



Cite this: *Chem. Sci.*, 2018, 9, 2295

Received 14th November 2017  
Accepted 19th January 2018

DOI: 10.1039/c7sc04900e

rsc.li/chemical-science

## Oxidative $\beta$ -C–H sulfonylation of cyclic amines†

R. J. Griffiths,<sup>ab</sup> W. C. Kong,<sup>ac</sup> S. A. Richards,<sup>a</sup> G. A. Burley,<sup>b</sup> M. C. Willis<sup>bc</sup>  
and E. P. A. Talbot<sup>†\*a</sup>

A transition metal-free strategy for the dehydrogenative  $\beta$ -sulfonylation of tertiary cyclic amines is described. *N*-Iodosuccinimide facilitates regioselective oxidative sulfonylation at C–H bonds positioned  $\beta$  to the nitrogen atom of tertiary amines, installing enaminyll sulfone functionality in cyclic systems. Mild reaction conditions, broad functional group tolerance and a wide substrate scope are demonstrated. The nucleophilic character of the enaminyll sulfone is harnessed, demonstrating potential application for scaffold diversification.

### Introduction

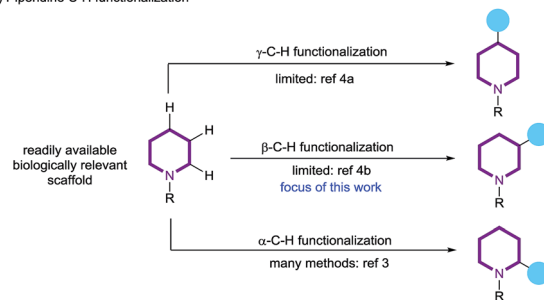
Aliphatic azacycles are essential motifs in drug discovery, with 59% of unique small-molecule drugs approved by the FDA containing at least one nitrogen heterocycle.<sup>1a</sup> Of these, the piperidine motif is the most prevalent nitrogen ring-system, highlighting the importance of this heterocycle in small-molecule drug discovery.<sup>1</sup> Simple piperidines are readily available, hence methods for the straightforward late-stage diversification of this ring-system, ideally exploiting C–H functionalization, are valuable tools for medicinal chemistry (Scheme 1a).<sup>2</sup> The majority of reported methods for the C–H functionalization of saturated nitrogen heterocycles have primarily focused on activation of the position  $\alpha$  to the nitrogen atom, with methods based on direct lithiation, as well a catalytic C–H bond cleavage being described.<sup>3</sup> Sanford has recently reported an elegant process for the palladium-catalyzed transannular C–H arylation of piperidines ( $\gamma$ -functionalization),<sup>4a</sup> and Bull has reported the palladium catalyzed C-3 arylation of proline derivatives ( $\beta$ -functionalization);<sup>4b</sup> it should be noted that both of these systems rely on a pre-installed directing group. Additional reports of functionalization remote to the nitrogen atom of cyclic amines are somewhat less well-precedented.<sup>4</sup>

Sulfones are privileged functional groups in the pharmaceutical and agrochemical industries,<sup>5</sup> and serve as versatile intermediates for organic synthesis.<sup>6</sup> Recent methods for the

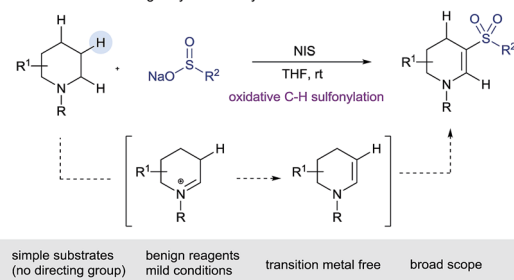
preparation of sulfones have focused on the utilization of higher valent sulfur reagents in order to avoid oxidative transformations.<sup>7</sup> Sulfinates salts have been employed for the direct formation of vinyl and aryl sulfones,<sup>8</sup> and methods based on the trapping of sulfur dioxide have also been exploited.<sup>9</sup> The varied methods available for sulfone preparation, together with their proven worth in medicinal chemistry, make them ideal functional groups to install using a C–H functionalization approach.

