



Cite this: *Green Chem.*, 2016, **18**, 4623

Received 13th June 2016,
Accepted 14th July 2016

DOI: 10.1039/c6gc01601d

www.rsc.org/greenchem

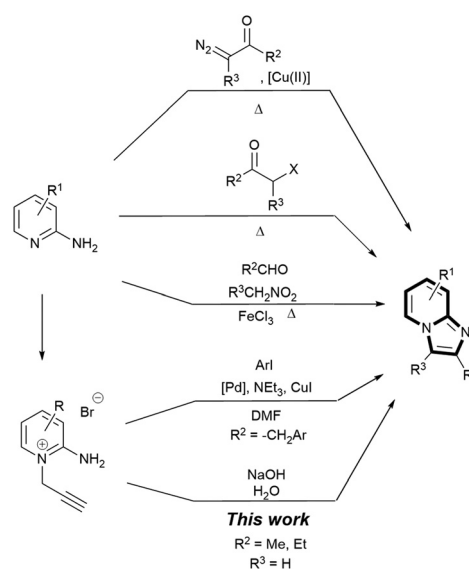
Rapid, metal-free and aqueous synthesis of imidazo[1,2-*a*]pyridine under ambient conditions†

Michael R. Chapman, Maria H. T. Kwan, Georgina E. King, Benjamin A. Kyffin, A. John Blacker, Charlotte E. Willans* and Bao N. Nguyen*

A novel, rapid and efficient route to imidazo[1,2-*a*]pyridines under ambient, aqueous and metal-free conditions is reported. The NaOH-promoted cycloisomerisations of *N*-propargylpyridiniums give quantitative yield in a few minutes (10 g scale). A comparison of common green metrics to current routes showed clear improvements, with at least a one order of magnitude increase in space-time-yield.

The imidazo[1,2-*a*]pyridine scaffold, found at the core of many pharmaceutical drugs such as zolimidine (peptic ulcer),¹ zolpidem (insomnia and brain disorders)² and rifaximin (hepatic encephalopathy),^{3,4} is one of the most privileged nitrogen-containing heterocycles in drug design.^{5–8} Industrial routes to imidazo[1,2-*a*]pyridines have often been *via* condensations between 2-aminopyridines and α -bromoketones/ α -chloroketones (Scheme 1),^{9,10} with an aryl or a carboxylate group at the β position for subsequent reduction to an OH group and derivatisation.^{11–13} Recent synthetic methods have focused on functionalisation of the core scaffold through metal catalysed coupling reactions (*e.g.* Cu,^{13–15} Fe,¹⁶ Au,⁷ Ru,¹⁸ and Pd^{19,20}),^{14,15} with attendant problems of product separation, and catalytic routes to assemble the scaffold.^{16,17} Furthermore, most of these processes employ undesirable solvents such as *N,N*-dimethylformamide,^{18–21} 1,2-dichloroethane,²² 1,4-dioxane,^{23,24} or acetonitrile,^{25,26} relatively high temperature, high catalyst loading and long reaction time.¹⁶

Bakherad and co-workers reported a Sonogashira-cyclisation cascade reaction catalysed by Pd catalysts.^{27,28} This reaction has been applied by Marugan *et al.* to generate a wide range of imidazopyridinium analogues as antagonists of neuropeptide S receptor.²⁹ Further functionalisations at the methyl position (R^2 in Scheme 1) are also well established.^{30–34} We were particularly interested in the cyclisation step, which



Scheme 1 Synthetic methods to assemble imidazo[1,2-*a*]pyridines.

was proposed to be catalysed by the Pd catalyst. We hypothesised that the same cyclisation could be achieved through a base-catalysed rearrangement of the propargyl fragment to an allenic group^{35–41} and subsequent Nazarov cyclisation.^{42–44} This led to a remarkably rapid, mild, general and high yielding NaOH-promoted heterocyclisation approach to imidazo[1,2-*a*]pyridines *via* pyridinium bromide precursors under ambient and aqueous conditions, which we are reporting here (Scheme 1).

