



Cite this: *Green Chem.*, 2017, **19**, 905

Received 18th November 2016,
Accepted 14th December 2016

DOI: 10.1039/c6gc03187k

rsc.li/greenchem

Difluoro- and trifluoro diazoalkanes – complementary approaches in batch and flow and their application in cycloaddition reactions†

Katharina J. Hock,‡ Lucas Mertens,‡ Friederike K. Metzke, Clemens Schmittmann and Rene M. Koenigs*

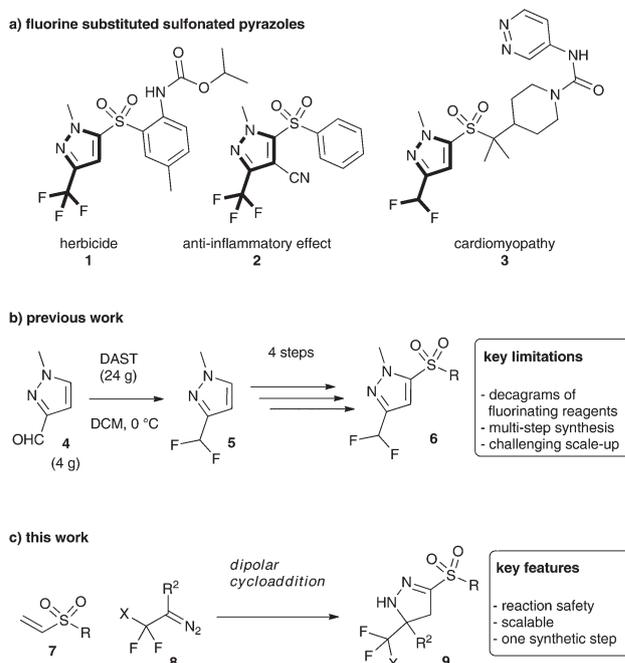
Herein we report on applications of fluorinated diazoalkanes in cycloaddition reactions, with the emphasis on studying subtle differences between diverse fluorinated diazo compounds. These differences led to two major synthetic protocols in batch and flow that allow the safe and scalable synthesis of fluoroalkyl-, sulfone-substituted pyrazolines.

Fluoroalkyl-substituted diazocompounds are a versatile class of reagents for the introduction of fluorinated groups and their synthetic potential has attracted significant interest in the past decade.¹ However, safe and scalable applications of fluoroalkyl-substituted diazo compounds are still highly desired, as this class of diazo compounds requires stringent safety precautions.²

Trifluoro diazoethane is probably the best-studied reagent among these diazo compounds and several groups reported its application.^{3,4} Interestingly, difluoro diazoethane only recently found its way into the organic synthesis repertoire, although it differs only in a single fluorine atom from well-studied trifluoro diazoethane.⁵ Additionally, fluoroalkyl-substituted donor-acceptor diazo compounds are studied only to a very limited extent.^{5b,6}

As part of our continuous interest in fluorinated diazo-compounds, we decided to investigate the differences of these diazoalkanes, which give important information on potential synthetic routes, required synthesis technology and subsequent scale-up of transformations using these versatile reagents.

Against this background, we started our investigations by studying the dipolar cycloaddition reaction of these diazoalkanes with vinyl sulfones (Scheme 1c). This transformation is of particular importance as the reaction product is a highly valuable sulfone- and fluoroalkyl-disubstituted pyrazoline (Scheme 1a).⁷ This fascinating class of heterocycles finds



Scheme 1 Applications and synthetic approaches towards sulfonated pyrazoles.

regular application,⁸ although current synthetic methodology does not allow an atom-economic, streamlined access to this class of compounds.^{8,9}

Sulfone-substituted heterocycles are typically prepared by late-stage introduction of the sulfone moiety and more importantly, the fluorinated analogues can only be accessed using hazardous fluorinating reagents on decagram-scale, which is far from being practical and scalable (Scheme 1b).^{8c}