We recently described the iodine-mediated conversion of cyclic amines to lactams, in what corresponds to an  $\alpha$ -C–H functionalization process.<sup>10</sup> Iodine has also been used, along with an excess of peroxide co-oxidant, for the formation of enaminyll sulfones using simple acyclic amines and sulfinates

a) Piperidine C–H functionalization



b)  $\beta$ -C–H functionalization leading to cyclic enaminyll sulfones



Scheme 1 (a) The C–H functionalization of piperidines, and (b) this work: the preparation cyclic enaminyll sulfones.

<sup>a</sup>GlaxoSmithKline Medicines Research, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK

<sup>b</sup>Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, UK

<sup>c</sup>Department of Chemistry, University of Oxford, CRL Mansfield Road, Oxford, OX1 3TA, UK. E-mail: michael.willis@chem.ox.ac.uk

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7sc04900e

‡ Present address: Pharmaron, Hertford Rd, Hoddesdon, EN11 9BU, UK. E-mail: eric.talbot@pharmaron-uk.com



salts as starting materials.<sup>11</sup> A related, visible light mediated transformation employing air sensitive sulfonyl chlorides and a large excess of amine substrate (>4 eq.) has also been reported by Zheng and Zhang, but in both cases the product enaminyll sulfones were obtained in only poor yields and selectivities.<sup>12</sup> Both of these reports focus mostly on acyclic amine substrates and propose that an intermediary enamine attacks an electrophilic sulfonyl species. Our previous work showed evidence of proceeding *via* an iminium/enamine pathway, thus we speculated that formation of cyclic enaminyll sulfones from cyclic amines and sulfonates should be feasible under oxidative iodine conditions, and that such a reaction would provide a valuable transformation for the  $\beta$ -C-H functionalization of piperidines (Scheme 1b). In this article we report the successful realization of this goal, and use the installed functionality as a unique nucleophile for wider functionalisation.

## Results and discussion

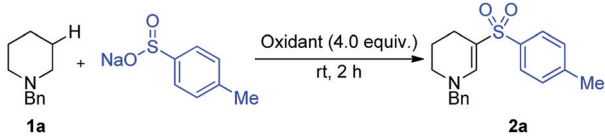
Important objectives at the start of our study were to define reaction conditions that would deliver efficient and selective reactions with good functional group tolerance. In particular, we were keen to avoid the use of *tert*-butyl hydroperoxide as a reagent, and also targeted ambient temperature reactions. Capitalizing on our prior report of iodine-mediated  $\alpha$ -C-H oxidation of amines, which proceeded at room temperature, we began our reaction optimization using iodine-based reagents. *N*-Benzyl piperidine **1a** was used as a model substrate and was combined with sodium *p*-tolylsulfinate in our optimization studies. A robust screen of conditions was undertaken, surveying the parameters of solvent, concentration, temperature, type of halo-oxidant and stoichiometry of oxidant and

sulfinate salt. The optimal conditions were identified, and THF proved to be the optimal solvent for this transformation, and *N*-iodosuccinimide (NIS) the optimal oxidant (Table 1).

In contrast to our previous work on the iodine-mediated formation of lactams, water and base were not found to be necessary for the formation of **2a**, with anhydrous DMSO providing the best conversion to **2a** (entry 4). Molecular iodine and iodine monochloride (entries 5 and 6) were significantly inferior oxidants than NIS. Shielding the reaction from light and oxygen was found to be crucial to achieving more reproducible results, and led to improved conversion to **2a** (entry 7). Finally, using THF as the solvent enabled a further increase in the formation of **2a** (entry 8), and also provided conditions that were amenable to reducing the amount of the more expensive sulfinate salt to only 1.5 equivalents (entry 10), with the reaction proceeding to 90% conversion. A slight decrease in conversion to **2a** (entry 11, 71%) was observed when using the lithium sulfinate salt, suggesting an importance the less tightly bound anion in the sodium sulfinate increases reactivity. However, the lithium sulfinate still proceeded well, which provides wider applicability for sulfonates synthesized *via* a lithiation protocol. Full details of the reaction optimization can be found in the ESI (Table S1†).

