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Journal Name

COMMUNICATION

Construction of Spirocycles Containing Highly Substituted Pyrrolidine and 1-Indanone Motifs with Spiro Quaternary Stereogenic Centers via 1,3-Dipolar Cycloaddition of 2-Alkylidene-1-Indanone and Azomethine Ylides Promoted by Simple Imidazolium Salts

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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The 1,3-dipolar cycloaddition of 2-alkylidene-1-indanone with azomethine ylides has been developed successfully promoted by simple imidazolium salts to construct a variety of spirocycles containing highly substituted pyrrolidines efficiently, affording the corresponding compounds in excellent yields (up to 99%). The highly efficient catalytic system exhibited broad substrate scopes under mild conditions.

The highly substituted pyrrolidines are prevalent in many natural products which exhibit a broad range of biological and pharmaceutical activities.¹ In particular, highly substituted pyrrolidine motifs containing a spiro quaternary stereogenic carbon center and fused with 1-indanone are versatile synthetic motifs for the biologically active natural products and pharmaceuticals.² The significance of those molecules has stimulated intensive interests to develop numerous excellent manufacturing approaches.^{3 and 4} Among them, 1,3-dipolar cycloaddition of 2-alkylidene-1-indanone with azomethine ylides is an extremely powerful and efficient strategy for the construction of spiro[pyrrolidine-1-indanone] derivatives and widely applied in organic synthesis.⁵ Wang⁶ reported the first example of 1,3-dipolar cycloaddition reaction of 2-alkylidene-ketones with azomethine ylide using Ag(I)/TF-BiphamPhos complex. To the best of our knowledge, no successful and efficient organocatalytic protocols for the 1,3-dipolar cycloaddition reaction of 2-alkylidene-1-indanone with azomethine ylides have been reported. And it is still highly challenging and desirable to develop new efficient catalytic systems for this transformation.⁴

Ionic liquids, which are powerful tools to activate donors or acceptors, can be designed for task-specific applications through smart choice of the respective cation and/or anion.⁷ Since the last century, ionic liquids (ILs) have been attracting organic chemists' attentions because of their advantages of friendly to environment, convenient to use, controlled properties and thermal stability.⁸ Especially, functionalized ILs, such as acidic, basic and other ionic liquids have been synthesized and used to promote various chemical reactions.⁹ Although several kinds of functionalized ILs have been used for excellent catalysts for a number of reactions,¹⁰ such as Michael addition,¹¹ Diels-Alder addition¹² etc, rarely functionalized ILs were applied to 1,3-dipolar cycloaddition of 2-alkylidene-1-indanone with azomethine ylides.

Herein, as a part of our program to explore the potential of functional ILs in chemical transformations, we described the first 1,3-dipolar cycloaddition reaction of 2-alkylidene-1-indanone with various azomethine ylide promoted by imidazolium salts, one kind of simple and useful functionalized ILs, for the synthesis of spiro heterocyclic compounds containing highly substituted pyrrolidine and 1-indanone motifs with excellent results.

For investigation on 1,3-dipolar cycloaddition of 2-alkylidene-1-indanone with azomethine ylides, we choose 2-alkylidene-1-indanone (**1a**) and azomethine ylide (**2a**) as model reactants to determine the optimal conditions and the results are summarized in Table 1. A variety of imidazolium salts (**3a-3h**) were synthesized and tested in the model reaction in acetonitrile, and moderate to excellent yields (52-99%) were obtained (Table 1, entries 4-11). Catalysts 1-butyl-3-methylimidazolium bromide ([bmim]Br) (**3a**) was first evaluated, and gave the desired product (**4aa**) in 66% yield (Table 1, entry 4). The anion of the imidazolium salts affected the results obviously (Table 1, entries 4-7). The catalyst with dicarbonate as anion (**3b**) was tested and 52% yield was obtained (Table 1, entry 5). With carboxylate as anion, catalysts **3e-3g** provided **4aa** in 90-99% yields (Table 1, entries 8-11). Especially, catalyst [bmim]CH₃(CH₂)₂CO₂ gave **4aa** in 99%

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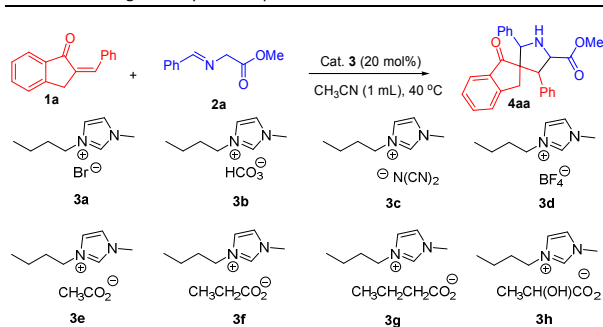
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yield, and it turned out to be efficient to promote the reaction (Table 1, entry 10).

