Metal free oxidation of alkyl substituted aromatics with aqueous *tert*-butyl hydroperoxide under microwave irradiation
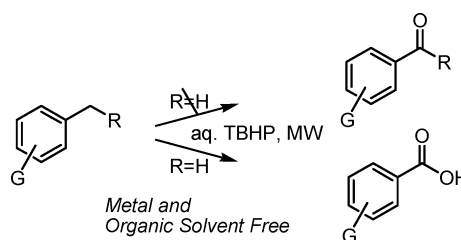
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Oxidation of alkyl substituted aromatic compounds to ketones and carboxylic acids can be achieved by 70% aqueous TBHP (*tert*-butyl hydroperoxide) under microwave irradiation with no additional organic solvent, metal based reagent or catalyst. Methyl aromatics (toluenes and xylenes) can be oxidized directly to the industrially important benzoic and phthalic acids. An addition of a tiny amount of ionic liquid and simultaneous cooling improves the efficiency of these oxidations. For other alkyl substituted aromatics, ketones are obtained in good yields.

1. Introduction

Oxidation is the core technology for converting petrochemical based materials to commodity chemicals of a higher oxidation state. For example, selective benzylic oxidations of alkyl substituted aromatics to ketones or carboxylic acids are fundamentally important laboratory and commercial transformations.[1] The oxidation products are important intermediates for the manufacture of high-value fine chemicals, agrochemicals, pharmaceuticals and high-tonnage commodities.[2] However, oxidation reactions also present some of the greatest challenges to the environment. Many of the industrial oxidation processes involved heavy metals or corrosive reagents, and are high in energy consumption. For example, benzylic oxidations can be achieved by various transition metal based oxidizing agents such as permanganate and chromate. If molecular oxygen, hydrogen peroxide or hydroperoxide is used as the oxidant, metal based catalysts, either homogeneous or heterogeneous, are needed.[1c,3]

In recent years, there are considerable efforts to develop environmentally conscious procedures for the production of carbon and aromatic feedstocks.[4] In these environmentally benign processes, the uses of heavy metals should be avoided due to their toxicities, negative environmental impacts and the need to remove residual metals from the reaction products. The use of flammable organic solvents should also be reduced, if not totally abandoned, to reduce VOC emission. This type of green chemistry is believed to be the future of a sustainable chemical industry. In this article, we would like to outline a metal and organic solvent free directed oxidation protocol of alkyl substituted aromatic hydrocarbons to ketones or carboxylic acids using aqueous *tert*-butyl hydroperoxide (TBHP) as the oxidant and microwave as the energy source. The overall approach is outlined in Scheme 1.

TBHP is an inexpensive oxidant widely used in industries.[5] As compared to concentrated hydrogen peroxide, TBHP is quite stable towards thermal decomposition. Actually, 70% aqueous

Scheme 1 Aqueous TBHP benzylic oxidation of alkyl substituted aromatics.

TBHP constitutes a bulk organic chemical and has been certified for truck shipment in many countries.

Microwave assisted organic synthesis is a fast growing research area.[6] The technique was first recognized as a method for reducing the reaction time, commonly by orders of magnitude, and for clean reaction with increasing yields of products. In addition, it also provides opportunities for new reactions which are otherwise not feasible by conventional heating methods. An analogy had been made that microwave reactions could be the "Bunsen burners of the 21st century".[7]

2. Experimental

2.1 Materials

Unless otherwise noted, solvents and starting materials were obtained from commercial suppliers. All chemicals used were of reagent grade without further purification before use. ^{1}H NMR spectra were recorded on a JEOL JNM-EX 270 (270 MHz for ^{1}H) in CDCl$_3$ or DMSO-d$_6$. Chemical shifts were recorded in ppm (δ) relative to CHCl$_3$ on 7.26 and DMSO on 2.60. Experiments were conducted either in a CEM Discover Unit (300W, CEM Corporation, NC, USA) or a CHEMPOWER Reactor (800W, Shanghai, China).