With the optimized conditions in hand, the scope of the reaction with respect to variation of sodium sulfinate salt was explored (Table 2). Electron-rich (**2b**), electron-poor (**2c**) and halide substituted (**2d-f**) aryl sulfonates provided access to enaminyll sulfones in good to excellent conversions and yields (68–98%). This provides an opportunity for subsequent diversification using the pre-installed halide functional group for the development of molecular libraries of biologically relevant molecules. *Meta*- and *ortho*-substitution on the aryl ring was

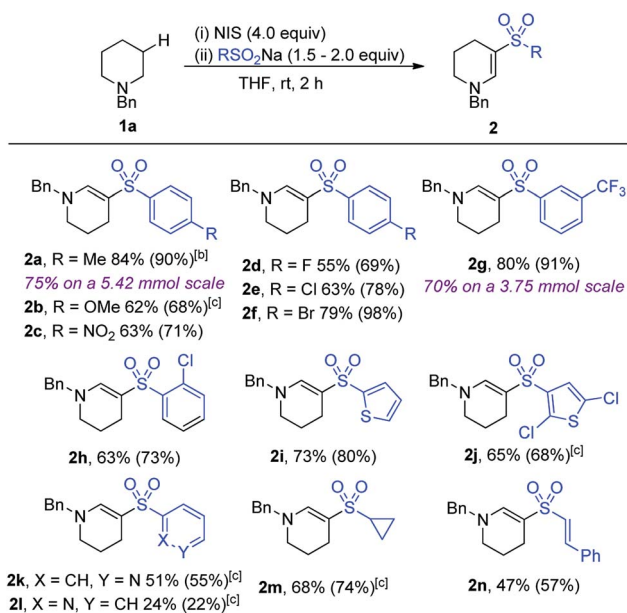
Table 1 Selected optimization data for the formation of enaminyll sulfone **2a**<sup>a</sup>



Entry	Equiv. <i>p</i> -TolSO <sub>2</sub> Na	Oxidant	Reaction conditions	% <b>2a</b> <sup>b</sup>
1	3	NIS	RT, 0.5 h actv <sup>c</sup> , 3 h, 2 : 1 THF <sup>d</sup> : water, 5 eq. NaHCO <sub>3</sub>	43
2	3	NIS	RT, 0.5 h actv, 3 h, 2 : 1 DMSO : water, 5 eq. NaHCO <sub>3</sub>	38
3	3	NIS	RT, 0.5 h actv, 2 h, DCM	27
4	3	NIS	RT, 0.5 h actv, 2 h, DMSO	60
5	3	I <sub>2</sub>	RT, 0.5 h actv, 2 h, DMSO	Trace
6	3	ICl	RT, 0.5 h actv, 2 h, DMSO	—
7	3	NIS	RT, 0.5 h actv, 2 h, DMSO, N <sub>2</sub> , dark	81
8	3	NIS	RT, 0.5 h actv, 2 h, THF <sup>e</sup> , N <sub>2</sub> , dark	95
9	3	NIS	RT, 0.5 h actv, 2 h, 2-MeTHF, N <sub>2</sub> , dark	65
10	1.5	NIS	RT, 0.5 h actv, 2 h, THF <sup>e</sup> , N <sub>2</sub> , dark	90
11	1.5 <sup>f</sup>	NIS	RT, 0.5 h actv, 2 h, THF <sup>e</sup> , N <sub>2</sub> , dark	71

<sup>a</sup> Reaction conditions: **1a** (1.0 eq.), oxidant (4.0 eq.), solvent, 0.5 h, then *p*-TolSO<sub>2</sub>Na, solvent (0.063 M), rt, 2 h. <sup>b</sup> % conversion to **2a** was measured by <sup>1</sup>H NMR analysis of the crude material against 3,4,5-trichloropyridine as an internal standard. <sup>c</sup> "actv" refers to the pre-stirring of oxidant with **1a**. <sup>d</sup> THF contained 250 ppm BHT radical inhibitor. <sup>e</sup> THF was inhibitor-free. <sup>f</sup> *p*-TolSO<sub>2</sub>Li was used as the sulfinate salt instead. *p*-Tol = *para*-tolyl.