Table 1 Screening of catalysts and optimized the conditions^a



Entry	Cat.	Solvent	Time (h)	Yield ^b (%)
1	K ₂ CO ₃	CH ₃ CN	48	trace
2	DABCO	CH ₃ CN	48	trace
3	NaOAc	CH ₃ CN	48	24
4	3a	CH ₃ CN	168	66
5	3b	CH ₃ CN	168	52
6	3c	CH ₃ CN	168	72
7	3d	CH ₃ CN	168	62
8	3e	CH ₃ CN	20	90
9	3f	CH ₃ CN	5	97
10	3g	CH ₃ CN	5	99
11	3h	CH ₃ CN	46	80
12	3g	toluene	48	66
13	3g	CHCl ₃	48	70
14	3g	ClCH ₂ CH ₂ Cl	48	21
15	3g	CH ₃ CO ₂ Et	48	82
16	3g	Et ₂ O	2	80
17	3g	THF	2	85
18	3g	MeOH	24	93
19	3g	DMF	3	92
20	3g	DMSO	3	69
21 ^c	3g	CH ₃ CN	46	81
22 ^d	3g	CH ₃ CN	29	86

^a Unless otherwise specified, all reaction carried out with 2-alkylidene-1-indanone (**1a**, 0.20 mmol, 1.0 equiv), azomethine ylide (**2a**, 0.2 mmol, 1.0 equiv), solvent (1 mL) and catalyst **3** (20 mmol%) at 40 °C; ^b Isolated yields; ^c Carried out at 25 °C; ^d Carried out with 10 mol% catalyst **3g**.

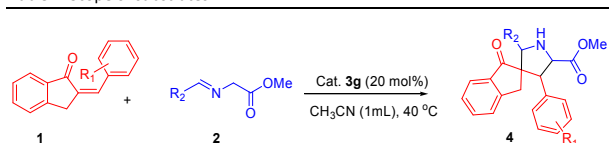
Then a series of solvents were evaluated with **3g** as catalyst and the results were presented in Table 1 (entries 12-20). All solvents gave moderate to good yields (66-92%). In polar solvents such as Et₂O, THF, DMF, DMSO, **3g** delivered high yields (80%-92%) (Table 1, entries 16, 17, 19 and 20). Protic solvents such as MeOH, afforded the cycloadduct **4aa** in 93% yield (Table 1, entries 18). Among the screened solvents, acetonitrile, affording the desired products in 99% yields, was chosen for further optimization (Table 1, entry 10). Reaction

temperature was studied with **3g** as catalyst and acetonitrile as the solvent. Decreasing the temperature to 25 °C, the reaction proceeded smoothly and afforded the desired adduct **4aa** in good yield (81%, Table 1, entry 21). Lowering catalyst loading to 10 mol%, the yields were decreased (Table 1, entries 22 vs 10). Thus, the optimized reaction conditions were found to be reaction of 1.0 equiv 2-alkylidene-1-indanone (**1a**) with 1.0 equiv azomethine ylide (**2a**), in the presence of 20 mol% of **3g**, in acetonitrile at 40 °C (Table 1, entry 10).

With the optimized reaction conditions in hand, the scopes of the substrates for this 1,3-dipolar cycloaddition of 2-alkylidene-1-indanone with azomethine ylides promoted by BILs were evaluated and the results are summarized in Table 2. Generally, a series of the azomethine ylides were successfully employed in this transformation and proceeded smoothly affording the corresponding adducts **4** in moderate to excellent yields (61-99%), and the results strongly depended on the substituents of the aromatic ring. Substrates bearing various electron-withdrawing groups on the aromatic ring at 4-position, such as fluoro, chloro, trifluoromethyl, and nitro group, were well-tolerated, delivering the products **4ab-4af** in 83-87% yields (Table 2, entries 2-6). The electron-donating substituents, such as methyl and methoxyl, obviously increased the reactivity of azomethine ylides in this reaction (Table 2, entries 7 and 8). Substrates with an electron-withdrawing or electron-donating groups on the aromatic ring at 2-position gave lower yields than those with substituents at 4-position, and the reaction rate was decreased (Table 2, entries 10, 11, 12 vs 3, 4, 8). For azomethine ylide **2m**, 90% yield was obtained (Table 2, entry 13). In addition, the 2-furyl substituted azomethine ylide gave 61% yield (Table 2, entry 14).