2.2 Method. A

Experiments with 0.5-1.0 mmole of substrates were conducted using a CEM Discover Unit (CEM Corporation, NC, USA) in 10 mL glass vessels sealed with rubber membranes in a

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stirred mode with or without simultaneous cooling. A targeted temperature together with a maximum microwave power (250 and 80 W respectively for reactions without or with ionic liquid) was set. The targeted temperature was reached within a few minutes. During the course of the reaction, the microwave power as well as the pressure (60 to 240 psi) varied. After the reaction, the reaction vessel was cooled down to room temperature, then the cap was carefully opened to slowly release the pressure. The reaction mixture was treated with a saturated aqueous sodium bisulfite solution and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, then evaporated to give the ketones or benzoic acid.

2.3 Method B

Experiments with 0.5-1.3 mmole of substrates were conducted using a CHEMPOWER microwave reactor (Shanghai, China) in 10 mL or 20 mL glass vessels sealed with rubber membranes in a stirred mode with or without simultaneous cooling. The highest power (750 W) was set at the beginning so the targeted temperature can be reached within 2 min. With simultaneous cooling, the microwave power was maintained at 160 to 400 W during the course of the reaction. If there was no simultaneous cooling, the microwave power was comparatively lower (80~180 W). During the reaction, the pressure in the vessel was maintained at 58 to 290 psi. After the reaction, the reaction vessel was cooled down to room temperature, then the cap was carefully opened to slowly release the pressure. For the case of *p*-xylene to terephthalic acid and *m*-xylene to isophthalic acid, the product was precipitated as white solids which were filtered and washed with ethyl acetate and diethyl ether. For the case of *o*-xylene to phthalic acid, the reaction mixture was concentrated under reduced pressure. The precipitated phthalic acid was washed with ethyl acetate and diethyl ether.

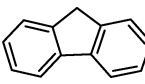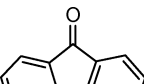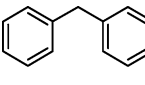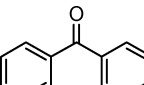### 2.4 NMR method for monitoring the oxidation of toluene

A sample of the reaction mixture was withdrawn and diluted with $CDCl_3$. After treated with D_2O, the ^1H NMR (270 MHz) spectrum was recorded. The percentage conversion can be calculated by comparing the integrations of the well resolved aromatic proton signals of benzoic acid (7.41–7.47, 7.54–7.57 and 8.05–8.08 ppm for the *meta*-, *para*- and *ortho*-protons, respectively) with the corresponding aromatic proton signals of toluene (7.06–7.09 and 7.13–7.18 ppm for the *ortho*-, *para*- and *meta*-protons respectively).

3. Results and discussion

3.1 Benzylic oxidation to ketones

Oxidation of methylene substituted benzylic aromatics to ketones (Scheme 1, R≠H) was first studied. When a mixture of fluorene and 10 equiv. (5 folds excess) of 70% aqueous TBHP was irradiated with microwave in a sealed vessel for 10 min, a quantitative yield of fluorenone was isolated (Table 1). As a control experiment, by simply refluxing the same reaction mixture by a conventional oil bath, heating for 8 h, only a trace amount of fluorenone could be detected by TLC. Oxidation of another substrate with a doubly activated benzylic

Table 1 TBHP oxidation of alkyl substituted aromatics to ketones under microwave irradiation

Substrate	Conditions[a]	MW power range[b]	Product	Yield
	170 °C, 10 min	250-138W		98%
	180 °C, 30 min	245-146W		85%
	180 °C, 30 min	250-79W		77%
	170 °C, 30 min	240-97W		53%

[a] Temperature was detected by the IR sensor of the reactor. [b] CEM Discover Unit, 0.5-0.6 mmol scale.

position, diphenylmethane, also afforded benzophenone in high yield. For the mono-activated methylene units, ethylbenzene to acetophenone and tetrahydronaphthalene to alpha-tetralone, the oxidations under this green protocol also went smoothly. The results are summarized in Table 1.