Table 2 Variation of the sulfinate reaction component<sup>a</sup>

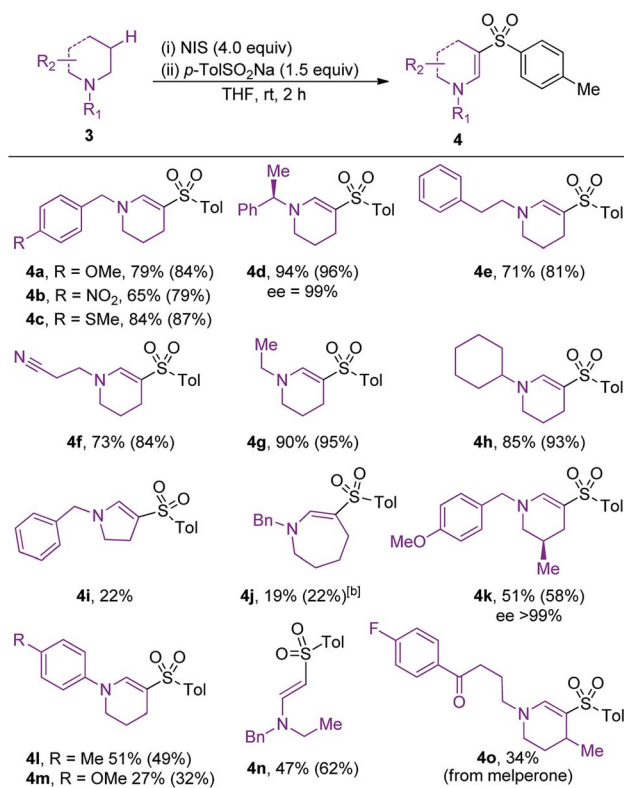
<sup>a</sup> Isolated yields shown; values in parentheses show conversion to product as measured by <sup>1</sup>H NMR analysis of crude product mixture using an internal standard. <sup>b</sup> 71% NMR conversion observed when TolSO<sub>2</sub>Li was used. <sup>c</sup> 2.0 equivalents of RSO<sub>2</sub>Na was used.

also tolerated well (**2g** and **h**, 91% and 73%, respectively), demonstrating good tolerance to steric crowding. Larger-scale reactions, performed on 5.42 mmol and 3.75 mmol of amine, delivered products **2a** (75%) and **2g** (70%), respectively, demonstrating the preparative utility of the method.

Heterocyclic sulfonates (**2i-l**) also performed well, although a lower conversion was observed for the 2-pyridyl sulfinate. Non-aryl sulfonates failed to provide the targeted enaminy sulfones, with the only exceptions being the use of sodium cyclopropylsulfinate and sodium styrylsulfinate, which provided enaminy sulfones **2m** and **2n** in 68% and 47% yield, respectively.

The scope of amine component was evaluated next (Table 3). Variation of the electronics of the *N*-benzyl substituent was tolerated (**4a, b**), with no benzylic functionalization observed in either reaction. Sulfone **4c**, featuring an arylmethylsulfide substituent, was obtained in 87% conversion, highlighting the tolerance of the reaction to oxidation-sensitive functional groups. Increasing the steric crowding around the nitrogen center was not detrimental to the reaction, and product **4d** was isolated in 94% yield.

Sulfones **4e** and **4f** were obtained with high selectivities and yields, confirming the preference for endocyclic over exocyclic oxidation, and tolerance of a nitrile functional group. The reaction was also tolerant and selective for different *N*-alkyl substituents on the amine, with ethyl and cyclohexyl examples performing well (**4g** and **h**). Disappointingly, variation of the ring size of the cyclic amine (**4i** and **j**) was not tolerated well, with the five- and seven-membered amines providing only moderate yields of the desired enaminy sulfones. The presence

Table 3 Variation of the amine reaction component<sup>a</sup>

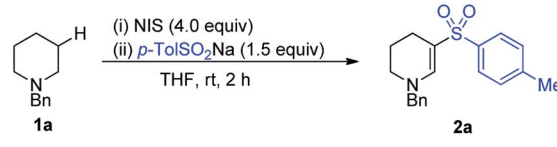
<sup>a</sup> Isolated yields shown; values in parentheses show conversion to product as measured by <sup>1</sup>H NMR analysis of crude product mixture using an internal standard. <sup>b</sup> 3.0 equivalents of *p*-TolSO<sub>2</sub>Na was used and DMSO as the reaction solvent. Tol = *para*-tolyl.

of a methyl-substituent on the framework of the piperidine ring steered sulfonation to the less-hindered position, and provided sulfone **4k** with high regioselectivity. *N*-Aryl amines performed moderately well, affording sulfones **4l** and **4m** in 49% and 32% conversion, respectively. The formation of sulfone **4n** established that oxidative sulfonation can be achieved for non-cyclic amines, and contrasts with our earlier iodine-mediated oxidative formation of amides, which was restricted to cyclic systems. The final example in Table 3 highlights the utility of the developed reaction for the late-stage C-H functionalization of medically relevant compounds; enaminy sulfone **4o** is derived from oxidative sulfonation of melperone, a marketed atypical antipsychotic. The formation of **4o** demonstrates how the developed reaction could be applied for the diversification of compound collections used in drug discovery.