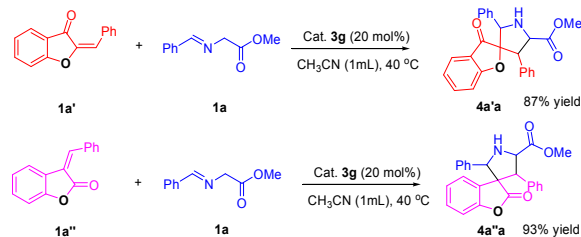
We next examined the scopes of this 1,3-dipolar cycloaddition by varying the 2-alkylidene-1-indanones under the optimized conditions (Table 2, entries 16-20). This transformation tolerated various 2-alkylidene-1-indanones with electron-donating or electron-withdrawing substituents on the aromatic ring at 4-position, affording the products (**4ba-4fa**) in moderate yields (Table 2, entries 16-20). The electron-withdrawing group, for example, fluoro, chloro, bromo and trifluoromethyl group, on the phenyl ring of the 2-alkylidene-1-indanones usually gave the slightly higher yield compared with the methoxyl-substituted one (Table 2, entries 20 vs 16-19).

Table 2. Scope of substrates^a



Entry	R ₁	R ₂	dr	Yield ^b (%)
1	H (1a)	Ph (2a)	1.00:0.63:0.21:0.78:0.73:0	99 (4aa)
2	H (1a)	4-FPh (2b)	1.00:0.06:0.21:0.16:0.26:0.66	85 (4ab)
3	H (1a)	4-ClPh (2c)	1.00:0.21:0.13:0.14:0.16:0.17	83 (4ac)
4	H (1a)	4-BrPh (2d)	1.00:0.05:0.04:0.11:0.11:0.16	87 (4ad)
5	H (1a)	4-NO ₂ Ph (2e)	1.00:0.80:0.35:0.36:0.76:0.79	86 (4ae)
6	H (1a)	4-CF ₃ Ph (2f)	1.00:0.05:0.17:0.82:0:0	85 (4af)
7	H (1a)	4-CH ₃ Ph (2g)	1.00:0.21:0.44:0.14:0.58:0.51	93 (4ag)
8	H (1a)	4-CH ₃ OPh (2h)	1.00:0.10:0.55:0.96:0:0	98 (4ah)
9	H (1a)	4-N(Me) ₂ Ph (2i)	1.00:0.13:0.52:0.71:0.61:0.10	71 (4ai)
10	H (1a)	2-ClPh (2j)	1.00:0.29:0.20:0.24:0:0	65 (4aj)
11	H (1a)	2-BrPh (2k)	1.00:0.34:0.16:0.10:0:0	85 (4ak)
12	H (1a)	2-CH ₃ OPh (2l)	1.00:0.81:0.40:0.26:0.47:0.79	67 (4al)
13	H (1a)	(2m)	1.00:0.27:0.29:0.59:0.71:0.35	90 (4am)
14	H (1a)	(2n)	1.00:0.07:0.03:0.25:0.23:0.58	61 (4an)
15	H (1a)	(CH ₃) ₂ CH ₂ CH ₂ (2p)	n.d.	trace
16	4-F (1b)	Ph (2a)	1.00:0.30:0.25:0.40:0.40:0.19	80 (4ba)
17	4-Cl (1c)	Ph (2a)	1.00:0.08:0.22:0.47:0.16:0.85	76 (4ca)
18	4-Br (1d)	Ph (2a)	1.00:0.08:0.32:0.26:0.54:0.52	68 (4da)
19	4-CF ₃ (1e)	Ph (2a)	1.00:0.06:0.29:0.13:0.25:0.18	78 (4ea)
20	4-CH ₃ O (1f)	Ph (2a)	1.00:0.91:0.56:0.90:0:0	64 (4fa)

^a Unless otherwise specified, all reaction carried out with 2-alkylidene-1-indanone (**1a**, 0.20 mmol, 1.0 equiv), azomethine ylide (**2a**, 0.2 mmol, 1.0 equiv), solvent (1 mL) and catalyst **3g** (20 mmol%) at 40 °C in 2-27 h; ^b Isolated yields.



