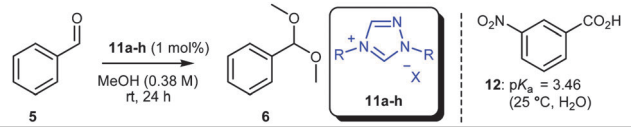
Fig. 1 (A) Examples of catalytically active BAILs. (B) The acetalisation of benzaldehyde catalysed by non-protic acid equivalents **4** and **7**. (C) Proposed mode of action of **4**. (D) Proposed *in situ* catalyst modification.

Another potential advantage associated with the use of **9** would be the development of a new paradigm in 'bifunctional catalysis'. Conventionally this term has described the activation of two distinct reaction components simultaneously (*e.g. via* general acid/base catalysis[6]). However, the use of **9** potentially allows an unprecedented *in situ* catalyst modification: *i.e.* **9** could first act as a promoter of a reaction traditionally involving specific acid catalysis (*e.g.* acetalisation), then, on addition of base, deprotonation to the corresponding carbene **10** would allow subsequent NHC-catalysed reactions[7] (*e.g.* the benzoin condensation – which under other circumstances would be completely incompatible with specific acid catalysis) to occur.

[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: Procedures, characterisation data, toxicity screening. See DOI: 10.1039/c3cc41588k

Table 1 Preliminary catalyst evaluation: acetalisation



Entry	Catalyst (X=)	Yield[a] (%)
1	**11a** (X = ClO_4)	81
2	**11b** (X = AcO)	82
3	**11c** (X = $MeOSO_3$)	86
4	**11d** (X = BF_4)[b]	86
5	**11e** (X = Cl)	90
6	**11f** (X = OTs)	97
7	**11g** (X = OTf)	>98
8	**11h** (X = I)	>98
9	**12**	37

[a] Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [b] Catalyst unstable on storage (light sensitive).

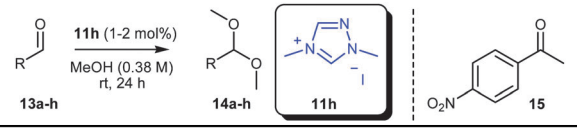
Thus the practitioner would have access to diametrically opposed modes of catalysis from a single species, in the same flask, depending on the choice of additive: protic (acid catalysis) or base (basic/nucleophilic/NHC-mediated catalysis).

In order to test this hypothesis, an examination of the catalytic competence of species such as **9** in acetalisation and benzoin condensations (chosen as representative of acid-catalysed and NHC-catalysed reactions respectively) was necessary. Our study began with the acetalisation of **5** by methanol under conditions previously utilised in catalysis by **4**.[5c] We chose the prototype triazolium species most simple to prepare: the dimethyl azolium ions **11a–h** (Table 1). As we found to be the case with pyridinium- and imidazolium-ion-based materials, the counteranion directly influences catalysis. An immediate improvement in activity relative to imidazolium ions is apparent: use of even the least efficient catalysts in the triazolium series (*i.e.* **11a–d**, entries 1–4) at 1 mol% loading facilitated the formation of **6** in comparable yield to that obtained using **4** at 5 mol% levels (*cf.* Fig. 1B). Gratifyingly, the chloride, tosylate, triflate and iodide ions **11e–h** exhibited excellent activity (entries 5–8), with **11h** (readily obtained from the dialkylation of inexpensive 1,2,4-triazole with MeI) able to mediate the formation of **6** in quantitative yield at 1 mol% loading. To facilitate some perspective – this is a considerably higher level of activity than that exhibited by the benzoic acid **12** (entry 9).[5a]

Next, the question of substrate scope was investigated (Table 2). Catalyst **11h** (at 1–2% levels) performed consistently across a range of substrates – allowing the isolation of acetals derived from electron neutral (*i.e.* **5**, entry 1), activated- (**13a–c**, entries 2–4), hindered- (**13d**, entry 5), deactivated- (**13e**, entry 6), heterocyclic- (**13f**, entry 7) and α,β-unsaturated (**13g**, entry 8) aldehydes in uniformly excellent yields. Ketalisation of **15** (entry, **9**; a consistently problematic substrate 5) proved difficult, however an appreciable yield was obtained. We also found that **11h** (at low loading) promoted smooth dithiane, dithiolane and dioxane protection (*i.e.* **16–18**, Scheme 1) at room temperature.