As a preliminary investigation into the mechanism of the developed reaction we performed several control reactions (Table 4). The inclusion of BHT as an additive did not lead to appreciable inhibition of the reaction (entry 2). Catechol, however, resulted in a substantial drop in conversion, while sulfone **2a** was not observed when TEMPO was added to the reaction (entries 3 and 4, respectively). Lack of inhibition by BHT despite inhibition occurring with the radical scavenger



Table 4 Control experiments highlighting a putative radical pathway



Entry	Variation from above	% 2a <sup>a</sup>
1	None	90
2	BHT (1.1 equiv.) added	70
3	Catechol (1.1 equiv.) added	29
4	TEMPO (1.1 equiv.) added	0

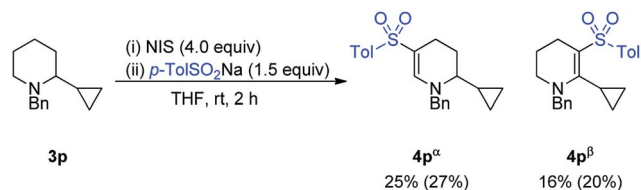
<sup>a</sup> As measured by <sup>1</sup>H NMR analysis of crude product mixture using an internal standard.

TEMPO has some precedent in related iodine/sulfonate reaction systems,<sup>8e</sup> thus a radical pathway could not be completely excluded at this stage.

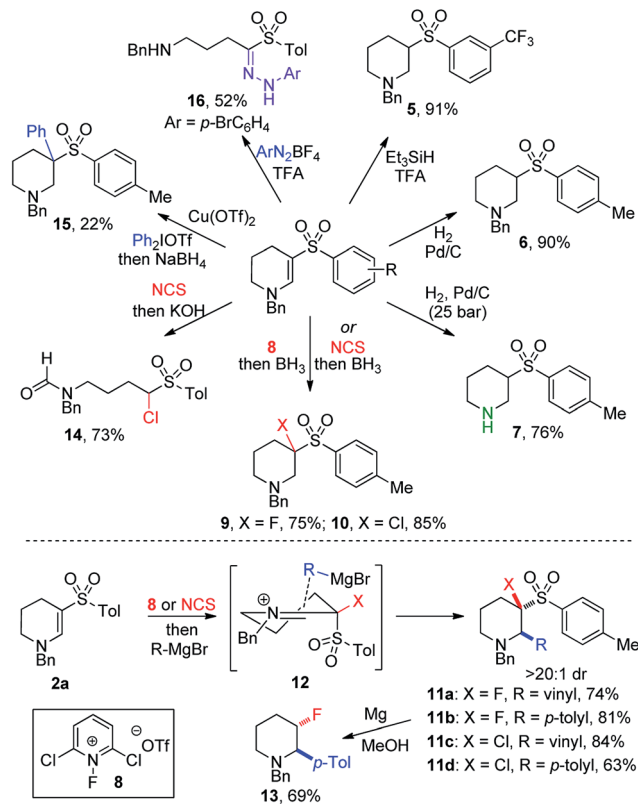
However, a radical clock experiment with **3p** provided a mixture of **4p<sup>α</sup>** and **4p<sup>β</sup>**, with no opening of the cyclopropyl ring observed (Scheme 2).

This result suggests that in fact the oxidative C–H sulfonylation reaction does not proceed *via* a radical-mediated pathway. The light and air-sensitivity of the reaction is indicative of formation of a sulfonyl iodide *in situ*, which are known to be unstable in the presence of light and oxygen.<sup>13</sup> This accounts for the poorer results observed for aliphatic and heteroaromatic sulfonate salts, as heteroaromatic and alkyl sulfonyl halides have been known to be unstable.<sup>14</sup> The inhibition of the reaction by known radical inhibitors is therefore proposed to arise as a result of reaction these additives accelerating the decomposition of the sulfonyl iodide. At this stage, the reaction is proposed to follow oxidation to an enamine, followed by nucleophilic attack of the sulfonyl iodide, though further studies are required.