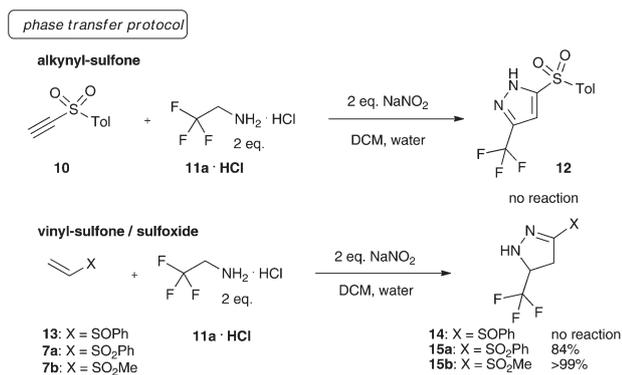
We initiated our investigations towards fluorinated, sulfone-substituted pyrazolines using a phase-transfer protocol for the generation of trifluoro diazoethane.¹⁰ Different retrosynthetically feasible precursors were investigated, though exclusively vinyl sulfones (**7a** and **7b**) yielded the desired sulfo-

RWTH Aachen University, Institute of Organic Chemistry, Landoltweg 1, D-52074 Aachen, Germany. E-mail: rene.koenigs@rwth-aachen.de

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c6gc03187k

‡ These authors contributed equally to this work.





Scheme 2 Preliminary investigations on sulfur-substituted pyrazolines.

nated heterocycles (**15a/b**). We also tested alkynyl sulfones (**10**) and vinyl sulfoxides (**13**) under the phase transfer conditions, yet both failed to give the desired product (Scheme 2).

Next, we examined a range of different organic solvents under phase transfer conditions and were delighted to observe that the desired trifluoromethyl substituted pyrazolines **15a** and **15b** could be obtained in different polar, and non-polar solvents in good to excellent yield. Dichloromethane and three equivalents of sodium nitrite proved to be the optimum reaction conditions to yield both aryl- and alkyl-sulfone substituted pyrazolines in excellent yield.¹¹

We next studied the substrate scope of the reaction of trifluoro diazoethane with vinyl sulfones under phase transfer conditions. To our delight a range of different aromatic and aliphatic vinyl sulfones (**7a–j**) could be converted to the corresponding trifluoromethyl- and sulfone-substituted pyrazolines (Table 1) in excellent yield. The sulfone substituent had only little influence on this transformation.

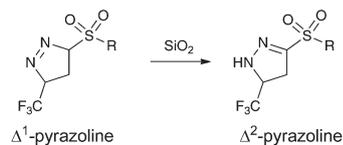
It should be noted, that we observed the initial formation of both Δ^1 - and Δ^2 -pyrazoline, after purification on silica gel we exclusively observed the Δ^2 -pyrazoline (Scheme 3).

In further investigations, we probed the closely related difluoro diazoethane. The difluoromethyl group differs only in

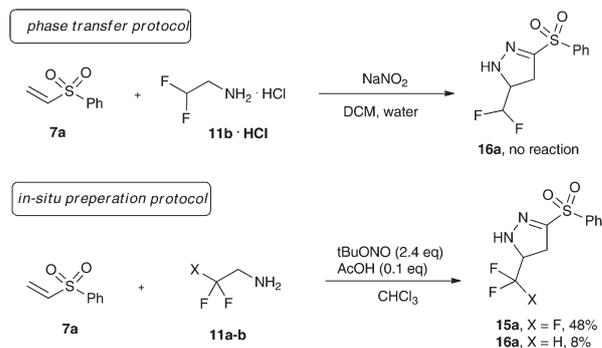
Table 1 Substrate scope of trifluoromethyl substituted pyrazolines

Entry	R	Yield	Entry	R	Yield
1	Phenyl	84%	6	4-Fluorophenyl	93%
2	Methyl	>99%	7	4-Chlorophenyl	91%
3	Ethyl	>99%	8	4-MeO-phenyl	93%
4	Benzyl	93%	9	3-Methylphenyl	>99%
5	4-Methylphenyl	98%	10	2-Methylphenyl	94%

Reaction conditions: vinyl sulfone (0.5 mmol, 1 eq.), trifluoroethylamine hydrochloride (2 eq.) and NaNO₂ (3 eq.) in DCM (8 mL)/water (2 mL) was vigorously stirred for 14 h at room temperature; isolated yields.



Scheme 3 Preliminary investigations on sulfur-substituted pyrazolines.