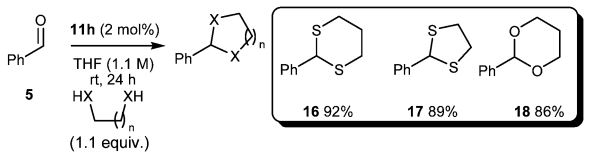
With the superiority of **11h** over **4** established, our attention turned to the benzoin condensation (BC). While the use of **11h** as a precatalyst in NHC-mediated chemistry is well precedented,[8] we were surprised to find that a detailed, systematic study of the utility of this simple system in the archetypal BC has not been reported.[9] We therefore compared the performance of **11f–h** with the pentafluorophenyl-substituted

Table 2 Acetalisation catalysed by **11h**: substrate scope



Entry	Substrate (Ar=)	Loading (mol%)	Yield[a] (%)
1	**5** (R = C_6H_5)	1	98
2	**13a** (R = 2-Cl–C_6H_4)	1	96
3	**13b** (R = 3-Cl–C_6H_4)	1	95
4	**13c** (R = 4-Cl–C_6H_4)	1	98
5	**13d** (R = 2-Me–C_6H_4)	2	91
6	**13e** (R = 4-OMe–C_6H_4)	2	91
7	**13f** (R = 2-furanyl)	2	92
8	**13h** (R = cinnamyl)	2	90
9	**15**	10	32

[a] Isolated yield.

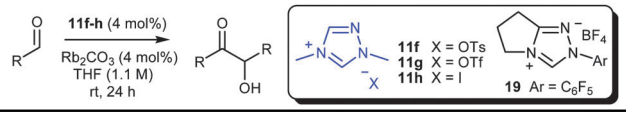


Scheme 1 Dithiane, dithiolane and dioxane formation.

19[10] – which has been shown to serve as an excellent BC precatalyst for the BC (Table 3).[11]

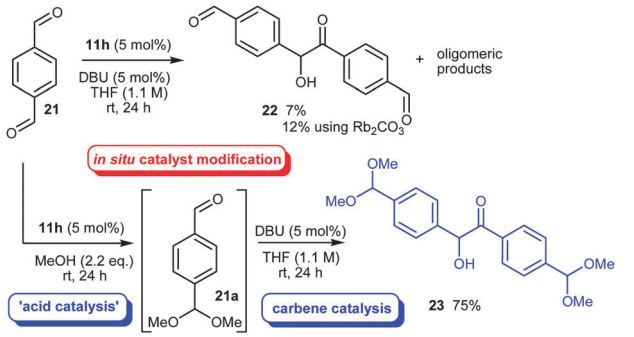
Catalysts **11f–h** all promoted the BC of **5** with excellent isolated product yield comparable to that obtained using the benchmark precatalyst **19** under literature conditions (entries 1–5).[11e] From a substrate scope standpoint, the carbene derived from **11h** responded to changes in the steric and electronic characteristics of the substrate in the same manner as **19** (entries 6–13); *i.e.* excellent yields using electron neutral-, activated, heterocyclic and mildly deactivated-aldehydes, and less efficient catalysis using either hindered or highly deactivated substrates (which pose a serious challenge for all triazolium catalyst systems). *Since **11h** is considerably more straightforward and less expensive to prepare*

Table 3 BC reactions by **11h**: catalyst evaluation and substrate scope



Entry	Catalyst	Substrate (Ar=)	Yield[a] (%)
1	**11f**	**5** (R = C_6H_5)	96
2	**11g**	**5** (R = C_6H_5)	97
3	**11h**	**5** (R = C_6H_5)	96
4[b]	**11h**	**5** (R = C_6H_5)	96
5	**19**	**5** (R = C_6H_5)	97
6	**11h**	**13i** (R = 2-naphthyl)	91
7	**11h**	**13a** (R = 2-Cl–C_6H_4)	27
8	**11h**	**13b** (R = 3-Cl–C_6H_4)	92
9	**11h**	**13c** (R = 4-Cl–C_6H_4)	93
10	**11h**	**13d** (R = 2-Me–C_6H_4)	18
11	**11h**	**13j** (R = 4-Me–C_6H_4)	89
12	**11h**	**13e** (R = 4-OMe–C_6H_4)	35
13	**11h**	**13f** (R = 2-furanyl)	93

[a] Isolated yield. [b] Using DBU (4 mol%) as the base.