Despite the combination of synthetically useful functional groups present in enaminy sulfones, their use in synthesis has not been well explored.<sup>15</sup> One reason for this is presumably the lack of convenient methods for their preparation. Accordingly, we set out to explore the utility of the cyclic enaminy sulfone products obtained in this study as templates for further diversification (Scheme 3). Selective reduction of the enamine could



Scheme 2 Radical-clock experiment with **3p**, indicating that the reaction does not proceed *via* a radical-based mechanism. Isolated yields shown; values in parentheses show conversion to product as measured by <sup>1</sup>H NMR analysis of crude product mixture using an internal standard. Tol = *para*-tolyl.



Scheme 3 Cyclic enaminy sulfones as templates for synthesis. Tol = *para*-tolyl.

be achieved under acidic silane conditions,<sup>16</sup> affording saturated system **5** in an excellent 91% yield. Alternatively, hydrogenation over Pd/C using Zn/HCl in COWare delivered sulfone **6** in comparable yield. Use of a flow hydrogenator enabled straightforward small-scale hydrogenation at high pressure; the use of 25 bar pressure enabled global hydrogenation to prepare piperidine **7** in which the *N*-benzyl group has been cleaved in 76% yield.

Incorporation of fluorine and chlorine atoms onto heterocyclic scaffolds is important for both modulating physicochemical properties,<sup>17</sup> and for the introduction of synthetic handles for subsequent chemical transformations.<sup>18</sup> Fluoropyridinium **8** proved to be the optimal reagent to yield β-fluorinated amine **9** (75%), and *N*-chlorosuccinimide enabled effective chlorination to provide β-chlorinated piperidine **10** (85%). These reductive halogenation reactions could be modified by replacing the borane reductant with a Grignard reagent, enabling the formation of a C–C bond in the α-position of the piperidines. Vinyl and *p*-tolyl Grignard reagents were used in both fluorination and chlorination procedures, providing trifunctionalized piperidines **11a–d** in high yields (63–81%). Only a single diastereomer was observed to form under these reaction conditions, suggesting an ordered transition state controlling the approach of the nucleophile to the iminium intermediate (**12**). Desulfonylation of **11b** could be achieved using magnesium in methanol,<sup>19</sup> to afford stereodefined β-fluoropiperidine **13** with good selectivity. Combining initial



chlorination with a hydroxide trap led to ring-opening of the piperidine and formation of formamide **14**. Arylation  $\beta$  to the amine was achieved using an arylidonium salt in the presence of a copper catalyst,<sup>20</sup> producing amine **15** in 22% yield. The formation of a congested quaternary center likely contributes to this low yield. Finally, reaction of **2a** with a diazonium salt induced ring-opening and loss of a methylene unit, producing hydrazone **16** in 52% yield *via* a Japp–Klingemann reaction.<sup>21</sup>

## Conclusions

In conclusion, we have developed a straightforward process for the  $\beta$ -C–H functionalization of piperidines. The reactions combine piperidines and sodium sulfonates, under the action of NIS, to provide enaminy sulfone products. The process is achieved under mild conditions, and shows good functional group tolerance. We also establish that the resultant cyclic enaminy sulfones are versatile templates for further elaboration. We envisage that this approach will expedite the generation of diverse compound libraries for use in drug discovery.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Financial support for this work was provided by GSK *via* the GSK/University of Strathclyde Centre for Doctoral Training in Synthetic and Medicinal Chemistry. We also thank Sean Lynn and Richard Upton (both GSK) for their assistance with NMR analysis.