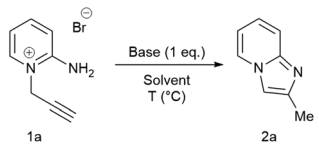
N-Propargylic pyridinium bromide **1a**, which was prepared by reaction of the corresponding 2-aminopyridine with propargyl bromide, was added to an aqueous solution of NaOH (1 equivalent) with vigorous stirring under ambient conditions. A suspension of a pale yellow oil was immediately evident which was subsequently extracted into ethyl acetate, concentrated and identified as spectroscopically pure imidazo[1,2-*a*]pyridine, **2a**, isolated in quantitative yield (Table 1, entry 1). Methanol and ethanol performed almost equally well as

Institute of Process Research and Development, School of Chemistry, University of Leeds, Leeds, LS2 9JT, UK. E-mail: b.nguyen@leeds.ac.uk

† Electronic supplementary information (ESI) available. CCDC 1471645, 1471647–1471650 and 1471653–1471656. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6gc01601d



Table 1 Optimisation of reaction conditions



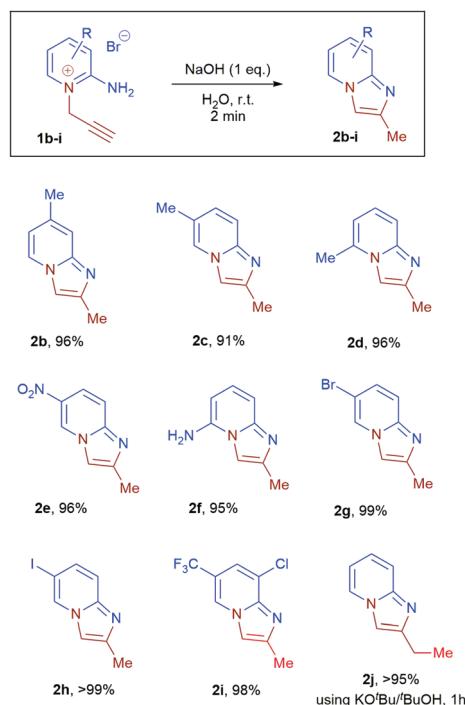
Entry	Base	Solvent	T (°C)	Time (min)	Yield ^{a,b} (%)
1	NaOH	H ₂ O	r.t.	2	>99
2 ^c	NaOH	H ₂ O	r.t.	2	>99
3	NaOH	MeOH	r.t.	5	95
4	NaOH	EtOH	r.t.	5	95
5	KOH	H ₂ O	r.t.	2	>99
6	DABCO	H ₂ O	r.t.	2	>99
7	Na ₂ CO ₃	H ₂ O	40	20	94
8	K ₂ CO ₃	H ₂ O	40	5	90
9	Cs ₂ CO ₃	H ₂ O	r.t.	5	93
10	NEt ₃	H ₂ O	r.t.	30	48
11	¹ Pr ₂ EtN	H ₂ O	r.t.	30	30
12 ^d	NaOH	H ₂ O	r.t.	10	18
13 ^e	DABCO	DMSO	r.t.	2	0
14 ^f	DABCO	DMSO	r.t.	2	15

^a Reaction conditions: pyridinium bromide (0.5 mmol), base (0.5 mmol), solvent (5 mL). ^b Isolated yield. ^c Extra pure NaOH assay: $\geq 99.9995\%$ metals basis. ^d Only 0.2 equivalent of NaOH was employed. ^e Using anhydrous *d*₆-DMSO. ^f Using anhydrous *d*₆-DMSO and 20 mol% of H₂O, giving 66% conversion after 24 hours.

solvent compared to water (entries 3 and 4), giving the desired product in high yield. The reaction in water, however, enabled a very simple workup either with an ethyl acetate extraction or simple phase separation at larger scales (*vide infra*). Employing KOH or DABCO instead of NaOH in water provided the product in quantitative yield (entries 5 and 6). Interestingly, using DABCO as the base in anhydrous DMSO gave no conversion (entry 13). Addition of catalytic amount of water led to some conversion (entry 14), but at much lower rate than that of the same reaction in water. A proton source is therefore essential to the reaction. Weaker bases such as Na₂CO₃, Cs₂CO₃ and K₂CO₃ proved less soluble, requiring slightly elevated temperatures and longer reaction times to achieve comparable yields (entries 7–9). Other organic bases, *i.e.* NEt₃ and (¹Pr)₂EtN, led to biphasic reaction mixtures and low yield of the desired product (entries 10 and 11, respectively), despite similar basicity to DABCO in DMSO.⁴⁵