3.2 Oxidation of toluene and substituted toluenes

With the preliminary success in the oxidation of the benzylic methylene units, we then moved on to a more challenging task, oxidation of methyl substituted aromatics (Scheme 1, R=H). Selective oxidation of methyl substituted aromatics to the corresponding carboxylic acids is of industrial importance and academic interest.[2b,3] In laboratories, various transition metals based oxidizing agents such as permanganate and chromate have been used. In industry, such oxidations are achieved by using heavy metals based catalysts at high temperature. For example, benzoic acid is produced commercially by oxidation of toluene with oxygen catalyzed by cobalt or manganese naphthenates.

Oxidation of toluene to benzoic acid was first used as the model study. The results are summarized in Table 2. Each methyl oxidation requires three equivalents of the oxidant. With two folds excess of 70% aqueous TBHP (toluene/TBHP 1 : 6), toluene was converted 9.1% to benzoic acid under microwave irradiation in a 300 W reactor at 160 °C for 1 h (Table 2, entry 1). It is well documented that solvents with high dielectric constants would enhance microwave absorption. When the oxidation reactions were carried out in *tert*-butanol, nitrobenzene or acetonitrile (entries 2, 3, 4) as the co-solvents, the percentage conversions were increased to 20–27%. We also explored the use of other TBHP formulations such as TBHP in isooctane and toluene.[8] Oxidation can still take place but the results are inferior to the use of aqueous TBHP. As a control experiment, we carried out the oxidation at reflux (130 °C) by conventional
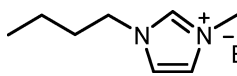
Table 2 Aqueous TBHP oxidation of toluene to benzoic acid under microwave irradiation

Entry	TBHP/equiv.	Solvent	Ionic liquid[a]	Temp.[b]/°C	Simultaneous cooling[c]	MW power range/W	Time/min	Conversion/%
1	2	/	/	160	no	250–133[d]	60	9.1
2	2	t-BuOH	/	160	no	250–85[d]	60	20
3	2	$C_6H_5NO_2$	/	160	no	250–46[d]	60	26
4	2	CH_3CN	/	160	no	250–103[d]	60	27
5	2	/	2%	160	no	100–36[d]	60	31
6	6.6	/	2%	150	no	80–10[d]	60	41
7	6.6	/	2%	150	yes	80–49[d]	60	71
8	6.6	/	2%	150	yes	80–41[d]	120	94
9	6.6	/	1%	150	no	280–180[e]	2	55
10	5	/	1%	130	yes	400–240[e]	20	74
11	5	/	1%	130	yes	410–250[e]	30	90 (71)[f]

[a] 1-butyl-3-methylimidazolium tetrafluoroborate. [b] Temperature was detected by the IR sensor of the reactor. [c] Homemade simultaneous cooling unit with 7 psi compress air. [d] CEM Discover Unit, 1 mmol scale. [e] CHEMPOWER Microwave Reactor, 1.3 mmol scale. [f] Isolated yield.

heating for 7 h. No benzoic acid could be detected from the reaction mixture.

Recently, it has been reported that addition of a small quantity of an ionic liquid can greatly increase the heating efficiency of a microwave reaction.[9] To improve the yield of toluene oxidation, the TBHP oxidation was carried out with 2% of 1-butyl-3-methylimidazolium tetrafluoroborate. The conversion was jumped to 31% as compared to 9.1% without the ionic liquid (entry 5 vs. 1). This result indicated that ionic liquids could replace the use of polar organic solvents. When the amount of TBHP was increased to 6.6 equiv., the conversion was jumped up to 41% (entry 6).