## References

- (a) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274; (b) P. A. Petukhov, J. Zhang, C. Z. Wang, Y. P. Ye, K. M. Johnson and A. P. Kozikowski, *J. Med. Chem.*, 2004, **47**, 3009–3018; (c) M. Nakanishi, C. Tashiro, T. Munakata, K. Araki, T. Tsumagari and H. Imamura, *J. Med. Chem.*, 1970, **13**, 644–648; (d) B. Pati and S. Banerjee, *J. Pharma Res.*, 2012, **5**, 5493–5509.
- T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal and S. W. Krska, *Chem. Soc. Rev.*, 2016, **45**, 546–576.
- (a) J. E. Spangler, Y. Kobayashi, P. Verma, D.-H. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2015, **137**, 11876–11879; (b) S. J. Pastine, D. V. Gribkov and D. Sames, *J. Am. Chem. Soc.*, 2006, **128**, 14220–14221; (c) J. He, L. G. Hamann, H. M. L. Davies and R. E. J. Beckwith, *Nat. Commun.*, 2015, **6**, 5943–5951; (d) L. Shi and W. Xia, *Chem. Soc. Rev.*, 2012, **41**, 7687; (e) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel and B. U. W. Maes, *Chem.–Eur. J.*, 2012, **18**, 10092–10142.
- (a) J. J. Topczewski, P. J. Cabrera, N. I. Saper and M. S. Sanford, *Nature*, 2016, **531**, 220–224; (b) D. P. Affron, O. A. Davis and J. A. Bull, *Org. Lett.*, 2014, **16**, 4956–4959; (c) G. Asensio, M. E. Gonzalez-Nunez, C. B. Bernardini, R. Mello and W. Adam, *J. Am. Chem. Soc.*, 1993, **115**, 7250–7253; (d) M. Lee and M. S. Sanford, *J. Am. Chem. Soc.*, 2015, **137**, 12796–12799; (e) N. Takasu, K. Oisaki and M. Kanai, *Org. Lett.*, 2013, **15**, 1918–1921; (f) W. Chen, Y. Kang, R. G. Wilde and D. Seidel, *Angew. Chem., Int. Ed.*, 2014, **53**, 5179–5182; (g) L. Ma, A. Paul, M. Breugst and D. Seidel, *Chem.–Eur. J.*, 2016, **22**, 18179–18189; (h) J. M. Howell, K. Feng, J. R. Clark, L. J. Trzepkowski and M. C. White, *J. Am. Chem. Soc.*, 2015, **137**, 14590–14593; (i) D. M. Schultz, F. Lévesque, D. A. DiRocco, M. Reibarkh, Y. Ji, L. A. Joyce, J. F. Dropinski, H. Sheng, B. D. Sherry and I. W. Davies, *Angew. Chem., Int. Ed.*, 2017, **56**, 15274–15278.
- (a) E. Fromm and J. Wittmann, *Ber. Dtsch. Chem. Ges.*, 1908, **41**, 2264–2273; (b) H. Tucker, J. W. Crook and G. J. Chesterson, *J. Med. Chem.*, 1988, **31**, 954–959; (c) M. Couderchet, J. Schmalfuß and P. Böger, *Pestic. Sci.*, 1998, **52**, 381–387; (d) Smithkline Beecham Corporation, J. Busch-Petersen and Glaxosmithkline Llc, Ca. Pat., CA2650009 C, 2014; (e) Vertex Pharmaceuticals Incorporated, *US Pat.*, US2013/115310, 2013; (f) Bristol-Myers Squibb Company, WO2015/103510, 2015.
- (a) N. Simpkins, *Sulfones in Organic Synthesis*, Pergamon Press, Oxford, 1st edn, 1993; (b) N. S. Simpkins, *Tetrahedron*, 1990, **46**, 6951–6984.
- (a) L. K. Liu, Y. Chi and K.-Y. Jen, *J. Org. Chem.*, 1980, **45**, 406–410; (b) H. Goldwhite, M. S. Gibson and C. Harris, *Tetrahedron*, 1964, **20**, 1613–1624; (c) T. G. Back and S. Collins, *J. Org. Chem.*, 1981, **46**, 3249–3256; (d) Y. H. Kang and J. L. Kice, *J. Org. Chem.*, 1984, **49**, 1507–1511; (e) D. Duan and X. Huang, *Synlett*, 1999, **1999**, 317–318; (f) X. Li, X. Shi, M. Fang and X. Xu, *J. Org. Chem.*, 2013, **78**, 9499–9504; (g) Y. Xi, B. Dong, E. J. McClain, Q. Wang, T. L. Gregg, N. G. Akhmedov, J. L. Petersen and X. Shi, *Angew. Chem., Int. Ed.*, 2014, **53**, 4657–4661; (h) Y. Xu, J. Zhao, X. Tang, W. Wu and H. Jiang, *Adv. Synth. Catal.*, 2014, **356**, 2029–2039; (i) N. Taniguchi, *Tetrahedron*, 2014, **70**, 1984–1990.
- (a) B. P. Bandgar, S. V. Bettigeri and J. Phopase, *Org. Lett.*, 2004, **6**, 2105–2108; (b) S. Cacchi, G. Fabrizi, A. Goggiamani, L. M. Parisi and R. Bernini, *J. Org. Chem.*, 2004, **69**, 5608–5614; (c) A. U. Meyer, S. Jäger, D. Prasad Hari and B. König, *Adv. Synth. Catal.*, 2015, **357**, 2050–2054; (d) P. Katrun, S. Chiampanichayakul, K. Korworapan, M. Pohmakotr, V. Reutrakul, T. Jaipetch and C. Kuhakarn, *Eur. J. Org. Chem.*, 2010, 5633–5641; (e) Y. Sun, A. Abdukader, D. Lu, H. Zhang and C. Liu, *Green Chem.*, 2017, **19**, 1255–1258.
- (a) E. J. Emmett, B. R. Hayter and M. C. Willis, *Angew. Chem., Int. Ed.*, 2014, **53**, 10204–10208; (b) A. S. Deeming, C. J. Russell and M. C. Willis, *Angew. Chem., Int. Ed.*, 2016, **55**, 747–750; (c) Y. Chen and M. C. Willis, *Chem. Sci.*, 2017, **8**, 3249–3253; (d) E. J. Emmett and M. C. Willis, *Asian J. Org. Chem.*, 2015, **4**, 602–611; (e) A. S. Deeming and M. C. Willis, in *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, Chichester, UK, 2016, pp. 1–4.