To rule out the possibility of a reaction catalysed by trace amount of metal, ultra-high purity NaOH was employed as base (entry 2). The same quantitative yield and reaction time was obtained as with NaOH of standard purity, confirming the metal-free nature of the reaction. Reducing the amount of NaOH to 0.2 eq., however, resulted in only fractional conversion of the starting material (entry 12). Reaction conditions using NaOH as the least expensive and most readily available base, were taken forward for the rest of the study.

The substrate scope of the reaction was subsequently explored (Scheme 2, **2b–i**). Near-quantitative isolated yields were obtained from substrates **1b–i** containing electron donating and electron withdrawing substituents. Analytically pure



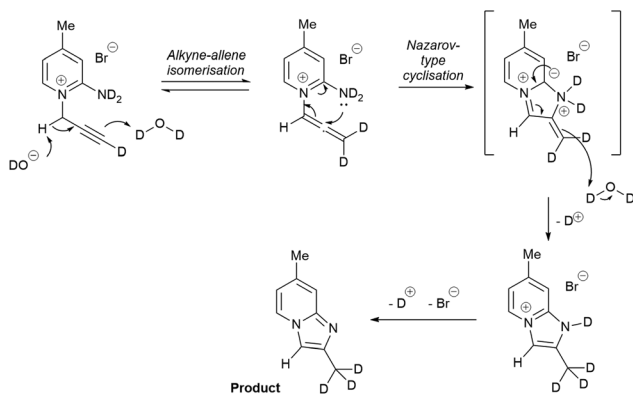
Scheme 2 Scope of substrates for aqueous cyclisation of 2-amino-1-propargylpyridiniums **1b–j** to product **2b–j**. Reaction performed on 1.0 mmol scale in 10 mL of water.

(NMR and microanalysis) imidazopyridines **2b–i** were obtained in all cases after a simple extraction. Importantly, the method is tolerant of methyl, chloro, bromo, iodo, trifluoromethyl, nitro and amino-substituents. X-ray crystallographic analysis of **2e**, **2g** and **2i** confirmed their solid-state structures and the positions of substituents on the imidazopyridines (see ESI†). This synthetic method represent a significant advantage over current metal-catalysed routes to imidazo[1,2-*a*]pyridines as halogens, which are required for subsequent functionalisation, and are well tolerated without compromise in yield and selectivity.

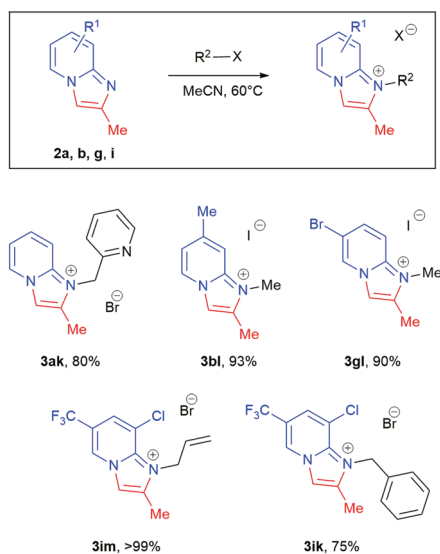
Disubstituted internal alkyne 2-amino-1-(2-butynyl)pyridinium bromide **1j**, however, gave no conversion under standard conditions. This was attributed to a decrease in the acidity of the propargyl CH₂, which is crucial for isomerisation to the corresponding allene. When ^tBuOK in ^tBuOH was employed, nearly quantitative conversion of **1j** to product **2j** was observed. Further functionalisation of the resulting imidazopyridines **2a**, **2b**, **2e**, **2g** and **2i** by treatment with benzyl bromide, methyl iodide and allyl bromide led to isolation of imidazopyridiniums **3ak**, **3bl**, **3gl**, **3im**, and **3ik** in good to excellent yield (Scheme 4).