Scheme 4 Attempts to the synthesis of difluoromethyl substituted pyrazolines.

a single fluorine atom from the well-studied trifluoromethyl group; still, its introduction, physical-chemical and biological properties are very much different.¹²

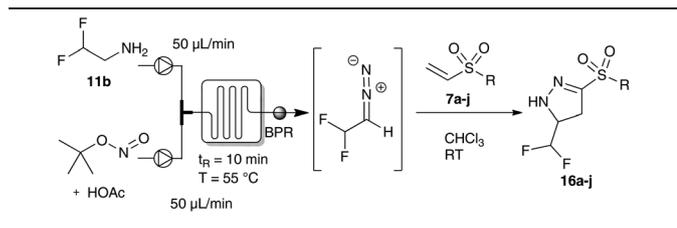
Hence, we investigated difluoro ethylamine hydrochloride as a source of difluoro diazoethane. Yet, we could never observe the formation of the desired reaction product (Scheme 4).

We hypothesized this surprising observation with a significantly reduced stability in aqueous solution of difluoro diazoethane and hydrolysis of the diazoalkane. Recently, Mykhailiuk and our group reported on *tert*-butyl nitrite as an efficient organic nitrite source for the formation of difluoro diazoethane.⁵ We thus examined this transformation using a purely organic medium (Scheme 4) and both trifluoro and difluoro ethylamine for comparison. We could observe formation of the corresponding trifluoromethylated pyrazoline **15a** only in moderate yield (48%), the difluoromethyl-substituted pyrazoline **16a** could be isolated in 8% yield.

Thus, we focused our efforts for the dipolar cycloaddition reaction of difluoro diazoethane using continuous flow technology.^{4j,5b,c,13} Using a 200 μL micromixer (Little Things Factory, MR-LAB MST) and an 800 μL microreactor (PTFE tubing) we were able to mix a stream of difluoroethylamine with a second stream of *tert*-butyl nitrite and catalytic amounts of acetic acid providing a continuous access to difluoro diazoethane. After optimization of the reaction conditions, we were able to obtain the desired pyrazolines **16a** and **16b** in excellent yield. Under these reaction conditions we next probed trifluoro diazoethane but unexpectedly, the desired pyrazoline **15a** could only be obtained in significantly decreased yield.¹¹

Similarly, as in the phase-transfer protocol, we observed the formation of Δ^1 - and Δ^2 -pyrazoline and subsequent isomerization to the Δ^2 -pyrazoline after chromatography.



Table 2 Substrate scope of difluoromethyl substituted pyrazolines

Entry	Substrate	Yield	Entry	Substrate	Yield
1	Phenyl	93%	6	4-Fluorophenyl	97%
2	Methyl	92%	7	4-Chlorophenyl	89%
3	Ethyl	99%	8	4-MeO-phenyl	83%
4	Benzyl	98%	9	3-Methylphenyl	>99%
5	4-Methylphenyl	95%	10	2-Methylphenyl	>99%

Reaction conditions: a solution of amine (0.2 M in CHCl_3 , 4 eq.) and of $t\text{BuONO}$ plus AcOH (2.4 M/0.08 M in CHCl_3) were placed in two separate syringes and added by syringe pump at a flow rate of $50 \mu\text{L min}^{-1}$ for each syringe into a microreactor (residence time 10 min, temperature = 55°C). The outlet was connected *via* a back pressure regulator (20 psi) to a reaction flask containing the vinyl sulfone (0.5 mmol) in CHCl_3 and stirred for 14 h at room temperature. Isolated yields.

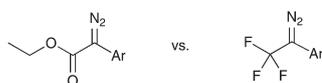
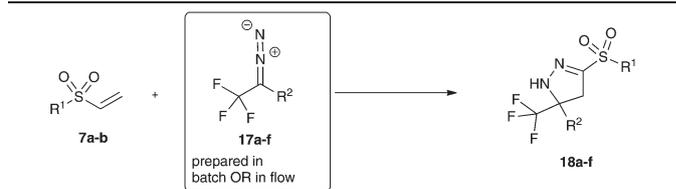
Next, we examined the flow protocol in detail and evaluated different vinyl sulfones. Under the optimum flow conditions for this transformation, we were able to show that difluoro-methyl- and sulfone-substituted pyrazolines could be obtained in excellent yield. The effect of different linear aliphatic, or differently substituted aromatic substituents had only a negligible effect on the yield of the desired pyrazolines (Table 2).