With the use of ionic liquids, heating was so efficient that the reaction mixture could be easily overheated within a few seconds. Therefore, the microwave power cannot be set too high. In addition, the microwave power drops to a rather low level (around 10 to 30 W) after the preset temperature had been reached. In order to maintain a reasonable level of microwave energy to sustain the reaction, we adopted the simultaneous cooling approach reported recently in literature.[10] A steam of compressed air or nitrogen at room temperature was passed over the reaction vessel during the microwave irradiation.

With the use of ionic liquid coupled with simultaneous cooling, the microwave power can be maintained within a reasonable level during the course of the reaction (1 h). The percentage conversion was increased to 71% (entry 7). To drive the toluene oxidation to completion, the microwave reaction was run for 2 h with simultaneous cooling. Conversion up to 94% was achieved (entry 8).

Moving to a more powerful 800 W microwave reactor, the efficiency of toluene to benzoic acid oxidation can be further improved. Using just 1% of ionic liquid and no simultaneous cooling, 55% conversion could be achieved in just 2 min at 150 °C (entry 9). However, the heating efficiency was so high

that the reaction pressure reached the machine's limit and the microwave power shut down automatically. Lowering the reaction temperature to 130 °C and with simultaneous cooling, 74% conversion was achieved in 20 min (entry 10). Extending the reaction time to 30 min, conversion was up to 90% (entry 11). After simple work up and recrystallization, benzoic acid could be isolated in 71% yield.

With the more powerful microwave reactor, the reaction time can be shortened and the amount of ionic liquid and TBHP can be lowered to 1% and 5 equiv., respectively. Lowering the temperature of the cooling gas to −20 °C (from a tank of pressured liquid nitrogen), the efficiency of the TBHP oxidation was only slightly improved. The oxidation of substituted toluenes was also performed and the results are listed in Table 3. It is obvious that electron withdrawing substitutents slow down the oxidation process.[11]

Table 3 Oxidation of substituted toluenes

Entry	G	Ionic liquid	MW power range[a]	Conversion
1	o-Cl	2%	60-31W	46%
2	m-Cl	2%	70-15W	50%
3	p-Cl	2%	65-27W	57%
4	p-Br	2%	70-33W	51%
5	o-NO₂	2%	75-34W	39%
6	p-OEt	/	70-30W	80%

[a] CEM Discover Unit
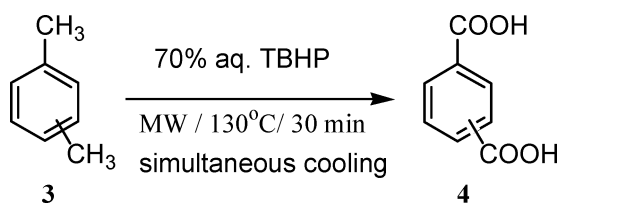
4. Proposed mechanism

A proposed free radical mechanism of this microwave assisted direct oxidation is depicted in Scheme 2. Upon microwave irradiation, TBHP is broken down into *t*-butoxide and hydroxyl radicals. Abstraction of a hydrogen radical from toluene gives a benzyl radical that reacts with TBHP to yield benzyl alcohol. Further oxidation could lead to benzaldehyde (or its hydrate), then benzoic acid. In fact, if we limited the amount of TBHP to 4 equiv., a tiny amount of benzaldehyde was detected in the ^{1}H NMR spectra of the reaction mixture.

5. Oxidation of xylenes

The oxidation of xylene isomers was then studied. The oxidized benzene dicarboxylic acids are important raw materials for many important commodities. For example, terephthalic acid (**4a**) is ranked as one of the top 50 industrial chemicals with a global demand amounting to 40 million tonnes per year and an annual growth rate of around 5–10%. It is the key monomer of polyethylene terephthalate (PET), and PET is the common material for making soft drink bottles and other packaging resins. Textile and synthetic fibres such as polyesters (Terylene) are also made from terephthalic acids. On the other hand, isophthalic acid (**4b**) is also the monomer of several synthetic polymers and phthalic acid (**4c**) is the key precursor of many plasticizers.