Scheme 2 *In situ* catalyst modification allows a chemoselective synthesis.

than **19** *(or variants thereof), we would suggest that it represents an attractive general system for use in the BC.*

A key objective of this study was to ensure that the catalysts are of low antimicrobial toxicity. We screened **11h** for toxicity against 12 representative fungi and 8 bacteria (both Gram positive and Gram negative). The salt was found to be of low toxicity to all the microorganisms up to 2 mM concentration. The ability of **11h** to inhibit bacterial growth was also evaluated using 5 bacterial strains – IC_{50} values ranged from 50 to >100 mM, indicating that **11h** has low antibacterial toxicity and would not be harmful to microbial life in the environment (see the ESI† for details).

Finally, the bis-aldehyde **21** was selected as a candidate substrate to demonstrate an *in situ* catalyst modification strategy. The aldehyde, when treated with **1h** and base, furnishes oligiomeric products due to uncontrolled BC chemistry, with only 7% of the dimeric benzoin **22** isolable (Scheme 2). We therefore treated **21** with MeOH in the presence of **11h**, which resulted in the quantitative formation of mono-acetal **21a.** Subsequent addition of DBU to generate the carbene derivative of **11h** and THF solvent led to the isolation of the protected benzoin product **23** in good yield. It is noteworthy that only 2.2 equivalents of methanol (usually used as solvent) are required for the acetalisation (no reaction was detected in the absence of **11h**).

In summary, it has been shown that simple, stable, low toxicity and readily prepared triazolium salts are highly active promoters of a specific acid-catalysed reaction – allowing the room temperature protection of a broad range of aldehydes in excellent yield at low catalyst loadings. While it was previously known that these materials are precursors to NHCs, a systematic study revealed that these materials are actually optimal for the promotion of the BC reaction; affording the practitioner an identical activity profile to the literature benchmark system from a considerably less expensive and more readily prepared salt. The best catalyst (*i.e.* **11h**) was found to have low antimicrobial toxicity. The ability of **11h** to serve as a precatalyst for both a strong acid and a powerful base/nucleophile was exploited in a unique *in situ* modification in which the role played by the triazolium salt is completely controlled by the addition of either methanol or a base. Studies to further explore the potential of this and related strategies in chemoselective tandem processes are underway.

Financial support from the Environmental Protection Agency (EPA) is gratefully acknowledged. We thank C. McGlinchey for preliminary experiments and M. Spulak, M. Pour and B. Quilty for toxicity screening.