For a comprehensive evaluation of fluoroalkyl-substituted diazoalkanes in this cycloaddition reaction, we next investigated fluoroalkyl-aryl substituted diazoalkanes. These diazoalkanes are closely related to donor-acceptor diazoalkanes due to the strong electron-withdrawing nature of the fluoroalkyl group (Fig. 1).¹⁴

In initial experiments we examined both protocols described above for the synthesis of fluorinated donor-acceptor diazo compounds. Yet, the phase transfer protocol and the water-free domino reaction protocol both failed to give the desired product in acceptable yield.¹¹ However, if the diazo compound is prepared *in situ* and methyl vinyl sulfone is added subsequently after three hours in a one-pot protocol, the desired pyrazoline can be isolated in excellent yield.

This observation prompted us to examine the continuous-flow protocol for these substrates. To our delight the desired pyrazolines could be obtained in excellent yield (Table 3, entry 1).

We next investigated the substrate scope for this transformation and could demonstrate, that both the batch and the continuous-flow protocol can be used to deliver the desired pyrazolines in excellent yield. In general, different donor-acceptor

**Fig. 1** Donor-acceptor substituted diazoalkanes.**Table 3** Fluorinated donor-acceptor diazo compounds in [2 + 3] cycloaddition reaction

Entry	R ¹	R ² (diazo compound)	Yield batch	Yield flow
1	Methyl	Phenyl	97%	99%
2	Methyl	4-Methylphenyl	75%	97%
3	Methyl	4-Fluorophenyl	80%	98%
4	Methyl	-CH ₂ -CH ₂ -Ph	67%	97%
5	Methyl	Methyl	96%	99%
6	Phenyl	Methyl	99%	99%

Reaction conditions: for the batch reactions: the diazo compound is prepared by heating the amine (4 eq.), $t\text{BuONO}$ (4.8 eq.) and AcOH (1.6 eq.) in CHCl_3 to 55°C for 3 h, then after cooling to RT, vinyl sulfone (0.5 mmol) is added; isolated yields after chromatography. For the flow reactions: a solution of amine (0.2 M in CHCl_3 , 4 eq.) and of $t\text{BuONO}$ plus AcOH (2.4 M/0.08 M in CHCl_3) were placed in two separate syringes and added by syringe pump at a flow rate of $50 \mu\text{L min}^{-1}$ for each syringe into a microreactor (residence time 10 min). The outlet was connected *via* a back pressure regulator (20 psi) to a reaction flask containing the vinyl sulfone (0.5 mmol) in CHCl_3 and stirred for 14 h; isolated yields.

substituted fluorinated diazoalkanes can be prepared very efficiently using either batch or flow conditions. The advantages of the batch transformation being: no isolation of the diazo compound as well as fast and routine reaction setup for small-scale transformations. The advantages of the flow protocol being: process safety and a little better performance in terms of yield.

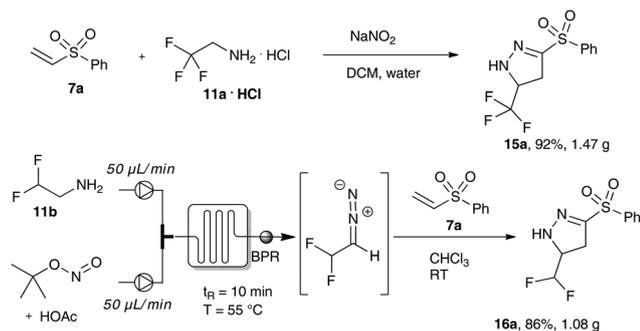
In further experiments, we investigated the robustness and scalability of these transformations. This is of particular importance, as organic synthesis with diazo compounds needs to be conducted with greatest care to prevent serious incidents.

Firstly, we examined the phase transfer protocol for the reaction of trifluoro diazoethane with vinyl sulfones on a gram-scale reaction. To our delight, the sulfone-substituted pyrazoline **15a** could be isolated in excellent yield. Similarly, difluoro diazoethane can be prepared in a continuous flow fashion for more than 10 hours and the subsequent cycloaddition reaction was scaled-up to gram scale yielding 1.08 g of the difluoromethyl substituted pyrazoline **16a** (Scheme 5).

In summary, we have reported on robust and atom-economic batch and flow protocols for the preparation of fluoroalkyl-substituted, sulfonated pyrazolines in one synthetic step without the need for hazardous fluorinating reagents. Small subtle differences in reactivity and stability between fluorinated diazo compounds have been observed resulting in two complementary synthetic protocols for the synthetic application of these diazo compounds.