The mechanism of the reaction was probed in a deuterium labelling experiment. Cyclisation of 4-methyl substituted pyridinium bromide **1b** to **2b** upon treatment with 1 eq. of NaOH was performed in D₂O and the deuterium incorporation evaluated by ¹H NMR spectroscopy. Only one methyl signal was observed in the ¹H NMR spectrum of the product. The new





Scheme 3 Proposed mechanism for the cyclisation based on deuterium labelling results.



Scheme 4 Scope of substrates for functionalisation of imidazo[1,2-*a*]pyridines. Reaction conditions: imidazo[1,2-*a*]pyridine (1.5 mmol), R^2-X 2.0–2.6 eq., MeCN (30 mL).

methyl group, formed at the terminal alkyne position of the substrate, was fully deuterated. An exchange experiment of the non-deuterated product **2b** with D_2O in the presence of NaOH showed no exchange with deuterium at the same methyl group.

Based on the experimental evidence above, a plausible mechanism is proposed in Scheme 3. It starts with a base-induced alkyne–allene isomerisation.^{35–41} This process normally requires a stronger base, e.g. KO^tBu , BuLi, but the presence of the pyridinium next to the propargyl CH_2 makes it significantly more acidic and enables the use of NaOH. Subsequent cyclisation in a Nazarov-type mechanism and tautomerisation leads to the product with a fully deuterated methyl group in D_2O . The base plays a dual role as catalyst for the isomerisation to allene and as a reagent to remove the byproduct DBr.

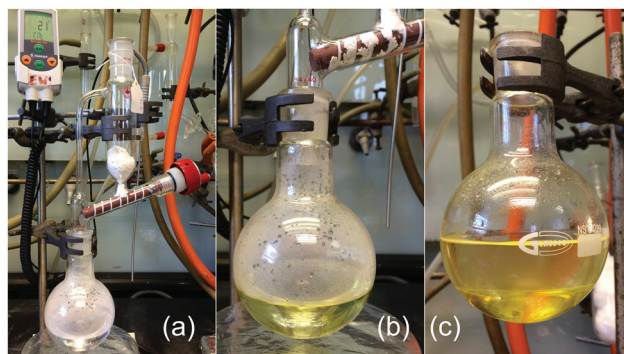


Fig. 1 A scaled up reaction setup. (a) before reaction; (b) during addition of **1a** (zoomed in); (c) phase separation at the end of the reaction (zoomed in).

The remarkably facile and very rapid nature of the reaction led us to explore the scalability of this novel route to imidazo-pyridines. Substrate **1a** was added over 5 minutes to a vigorously stirred aqueous solution of NaOH using a powder addition funnel on a 47 mmol (10.0 g) scale (Fig. 1). The product was easily separated at the end of the addition, giving the product **2a** in the same quantitative yield and high purity.

The green metrics for this process were calculated and are summarised in Table 2. These are compared with similar metrics from two industrial syntheses, one on lab scale and one optimised on kilogram scale.^{9,46} Atom Economy (AE),⁵⁰ reaction mass efficiency (RME)⁴⁹ and process mass intensity (PMI)^{49,51} are three of the currently preferred measures for evaluation of process sustainability.⁵² These metrics for our

Table 2 Green metrics comparison between the scaled-up process and the current industrial route to close analogues^{9,46}

	4a X = F	4b X = Br	
Metrics	This work (2a , 10 g scale) ^a	Current route 1 (4a) , 2.8 g scale) ⁴⁷	Current route 2 (4b , 3 kg scale) ⁹
Atom economy (%)	52	36	51
E-factor without water (g waste/g product) ^{47,48}	40.1	41.9	12.0
E-factor with water (g waste/g product)	51.5	77.6	22.8
Effective mass yield ^b (%)	39	7.2	27
Reaction mass efficiency ^c (%)	72 and 51	7.2	27
Process mass intensity (material/product) ^d	42.7	45.1	19.4
Space-time-yield ^e (g L ⁻¹ min ⁻¹)	0.42 and 10.9	0.03	0.059