- 10 R. J. Griffiths, G. A. Burley and E. P. A. Talbot, *Org. Lett.*, 2017, **19**, 870–873.
- 11 J. Lai, L. Chang and G. Yuan, *Org. Lett.*, 2016, **18**, 3194–3197.
- 12 (a) M. Chen, Z.-T. Huang and Q.-Y. Zheng, *Org. Biomol. Chem.*, 2014, **12**, 9337–9340; (b) Y. Cai, R. Zhang, D. Sun, S. Xu and Q. Zhou, *Synlett*, 2017, **28**, 1630–1635.
- 13 L. K. Liu, Y. Chi and K.-Y. Jen, *J. Org. Chem.*, 1980, **45**, 406–410.
- 14 (a) S. W. Wright and K. N. Hallstrom, *J. Org. Chem.*, 2006, **71**, 1080–1084; (b) A. García-Rubia, B. Urones, R. Gómez Arrayás and J. C. Carretero, *Angew. Chem., Int. Ed.*, 2011, **50**, 10927–10931; (c) E. Wedekind and D. Schenk, *Ber. Dtsch. Chem. Ges.*, 1911, **44**, 198–202; (d) J. F. King, *Acc. Chem. Res.*, 1975, **8**, 10–17.
- 15 (a) W. Zhu, G. Cai and D. Ma, *Org. Lett.*, 2005, **7**, 5545–5548; (b) D.-J. Zhang, M.-S. Xie, G.-R. Qu, Y.-W. Gao and H.-M. Guo, *Org. Lett.*, 2016, **18**, 820–823.
- 16 A. E. Lanzilotti, R. Littell, W. J. Fanshawe, T. C. McKenzie and F. M. Lovell, *J. Org. Chem.*, 1979, **44**, 4809–4813.
- 17 (a) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315–8359; (b) C. Bissantz, B. Kuhn and M. Stahl, *J. Med. Chem.*, 2010, **53**, 5061–5084.
- 18 (a) M. Dryzhakov, E. Richmond, G. Li and J. Moran, *J. Fluorine Chem.*, 2017, **193**, 45–51; (b) M. Dryzhakov and J. Moran, *ACS Catal.*, 2016, **6**, 3670–3673; (c) F. González-Bobes and G. C. Fu, *J. Am. Chem. Soc.*, 2006, **128**, 5360–5361; (d) H. Tateno, Y. Matsumura, K. Nakabayashi, H. Senboku and M. Atobe, *RSC Adv.*, 2015, **5**, 98721–98723; (e) M. Sidera and S. P. Fletcher, *Nat. Chem.*, 2015, **7**, 935–939.
- 19 T. Shibue and Y. Fukuda, *J. Org. Chem.*, 2014, **79**, 7226–7231.
- 20 A. Bigot, A. E. Williamson and M. J. Gaunt, *J. Am. Chem. Soc.*, 2011, **133**, 13778–13781.
- 21 T. Laue and A. Plagens, *Named Organic Reactions*, Wiley, 2nd edn, 2005.