In industry, these oxidations of xylene isomers are carried out under aggressive conditions. In the industrial production of terephthalic acid, *p*-xylene is oxidized by air in acetic acid at 200 °C and a pressure of 294 psi. The catalyst system is made of bromides of heavy metals and salts of cobalt and manganese. The reaction must be carried out in a titanium-lined reactor because the reaction mixture is highly corrosive. On the other hand, gas-phase oxidation of *o*-xylene to phthalic acid is carried out with fluidized-bed V_2O_5 based catalyst, and the oxidation of *m*-xylene to isophthalic acid employs a cobalt–manganese catalyst. In

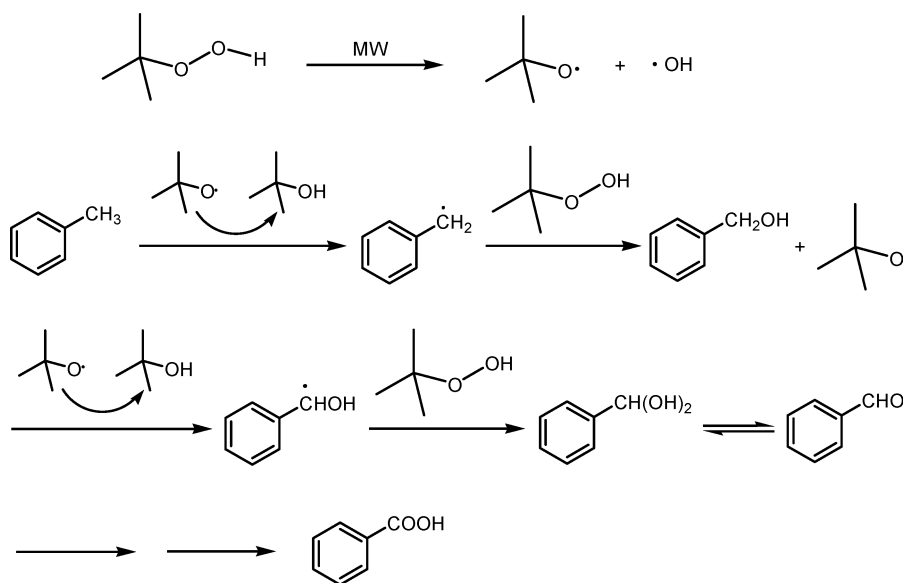**Table 4** TBHP oxidation of xylenes under microwave irradiation

Xylene	Phthalic acid	Microwave power range[a]/W	Yield crude (isolated)/%
p-CH$_3$	Terephthalic acid **4a**	220–170	53 (39)
m-CH$_3$	Isophthalic acid **4b**	380–200	45 (30)
o-CH$_3$	Phthalic acid **4c**	210–150	38 (29)

[a] CHEMPOWER Microwave Reactor, 1.3 mmol scale, 2% ionic liquid.

all these known oxidation processes of methyl aromatics, metal based oxidizing agents or catalysts are required.

Direct oxidation of the three xylene isomers (**3**) with a 5-fold excess of 70% aqueous TBHP (each oxidation requires 6 equiv. of oxidant) under simultaneous cooling were carried out in a 800 W microwave reactor. The results after 30 min irradiation are summarized in Table 4. Terephthalic, isophthalic and phthalic acids (**4a,b,c**) were obtained in moderate yields from *p*-, *m*- and *o*-xylene, respectively (Table 4). The oxidation of xylenes is probably a stepwise process. Around 20% of toluic acids (methylbenzoic) were also obtained. To our surprise, a small amount of benzoic acid was also detected. Using a less powerful 300 W reactor, similar results were obtained except the reaction time required was 2 h.