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*) 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; (*c*) X. Liu, H. Ma, Y. Wu, C. Wang, M. Yang, P. Yana and U. Welz-Biermann, *Green Chem.*, 2011, **13**, 697; (*d*) A. K. Ressmann, P. Gaertner and K. Bica, *Green Chem.*, 2011, **13**, 1442; (*e*) H.-F. Liu, F.-X. Zeng, L. Deng, B. Liao, H. Panga and Q. X. Guo, *Green Chem.*, 2013, **15**, 81.
3 For representative recent examples see: (*a*) H.-P. Zhu, F. Yang, J. Tang and M.-Y. He, *Green Chem.*, 2003, **5**, 38; (*b*) 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.
4 For representative recent examples of this strategy see: (*a*) A. Arfan and J. P. Bazureau, *Org. Process Res. Dev.*, 2005, **9**, 743; (*b*) D.-Q. Xu, W.-L. Yang, S.-P. Luo, B.-T. Wang, J. Wu and Z.-Y. Xu, *Eur. J. Org. Chem.*, 2007, 1007.
5 (*a*) B. Procuranti and S. J. Connon, *Org. Lett.*, 2008, **10**, 4935; (*b*) B. Procuranti, L. Myles, N. Gathergood and S. J. Connon, *Synthesis*, 2009, 4082; (*c*) L. Myles, R. Gore, N. Gathergood and S. J. Connon, *Green Chem.*, 2010, **12**, 1157.
6 For a review of one representative class of such catalysts see: S. J. Connon, *Chem. Commun.*, 2008, 2499.
7 Reviews: (*a*) *N-Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools*, ed. S. Díez-González, RSC Publishing, London, 2011; (*b*) H. U. Vora and T. Rovis, *Aldrichimica Acta*, 2011, **44**, 3; (*c*) A. T. Biju, N. Kuhl and F. Glorius, *Acc. Chem. Res.*, 2011, **44**, 1182; (*d*) J. L. Moore and T. Rovis, *Top. Curr. Chem.*, 2009, **291**, 77; (*e*) D. Enders, *J. Org. Chem.*, 2008, **73**, 7857; (*f*) K. Zeitler, *Ernst Schering Found. Symp. Proc.*, 2007, **2**, 183; (*g*) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5506.
8 (*a*) Z.-X. Sun and Y. Cheng, *Org. Biomol. Chem.*, 2012, **10**, 4088; (*b*) M. Rueping, H. Sundén, L. Hubener and E. Sugiono, *Chem. Commun.*, 2012, **48**, 2201; (*c*) S. De Sarkar and A. Studer, *Angew. Chem., Int. Ed.*, 2010, **49**, 9266; (*d*) H. Kim, Y. Park and J. Hong, *Angew. Chem., Int. Ed.*, 2009, **48**, 7577; (*e*) S. De Sarkar and A. Studer, *Org. Lett.*, 2010, **12**, 1992; (*f*) S. De Sarkar, S. Grimme and A. Studer, *J. Am. Chem. Soc.*, 2010, **132**, 1190; (*g*) J. Guin, S. De Sarkar, S. Grimme and A. Studer, *Angew. Chem., Int. Ed.*, 2008, **47**, 8727; (*h*) B. E. Maki, A. Chan, E. M. Phillips and K. A. Scheidt, *Tetrahedron*, 2009, **65**, 3102; (*i*) B. E. Maki and K. A. Scheidt, *Org. Lett.*, 2008, **10**, 4331; (*j*) A. Chan and K. A. Scheidt, *J. Am. Chem. Soc.*, 2006, **128**, 4558; (*k*) A. Miyashita, Y. Suzuki, I. Nagasaki, C. Ishiguro, K.-I. Iwamoto and T. Higashino, *Chem. Pharm. Bull.*, 1997, **45**, 1254.
9 Miyashita *et al.* demonstrated the use of **11h** in the BC under forcing conditions, isolating benzoin from **5** in 69% yield. Curiously, **11h** was inferior to other azolium ion precatalysts evaluated in THF at reflux temperature: A. Miyashita, Y. Suzuki, M. Kobayashi, N. Kuriyama and T. Higashino, *Heterocycles*, 1996, **43**, 509.
10 M. S. Kerr, J. R. de Alaniz and T. Rovis, *J. Org. Chem.*, 2005, **70**, 5725.
11 Recent references concerning the BC reaction catalysed by **19** (and variants): (*a*) J. Mahatthananchai and J. W. Bode, *Chem. Sci.*, 2012, **3**, 192; (*b*) C. A. Rose, S. Gundala, C.-L. Fagan, J. F. Franz, S. J. Connon and K. Zeitler, *Chem. Sci.*, 2012, **3**, 735; (*c*) S. E. O'Toole, C. A. Rose, S. Gundala, K. Zeitler and S. J. Connon, *J. Org. Chem.*, 2011, **76**, 347; (*d*) C. A. Rose, S. Gundala, S. J. Connon and K. Zeitler, *Synthesis*, 2011, 190; (*e*) L. Baragwanath, C. A. Rose, K. Zeitler and S. J. Connon, *J. Org. Chem.*, 2009, **74**, 9214.