Scheme 1 The results of 1,3-dipolar cycloaddition of 2-alkylidene-3-benzofuranone or 3-alkylidene-2-benzofuranone with azomethine ylides.

Encouraged by these results for the 2-alkylidene-ketones, we then investigated the 1,3-dipolar cycloaddition of 2-alkylidene-3-benzofuranone (**1a'**) or 3-alkylidene-2-benzofuranone (**1a''**) with azomethine ylides (Scheme 1). To our delight, the reaction smoothly proceeded with ILs **3g** as catalyst, and the highly substituted pyrrolidines were still successfully obtained to give the corresponding cycloadduct **4a'a** and **4a''a** in 87% and 93% yields, respectively.

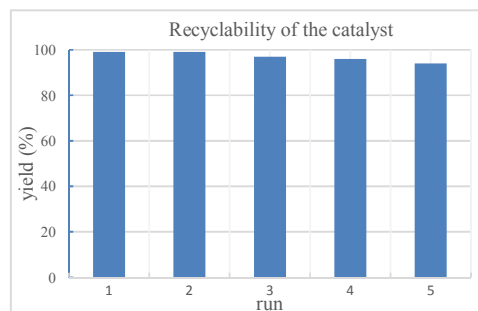
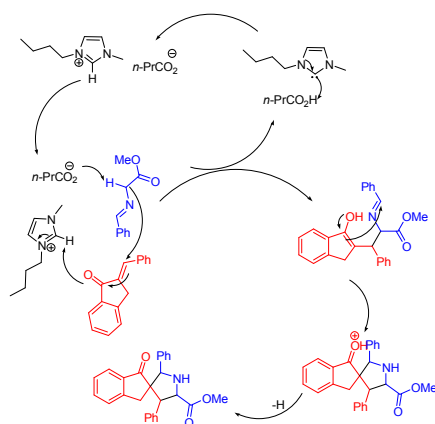


Figure 1 Recyclability of the catalyst. Reaction conditions: **1a** (0.20 mmol, 1.0 equiv), **2a** (0.20 mmol, 1.0 equiv), catalyst **3g** (20 mol%), in CH₃CN at 40 °C.

To test the catalyst reusability and be convenient for recycling, the reaction was carried out in the presence of a catalytic amount of imidazolium salts under the conditions with **1a** (0.20 mmol), **2a** (0.20 mmol), catalyst **3g** (20 mol%), at 40 °C and the reaction was monitored by TLC. When the reaction was completed, the reaction mixture was concentrated in-vacuo, and extracted with DCM, the ionic liquid left in the aqueous phase was concentrated in-vacuo. Recycled **3g** was directly used in the next run and the results indicated that the isolated yield of the product **4a** was almost consistent after five runs and **3g** could be reused at least five times (Figure 1).



Scheme 2 Proposed mechanism

Based on the experimental results, we suggested a plausible bifunctional catalytic mechanism involving nucleophilic butyric anion as a base to capture a proton of azomethine ylides and an electrophilic imidazolium cation to accept the transferred electron to complete the reaction cycle as shown in Scheme 2. Azomethine ylides was activated by the butyric anion and 2-alkylidene-1-indanone might be activated by the imidazolium cation (Scheme 2).

Conclusions

In summary, we have developed an efficient catalyst to promote 1,3-dipolar cycloaddition of 2-alkylidene-1-indanone with azomethine ylides leading to the formation of useful spirocycles containing highly substituted pyrrolidines and 1-indanone motifs with spiro quaternary stereogenic centers. This is the first example of 1,3-dipolar cycloadditions of 2-alkylidene-1-indanone with azomethine ylides. Moreover, this transformation provides an efficient and practical method for the synthesis of structurally diverse 1-indanone derivatives under mild conditions.