^a Calculated as combined alkylation and cyclisation stages or shown separately. ^b NaOH, NaHCO₃ and CaCO₃ were estimated based on assumed stoichiometries. ^c Curzons' method of calculating reaction mass efficiency was used, ignoring water.⁴⁹ ^d This measure includes solvents but not water. ^e Space-time-yields exclude work-up time which are not optimised and can be variable.



reported process are consistently superior to those of the established route using α -halogencarbonyl reagents for 5-fluoro and 5-bromo imidazo[1,2-*a*]pyridine-2-carbaldehyde, albeit without one functional group in the product.^{9,46} It is worth noting that the latter has been operated at kilogram scale with optimised work-up to improve E-factor and PMI through reduction of solvent use. The effective mass yield (EMY)⁵³ shows higher efficiency for the new route, even compared to the optimised current process, although this metric requires definition of benign substances which can be contentious. Importantly the space-time-yield (STY) in the alkylation step is 7–14 times higher, and the STY in the cyclisation step is 185–363 times higher, than the comparative processes. In addition, the solvents in our process, *i.e.* ¹PrOH, EtOAc and water, are all ‘recommended’ solvents, while the main solvent in the current processes, 1,2-dimethoxyethane, is considered ‘hazardous’.⁵² Finally, the much faster reactions reported here mean that a telescoped process can potentially be carried out with acceptable solvents, heating and cooling.

In conclusion, we report a novel and green route to imidazo[1,2-*a*]pyridines which involves no metal catalyst and is extremely fast when performed in water. This route benefits from highly competitive green metrics and 1–2 magnitude higher STY compared to current synthetic processes. Investigation to expand the substrate scope and to understand the effect of water in this reaction is in progress and will be disseminated in the near future.

Acknowledgements

BAK thanks AstraZeneca for an industrial CASE studentship. MRC thanks the University of Leeds and AstraZeneca for a studentship. MHTK thanks the EPSRC, AstraZeneca and YPro-Tech for an Industrial CASE studentship.