In the case of *p*- and *m*-xylene, the oxidized benzenedicarboxylic acids (terephthalic **4a** and isophthalic **4b**) precipitated from the reaction mixtures. This made the isolations of these two products straightforward. After filtration and recrystallization, purified terephthalic and isophthalic acids can be obtained in moderate yields.

Scheme 2 Mechanism of microwave-assisted TBHP oxidation.

6. Conclusions

This is the first report of direct microwave assisted oxidation of alkyl aromatics with aqueous TBHP without involving any metal reagent. This oxidation of alkyl substituted aromatics to ketones, mono- and dicarboxylic acids is also an environmentally friendly green chemical process. It is free of heavy metals with no added organic solvent. The only solvent involved is water[12] that comes with TBHP. A tiny amount of ionic liquid which is also viewed as a "green" reagent[13,14] enhanced the oxidation efficiency. Finally, focused microwave is also a "green" energy source as compared to conventional heating.[15–17]

The oxidation of xylene isomers to the corresponding phthalic acids opens up a green alternative to the synthesis of these economically important fine chemicals. Of course, in order to be commercially viable, the yields will need to be improved. Using a continuous flow reactor[18–20] may be a possibility. Under a continuous flow system, the precipitated diacid can be filtered off and the solution recycled back to the microwave reaction.

Acknowledgements

References

1 (a) M. Hudlicky, *Oxidation in Organic Chemistry*, ACS Monographs 186, Washington, DC, 1990; (b) *Comprehensive Organic Synthesis (Oxidation)*, ed. B. M. Trost, Pergamon, New York, 1991, vol. 7; (c) M. D. Hughes, Y.-J. Xu, P. Jenkins, P. McMorn, P. Landon, D. I. Enache, A. F. Carley, G. A. Attard, G. J. Hutchings, F. King, E. H. Stitt, P. Johnston, K. Griffin and C. J. Kiely, *Nature*, 2005, **437**, 1132.

2 (a) *Fine Chemicals Through Heterogeneous Catalysis*, ed. R. A. Sheldon and H. Bekkum, Wiley-VCH, Weinheim, 2001, Chapter 9; (b) *Industrial Organic Chemicals*, ed. H. A. Wittcoff, B. G. Reuben and J. S. Plotkin, Wiley, New Jersey, 2004.

3 *Industrial Organic Chemistry*, ed. K. Weissermel and H.-J. Arpe, Wiley-VCH, Weinheim, 2003.

4 (a) M. Poliakoff, J. M. Fitzpatrick, T. R. Farren and P. T Anastas, *Science*, 2002, **297**, 807; (b) I. T. Horvth and P. T. Anastas, *Chem. Rev.*, 2007, **107**, 2169–2173; (c) An example for green production of adipic acid: K. Sato, M. Aoki and R. Noyori, *Science*, 1998, **281**, 1646; (d) See also: J. Freitag, M. Nüchter and B. Ondruschka, *Green Chem.*, 2003, **5**, 291–295; (e) R. Noyori, M. Aoki and K. Sato, *Chem. Commun.*, 2003, 1977–1986.

5 (a) K. B. Sharpless and T. R. Verhoeven, *Aldrichim. Acta.*, 1979, **12**, 63; (b) R. A. Sheldon, In *The Chemistry of Peroxides*, ed. S. Patai, Wiley, New York, 1983.

6 (a) C. O. Kappe, *Chem. Soc. Rev.*, 2008, **37**, 1127; (b) V. Polshettiwar and S. Varma, *Acc. Chem. Res.*, 2008, **41**, 629; (c) *Microwave-Assisted Organic Synthesis*, ed. P. Lidström and J. P. Tierney, Blackwell, Oxford, 2005; (d) A. Miyazawa, K. Tanaka, T. Sakakura, M. Tashiro, H. Tashiro, G. K. S. Prakash and G. A. Olah, *Chem. Commun.*, 2005, 2104; (e) N. E. Leadbeater, *Chem. Commun.*, 2005, 2881.