Acknowledge

This work was supported by the National Natural Science Foundations of China (No. 21206031), the fundamental research foundations for provincial colleges and universities (No. zzzj20140006) and the key project of science and technology of Henan Province (No. 15A150034).

Notes and references

- 1 a) S. Yu, D. Qin, S. Shangary, J. Chen, G. Wang, K. Ding, D. McEachern, S. Qiu, Z. Nikolovska-Coleska, R. Miller, S. Kang, D. Yang and S. Wang, *J. Med. Chem.*, 2009, **52**, 7970; b) G. Gilles and S. L. Claudine, *Stress*, 2003, **6**, 199; c) K. Bernard, S. Bogliolo and J. Ehrenfeld, *Br. J. Pharmacol.*, 2005, **144**, 1037; d) S. G. Pyne, A. S. Davis, N. J. Gates, J. Nicole, J. P. Hartley, K. B. Lindsay, T. Machan and M. Tang, *Synlett*, 2004, 2670; e) L. M. Harwood and R. J. Vickers, in: *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles*

and Natural Products, (Eds.: A. Padwa, W. Pearson), Wiley & Sons, New York, 2002.

- 2 Selected example: A. C. Wei, M. A. Ali, Y. K. Yoon, R. Ismail, T. S. Choon, R. S. Kumar, N. Arumugam, A. I. Almansour and H. Osman, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4930.
- 3 Selected examples: a) S. Sternativo, B. Battistelli, L. Bagnoli, C. Santi, L. Testaferri and F. Marini, *Tetrahedron Lett.*, 2013, **54**, 6755; b) W. Fang, M. Presset, A. Guerinot, C. Bour, S. Bezenine-Lafolle and V. Gandon, *Chem. Eur. J.*, 2014, **20**, 5439; c) G. M. Schwarzwald, S. E. Steinhardt, H. V. Pham, K. N. Houk and C. D. Vanderwal, *Org. Lett.*, 2013, **15**, 6014; d) F. Behler, F. Habecker, W. Saak and T. Kluener, J. Christoffers, *Eur. J. Org. Chem.*, 2011, 4231; e) A. C. Wei, M. A. Ali, Y. K. Yoon, R. Ismail, T. S. Choon and R. S. Kumar, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 1383; f) M. T. Ardolino and P. Morken, *J. Am. Chem. Soc.*, 2014, **136**, 7092; g) Z. Y. Cao, X. M. Wang, C. Tan, X. L. Zhao, J. Zhou and K. L. Ding, *J. Am. Chem. Soc.*, 2013, **135**, 8197.
- 4 H. Huang, W. Wu, K. Zhu, J. Hu and J. Ye, *Chem. Eur. J.*, 2013, **19**, 3838.
- 5 Selected examples: a) J. Casas, R. Grigg, C. Nájera and J. M. Sansano, *Eur. J. Org. Chem.*, 2001, 1971; b) A. S. Gothelf, K. V. Gothelf, R. G. Hazell and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2002, **41**, 4236; c) R. Narayan, M. Potowski, Z.-J. Jia, A. P. Antonchick and H. Waldmann, *Acc. Chem. Res.*, 2014, **47**, 1296; d) T. Liu, Q. Li, Z. He, J. Zhang and C. Wang, *Chin. J. Catal.*, 2015, **36**, 68; e) X. H. Chen, Q. Wei, S. W. Luo, H. Xiao and L. Z. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 13819; f) F. Shi, Z.-L. Tao, S.-W. Luo, S.-J. Tu and L.-Z. Gong, *Chem. Eur. J.*, 2012, **18**, 6885; g) F. Shi, R. Y. Zhu, X. Liang and S. J. Tu, *Adv. Synth. Catal.*, 2013, **355**, 2447; h) C. S. Wang, R. Y. Zhu, J. Zheng, F. Shi and S. J. Tu, *J. Org. Chem.*, 2015, **80**, 512; i) W. Dai, X. L. Jiang, Q. Wu, F. Shi and S. J. Tu, *J. Org. Chem.*, 2015, **80**, 5737.