Notes and references

- 1 L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Biancotti, A. Gamba and W. Murmann, *J. Med. Chem.*, 1965, **8**, 305–312.
- 2 S. Z. Langer, S. Arbilla, J. Benavides and B. Scatton, *Adv. Biochem. Psychopharmacol.*, 1990, **46**, 61–72.
- 3 K. R. Lawrence and J. A. Klee, *Pharmacotherapy*, 2008, **28**, 1019–1032.
- 4 H. L. DuPont, *Clin. Infect. Dis.*, 2007, **45**, S78–S84.
- 5 Q. Li, M. Zhou, L. Han, Q. Cao, X. Wang, L. Zhao, J. Zhou and H. Zhang, *Chem. Biol. Drug Des.*, 2015, **86**, 849–856.
- 6 S. Kang, R. Y. Kim, M. J. Seo, S. Lee, Y. M. Kim, M. Seo, J. J. Seo, Y. Ko, I. Choi, J. Jang, J. Nam, S. Park, H. Kang, H. J. Kim, J. Kim, S. Ahn, K. Pethe, K. Nam, Z. No and J. Kim, *J. Med. Chem.*, 2014, **57**, 5293–5305.
- 7 G. C. Moraski, L. D. Markley, P. A. Hipkind, H. Boshoff, S. Cho, S. G. Franzblau and M. J. Miller, *ACS Med. Chem. Lett.*, 2011, **2**, 466–470.
- 8 E. J. Barreiro, in *Privileged Scaffolds in Medicinal Chemistry: Design, Synthesis, Evaluation*, ed. S. Bräse, 2015, ch. 1, pp. 1–15.
- 9 S. Boggs, V. I. Elitzin, K. Gudmundsson, M. T. Martin and M. J. Sharp, *Org. Process Res. Dev.*, 2009, **13**, 781–785.
- 10 R. Bellingham, A. M. Buswell, B. M. Choudary, A. H. Gordon, S. O. Moore, M. Peterson, M. Sasse, A. Shamji and M. W. J. Urquhart, *Org. Process Res. Dev.*, 2010, **14**, 1254–1263.
- 11 S. Feng, D. Hong, B. Wang, X. Zheng, K. Miao, L. Wang, H. Yun, L. Gao, S. Zhao and H. C. Shen, *ACS Med. Chem. Lett.*, 2015, **6**, 359–362.
- 12 H. Kishino, M. Moriya, S. Sakuraba, T. Sakamoto, H. Takahashi, T. Suzuki, R. Moriya, M. Ito, H. Iwaasa, N. Takenaga, A. Ishihara, A. Kanatani, N. Sato and T. Fukami, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 4589–4593.
- 13 M. Shiozaki, K. Maeda, T. Miura, M. Kotoku, T. Yamasaki, I. Matsuda, K. Aoki, K. Yasue, H. Imai, M. Ubukata, A. Suma, M. Yokota, T. Hotta, M. Tanaka, Y. Hase, J. Haas, A. M. Fryer, E. R. Laird, N. M. Littmann, S. W. Andrews, J. A. Josey, T. Mimura, Y. Shinozaki, H. Yoshiuchi and T. Inaba, *J. Med. Chem.*, 2011, **54**, 2839–2863.
- 14 J. Koubachi, S. El Kazzouli, M. Bousmina and G. Guillaumet, *Eur. J. Org. Chem.*, 2014, **2014**, 5119–5138.
- 15 S. El Kazzouli, J. Koubachi, N. El Brahmi and G. Guillaumet, *RSC Adv.*, 2015, **5**, 15292–15327.
- 16 A. K. Bagdi, S. Santra, K. Monir and A. Hajra, *Chem. Commun.*, 2014, **51**, 1555–1575.
- 17 Y. Tachikawa, Y. Nagasawa, S. Furuhashi, L. Cui, E. Yamaguchi, N. Tada, T. Miura and A. Itoh, *RSC Adv.*, 2015, **5**, 9591–9593.
- 18 R.-L. Yan, H. Yan, C. Ma, Z.-Y. Ren, X.-A. Gao, G.-S. Huang and Y.-M. Liang, *J. Org. Chem.*, 2012, **77**, 2024–2028.
- 19 Z. Wu, Y. Pan and X. Zhou, *Synthesis*, 2011, 2255–2260.
- 20 H. Yan, S. Yang, X. Gao, K. Zhou, C. Ma, R. Yan and G. Huang, *Synlett*, 2012, 2961–2964.
- 21 S. Santra, A. K. Bagdi, A. Majee and A. Hajra, *Adv. Synth. Catal.*, 2013, **355**, 1065–1070.
- 22 J. S. Yadav, B. V. Subba Reddy, Y. Gopal Rao, M. Srinivas and A. V. Narsaiah, *Tetrahedron Lett.*, 2007, **48**, 7717–7720.
- 23 N. Shao, G.-X. Pang, C.-X. Yan, G.-F. Shi and Y. Cheng, *J. Org. Chem.*, 2011, **76**, 7458–7465.
- 24 C. He, J. Hao, H. Xu, Y. Mo, H. Liu, J. Han and A. Lei, *Chem. Commun.*, 2012, **48**, 11073–11075.
- 25 M. Chioua, E. Soriano, L. Infantes, M. L. Jimeno, J. Marco-Contelles and A. Samadi, *Eur. J. Org. Chem.*, 2013, **2013**, 35–39.
- 26 D. C. Mohan, S. N. Rao and S. Adimurthy, *J. Org. Chem.*, 2013, **78**, 1266–1272.
- 27 M. Bakherad, H. Nasr-Isfahani, A. Keivanloo and N. Doostmohammadi, *Tetrahedron Lett.*, 2008, **49**, 3819–3822.
- 28 M. Bakherad, B. Bahramian, H. Nasr-Isfahani, A. Keivanloo and N. Doostmohammadi, *J. Heterocycl. Chem.*, 2009, **46**, 100–104.