Fluorinated donor-acceptor diazo compounds can be handled using either batch chemistry or flow technology.





Scheme 5 Gram-scale synthesis of sulfone-substituted fluorinated pyrazolines.

Trifluoro diazoethane can be handled on gram-scale most-efficiently in batch reactions. Contrarily, difluoro diazoethane necessitates the application of continuous-flow technology to access (a) new synthetic opportunities and (b) safe and scalable handling of this reagent.

The authors gratefully thank the Fonds der Chemischen Industrie for financial support (Sachkostenzuschuss).

Notes and references

- For a review article on fluoroalkyl-substituted diazoalkanes: L. Mertens and R. M. Koenigs, *Org. Biomol. Chem.*, 2016, **14**, 10547–10556.
- (a) R. Fields and J. P. Tomlinson, *J. Fluorine Chem.*, 1979, **13**, 147–158; (b) R. Fields and R. N. Haszeldine, *J. Chem. Soc.*, 1964, 1881–1889.
- H. Gilman and R. G. Jones, *J. Am. Chem. Soc.*, 1943, **65**, 1458–1460.
- Selected articles on trifluoro diazoethane. (a) B. Morandi and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2010, **49**, 938–941; (b) F. Li, J. Nie, L. Sun, Y. Zheng and J.-A. Ma, *Angew. Chem., Int. Ed.*, 2013, **52**, 6255–6258; (c) A.-J. Cai, Y. Zheng and J.-A. Ma, *Chem. Commun.*, 2015, **51**, 8946–8949; (d) Z. Chen, S.-Q. Fan, Y. Zheng and J.-A. Ma, *Chem. Commun.*, 2015, **51**, 16545–16548; (e) J.-J. Shen, S.-F. Zhu, Y. Cai, H. Xu, X.-L. Xie and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2014, **53**, 13188–13191; (f) O. A. Argintaru, D. Ryu, I. Aron and G. A. Molander, *Angew. Chem., Int. Ed.*, 2013, **52**, 13656–13660; (g) C. B. Liu, W. Meng, F. Li, S. Wang, J. Nie and J. A. Ma, *Angew. Chem., Int. Ed.*, 2012, **51**, 6227–6230; (h) B. Morandi, B. Mariampillai and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2011, **50**, 1101–1104; (i) S. Hyde, J. Veliks, B. Liegault, D. Grassi, M. Taillefer and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2016, **55**, 3785–3789; (j) B. Pieber and O. C. Kappe, *Org. Lett.*, 2016, **18**, 1076–1079; (k) A. V. Arkhipov, V. V. Arkhipov, J. Cossy, V. O. Kovtunencko and P. K. Mykhailiuk, *Org. Lett.*, 2016, **18**, 3406–3409.
- Articles on difluoro diazoethane: (a) P. K. Mykhailiuk, *Angew. Chem., Int. Ed.*, 2015, **54**, 6558–6561; (b) L. Mertens, K. J. Hock and R. M. Koenigs, *Chem. – Eur. J.*, 2016, **22**, 9542–9545; (c) K. J. Hock, L. Mertens and R. M. Koenigs, *Chem. Commun.*, 2016, **52**, 13783–13786.
- Selected references: (a) R. Barroso, A. Jimenez, M. C. Perez-Aguilar, M.-P. Cabal and C. Valdes, *Chem. Commun.*, 2016, **52**, 3677; (b) F. G. Adly, M. G. Gardiner and A. Ghanem, *Chem. – Eur. J.*, 2016, **22**, 3447–3461; (c) E. Emer, J. Twilton, M. Tredwell, S. Calderwood, T. L. Collier, B. Liegault, M. Taillefer and V. Gouverneur, *Org. Lett.*, 2014, **16**, 6004–6007; (d) J. F. Briones and H. M. L. Davies, *Org. Lett.*, 2011, **13**, 3984–3987; (e) M. Uehara, H. Suematsu, Y. Yasotomi and T. Katsuki, *J. Am. Chem. Soc.*, 2011, **133**, 170–171; (f) J. R. Denton, D. Sukumaran and H. M. L. Davies, *Org. Lett.*, 2007, **9**, 2625–2628; (g) G. Shi and Y. Xu, *J. Fluorine Chem.*, 1990, **46**, 173–178.