7 The term was first coined by Bose: A. K. Bose, B. K. Banik, N. Lavolinskaia, M. Jayaraman and M. S. Manhas, *Chemtech*, 1997, **27**, 18.

8 (a) T. Katsuki and V. Martin, in *Organic Reactions*, ed. L. A. Paquette, 1996, 48, 1-299; (b) R. M. Hanson and K. B Sharpless, *J. Org. Chem.*, 1986, **51**, 1922.

9 (a) S. V. Ley, A. G. Leach and R. I. Storer, *J. Chem. Soc., Perkin Trans. 1*, 2001, 358; (b) N. E. Leadbeater and H. M. Torenius, *J. Org. Chem.*, 2002, **67**, 3145; (c) N. E. Leadbeater, H. M. Torenius and H. Tye, *Tetrahedron*, 2003, **59**, 2253; (d) Y. Peng and G. Song, *Tetrahedron Lett.*, 2004, **45**, 5313–5316; (e) Y.-H. Yen and Y.-H. Chu, *Tetrahedron Lett.*, 2004, **45**, 8137–8140; (f) M.-C. Liao, X.-H. Duan and Y.-M. Liang, *Tetrahedron Lett.*, 2005, **46**, 3469–3472; (g) A. Shaabani and A. Rahmati, *Synth. Commun.*, 2006, **36**, 65–70; (h) Z.-Z. Zhou, F.-Q. Ji, M. Cao and G.-F. Yang, *Adv. Synth. Catal.*, 2006, **348**, 1826–1830.

10 (a) R. K. Arvela and N. E. Leadbeater, *Org. Lett.*, 2005, **7**, 21012101 and references therein; (b) P. Appukkuttan, M. Husain, R. K. Gupta, V. S. Parmar and E. Van der Eycken, *Synlett*, 2006, 1491–1496; (c) G. S. Vanier, *Synlett*, 2007, 131–135; (d) M. Hosseini, N. Stiasni, V. Barbieri and C. O. Kappe, *J. Org. Chem.*, 2007, **72**, 1417–1424.

11 *Homogeneous Catalysis*, G. W. Parshall and S. D. Ittel, Wiley, New York, 2nd edn, 1992.

12 (a) C.-J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68–82; (b) S. Narayan, S. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2005, **44**, 3275; (c) C. I. Herreras, X. Yao, Z. Li and C.-J. Li, *Chem. Rev.*, 2007, **107**, 2546–2562.

13 U. M. Lindström and F. Andersson, *Angew. Chem., Int. Ed.*, 2006, **45**, 548–551.

14 (a) R. D. Rogers and K. R. Seddon, *Ionic Liquids as Green Solvents*, ACS Symposium Series 856, American Chemical Society, Washington DC, 2003; (b) R. D. Rogers and K. R. Seddon, *Ionic Liquids Industrial Applications to Green Chemistry*, ACS Symposium Series 818, American Chemical Society, 2002; (c) *Ionic Liquids in Synthesis*, ed. P. Wasserscheid and T. Welton, Wiley-VCH, Weinheim, 2003.

15 M. Nüechter, B. Ondruschka, W. Bonrath and A. Gum, *Green Chem.*, 2004, **6**, 128.

16 *Handbook of Green Chemistry and Technology*, ed. J. H. Chark and D. J. Macquarie, Blackwell, Oxford, 2002.

17 D. Dallinger and C. O. Kappe, *Chem. Rev.*, 2007, **107**, 2563–2591.

18 E. Comer and M. G. Organ, *J. Am. Chem. Soc.*, 2005, **127**, 8160.

19 M. C. Bagley, R. L. Jenkins, M. C. Lubinu, C. Mason and R. Wood, *J. Org. Chem.*, 2005, **70**, 7003.

20 J. D. Moseley and E. K. Woodman, *Org. Process Res. Dev.*, 2008, **12**, 967–981.