- 6 T.-L. Liu, Z.-L. He, Q.-H. Li, H.-Y. Tao and C.-J. Wang, *Adv. Synth. Catal.*, 2011, **353**, 1713.
- 7 [7] Selected examples: a) P. Wasserscheid, W. Keim and *Angew. Chem., Int. Ed.*, 2000, **39**, 3772; b) T. Welton, *Chem. Rev.*, 1999, **99**, 2071; c) J. S. Wilkes, *Green Chem.*, 2002, **4**, 73; d) T. Welton, *Chem. Rev.*, 1999, **99**, 2071; e) E. Tina, V. Jürgen, W. Frank and S. S. Ulrich, *J. Mater. Chem.*, 2008, **18**, 5267; d) W. Wasserscheid and W. Keim, *Angew. Chem. Int. Ed.*, 2000, **39**, 3772.
- 8 Selected examples: a) J. N. Rosa, C. A. M. Afonso and A. G. Santos, *Tetrahedron.*, 2001, **57**, 4189; b) J.-C. Hsu, Y.-H. Yen and Y.-H. Chu, *Tetrahedron Lett.*, 2004, **45**, 4673; c) E. J. Kim and S. Y. Ko, *Helv. Chim. Acta.*, 2003, **86**, 894.
- 9 Selected examples: a) X. Mi, S. Luo and J.-P. Cheng, *J. Org. Chem.*, 2005, **70**, 2338; b) P. Langer, *Angew. Chem. Int. Ed.*, 2000, **39**, 3049; c) D. Basavaiah, P. D. Rao, R. S. Hyma, *Tetrahedron*, 1996, **52**, 8001; d) I. E. Marko, P. G. Giles and N. J. Hindley, *Tetrahedron*, 1997, **53**, 1015; e) S. E. Drewes, G. H. P. Roos, *Tetrahedron*, 1988, **44**, 4653; e) X. L. Mi, S. Z. Luo, J. Q. He and J.-P. Cheng, *Tetrahedron Lett.*, 2004, **45**, 4567; f) R. Sheldon, *Chem. Commun.*, 2001, 2399.
- 10 X. L. Fu, Z. Zhang, C. M. Li, L. B. Wang, H. Y. Ji, Y. Yang, T. Zou and G. H. Gao, *Catal. Commun.*, 2009, **10**, 665; b) L. F. Zhang, Y. Yang, Y. R. Xue, X. L. Fu, Y. An and G. H. Gao, *Catal. Today*, 2010, **158**, 279; c) M. Selva, A. Perosa and M. Fabris, *Green Chem.*, 2008, **10**, 1068; d) M. Selva, M. Fabris, V. Lucchini, A. Perosa and M. Noe, *Org. Biomol. Chem.*, 2010, **8**, 5187.
- 11 Selected examples: a) K. Nzaira, X. H. Liu, L. Petra, P. Dimitrios and S. Grace, *Tetrahedron*, 2006, **62**, 11039; b) C. J. Yu and C. J. Liu, *Molecules*, 2009, **14**, 3222; c) H. Guo, X. Li, J. L. Wang, X. H. Jin and X. F. Lin, *Tetrahedron*, 2010, **66**, 8300; d) B. C. Ranu and S. Banerjee, *Org. Lett.*, 2005, **7**, 3049; e) L. Yang, L. W. Xu, W. Zhou, L. Li and C. G. Xia, *Tetrahedron Lett.*, 2006, **47**, 7723; f) J. M. Xu, Q. Wu, Q. Y. Zhang, F. Zhang and

- X. F. Lin, *Eur. J. Org. Chem.*, 2007, 1798-1802; g) X. Xin, Y. Wang, W. Xu, Y. J. Lin, H. F. Duan and D. W. Dong, *Green Chem.*, 2010, **12**, 893.
- 12 Selected examples :a) D. A. Jaeger and C. E. Tucker, *Tetrahedron Lett.*, 1989, **30**, 178; b) P. Ludley and N. Karodia, *Tetrahedron Lett.*, 2001, **42**, 2011; c) C. M. Gordon, J. D. Holbrey and K. R. Seddon, *J. Mater. Chem.*, 1998, **8**, 2627; d) J. D. Holbrey and K. R. Seddon, *J. Chem. Soc. Dalton Trans.*, 1999, **13**, 2133; e) C. E. Song, E. J. Roh and J. H. Choi, *Chem. Commun.*, 2000, 1695; f) J. A. Boon, J. A.; Levisky, J. L. Pflug and J. S. Wilkes, *J. Org. Chem.*, 1986, **51**,480; g) J. S. Wilkes, *Green Chem.*, 2002, **4**, 73.