- For selected reviews on pyrazoles: (a) S. Güniz Küçükgülzel and S. Senkardes, *Eur. J. Med. Chem.*, 2015, **97**, 786–815; (b) M. L. Quan and J. M. Smallheer, *Curr. Opin. Drug Discovery Dev.*, 2004, **7**, 460–469; (c) D. B. Solit and G. Chiosis, *Drug Discovery Today*, 2008, **13**, 38–43; (d) F. K. Keter and J. Darkwa, *BioMetals*, 2012, **25**, 9–21; (e) J. Shonberg, P. J. Scammells and B. Capuano, *ChemMedChem*, 2011, **6**, 963–974; (f) H. Kumar, D. Saini, S. Jain and N. Jain, *Eur. J. Med. Chem.*, 2013, **70**, 248–258; (g) P. Chauhan, S. Mahajan and D. Enders, *Chem. Commun.*, 2015, **51**, 12890–12907.
- (a) C. J. Mathews and D. R. Baker, (Zeneca) *WO* 9718196, 1997; (b) C. Hassig, T. C. Gahman, M. R. Herbert and A. M. Thayer, (Kalypsys), *WO* 2007084868, 2007; (c) J. Oslob, D. Aubele, J. Kim, R. McDowell, Y. Song, A. Sran and M. Zhong, (MyoKardia) *WO* 2016118774, 2016.
- For selected references: (a) A. Padwa, M. Meske and A. Rodriguez, *Heterocycles*, 1995, **40**, 191–204; (b) A. Padwa and M. W. Wannamaker, *Tetrahedron*, 1990, **46**, 1145–1162; (c) A. Padwa, S. P. Craig, U. Chicchio and D. N. Kline, *J. Org. Chem.*, 1988, **53**, 2232–2238; (d) V. A. Vasin, V. V. Razin, E. V. Bezrukova, D. Y. Korovin, P. S. Petrov and N. V. Somov, *Russ. J. Org. Chem.*, 2015, **51**, 1144–1154.
- (a) E. Y. Slobodyanyuk, O. S. Artamonov, O. V. Shishkin and P. K. Mykhailiuk, *Eur. J. Org. Chem.*, 2014, 2487–2495; (b) P. K. Mykhailiuk, *Org. Biomol. Chem.*, 2015, **13**, 3438–3445; (c) P. K. Mykhailiuk, *Chem. – Eur. J.*, 2014, **20**, 4942–4947; (d) P. K. Mykhailiuk, *Beilstein J. Org. Chem.*, 2015, **11**, 16–24.
- For details see ESI.†
- Selected references on CF₂H groups: (a) G. K. S. Prakash and J. Hu, *Acc. Chem. Res.*, 2007, **40**, 921; (b) J. Hu, W. Zhang and F. Wang, *Chem. Commun.*, 2009, 7465–7478; (c) J. Hu and C. Ni, *Science of Synthesis: C-1 Building Blocks in Organic Synthesis*, 2014, vol. 2, p. 409; (d) C. Ni, J. Liu, L. Zhang and J. Hu, *Angew. Chem., Int. Ed.*, 2007, **46**, 786; (e) C. Ni and J. Ju, *Chem. Soc. Rev.*, 2016, **45**, 5441–5454.
- Selected review articles: (a) S. T. R. Mueller and T. Wirth, *ChemSusChem*, 2015, **8**, 245–250; (b) R. L. Hartman, J. P. McMullen and K. F. Jensen, *Angew. Chem., Int. Ed.*, 2011, **50**, 7502–7519; (c) J. Wegner, S. Ceylan and



- A. Kirschning, *Chem. Commun.*, 2011, **47**, 4583–4592; (d) S. V. Ley, *Chem. Rec.*, 2012, **12**, 378–390; (e) C. Wiles and P. Watts, *Green Chem.*, 2012, **14**, 38–54; (f) T. H. Rehm, *Chem. Eng. Technol.*, 2016, **39**(1), 66–68; (g) B. J. Deadman, S. G. Collins and A. R. Maguire, *Chem. – Eur. J.*, 2015, **21**, 2298–2308; (h) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley and C. V. Stevens, *Chem. Soc. Rev.*, 2016, **45**, 4892–4928.
- 14 Selected review articles: (a) H. M. L. Davies and D. Morton, *Chem. Soc. Rev.*, 2011, **40**, 1857–1869; (b) H. M. L. Davies and J. R. Denton, *Chem. Soc. Rev.*, 2009, **38**, 3061–3071.