- 29 S. Patnaik, J. J. Marugan, K. Liu, W. Zheng, N. Southall, S. J. Dehdashti, A. Thorsell, M. Heilig, L. Bell, M. Zook, B. Eskay, K. R. Brimacombe and C. P. Austin, *J. Med. Chem.*, 2013, **56**, 9045–9056.
- 30 R. P. Alexander, J. M. Bentley, G. N. Brace, D. C. Brookings, P. T. Chovatia, H. J. C. Deboves, C. Johnstone; E. P. Jones, B. Kroepfien, F. C. Lecomte, J. Madden, C. A. Miller, J. R. Porter, M. D. Selby, M. A. Shaw, D. G. Vaidya and I. A. Yule, *WO 2015086506A1*, 2015.
- 31 T. W. Johnson, P. F. Richardson, S. Bailey, A. Brooun, B. J. Burke, M. R. Collins, J. J. Cui, J. G. Deal, Y.-L. Deng, D. Dinh, L. D. Engstrom, M. He, J. Hoffman, R. L. Hoffman, Q. Huang, R. S. Kania, J. C. Kath, H. Lam, J. L. Lam, P. T. Le, L. Lingardo, W. Liu, M. McTigue, C. L. Palmer, N. W. Sach, T. Smeal, G. L. Smith, A. E. Stewart, S. Timofeevski, H. Zhu, J. Zhu, H. Y. Zou and M. P. Edwards, *J. Med. Chem.*, 2014, **57**, 4720–4744.
- 32 S. Bailey, B. J. Burke, M. R. Collins, J. J. Cui, J. G. Deal, R. L. Hoffman, Q. Huang, T. W. Johnson, R. S. Kania, J. C. Kath, P. T. Q. Le, M. A. McTigue, C. L. Palmer, P. F. Richardson and N. W. Sach, *WO 2013132376A1*, 2013.
- 33 K. Gudmundsson and E. M. Turner, *WO 2007087548A2*, 2007.
- 34 K. R. Reddy, G. R. Scarlato, Q. Dang, M. D. Erion, S. R. Kasibhatla and M. R. Reddy, *WO, 9839342A1*, 1998.
- 35 A. Navarro-Vázquez, *Beilstein J. Org. Chem.*, 2015, **11**, 1441–1446.
- 36 T. W. Bousfield and M. C. Kimber, *Tetrahedron Lett.*, 2015, **56**, 350–352.
- 37 W. B. Dickinson and P. C. Lang, *Tetrahedron Lett.*, 1967, **8**, 3035–3040.
- 38 J. Huang, H. Xiong, R. P. Hsung, C. Rameshkumar, J. A. Mulder and T. P. Grebe, *Org. Lett.*, 2002, **4**, 2417–2420.
- 39 A. G. Lohse and R. P. Hsung, *Org. Lett.*, 2009, **11**, 3430–3433.
- 40 Á. González-Gómez, L. Añorbe, A. Poblador, G. Domínguez and J. Pérez-Castells, *Eur. J. Org. Chem.*, 2008, 1370–1377.
- 41 H. Fuwa and M. Sasaki, *Org. Biomol. Chem.*, 2007, **5**, 2214–2218.
- 42 W. T. Spencer, M. D. Levin and A. J. Frontier, *Org. Lett.*, 2011, **13**, 414–417.
- 43 V. M. Marx and D. J. Burnell, *Org. Lett.*, 2009, **11**, 1229–1231.
- 44 M. A. Tius, *Chem. Soc. Rev.*, 2014, **43**, 2979–3002.
- 45 M. R. Crampton and I. A. Robotham, *J. Chem. Res., Synop.*, 1997, 22–23.
- 46 S. D. Boggs and K. Gudmundsson, *PTC Int. Appl. Pat., WO 2006026703*, 2006.
- 47 R. A. Sheldon, *Chem. Ind.*, 1992, 903–906.
- 48 R. A. Sheldon, *Chem. Ind.*, 1997, 12–15.
- 49 A. D. Curzons, D. J. C. Constable, D. N. Mortimer and V. L. Cunningham, *Green Chem.*, 2001, **3**, 1–6.
- 50 B. M. Trost, *Science*, 1991, **254**, 1471–1477.
- 51 D. J. C. Constable, A. D. Curzons and V. L. Cunningham, *Green Chem.*, 2002, **4**, 521–527.
- 52 C. R. McElroy, A. Constantinou, L. C. Jones, L. Summerton and J. H. Clark, *Green Chem.*, 2015, **17**, 3111–3121.
- 53 T. Hudlicky, D. A. Frey, L. Koroniak, C. D. Claeboe and L. E. Brammer Jr., *Green Chem.*, 1999, **1**, 57–59.

