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. Of these, the piperidine motif is the most prevalent nitrogen ring-system, highlighting the importance of this heterocycle in small-molecule drug discovery. 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). The majority of reported methods for the C–H functionalization of saturated nitrogen heterocycles have primarily focused on activation of the position α to the nitrogen atom, with methods based on direct lithiation, as well a catalytic C–H bond cleavage being described. Sanford has recently reported an elegant process for the palladium-catalyzed transannular C–H arylation of piperidines (γ-functionalization), and Bull has reported the palladium catalyzed C-3 arylation of proline derivatives (β-functionalization); 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.

Sulfones are privileged functional groups in the pharmaceutical and agrochemical industries, and serve as versatile intermediates for organic synthesis. Recent methods for the preparation of sulfones have focused on the utilization of higher valent sulfur reagents in order to avoid oxidative transformations. Sulfinates have been employed for the direct formation of vinyl and aryl sulfones, and methods based on the trapping of sulfur dioxide have also been exploited. 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 α-C–H functionalization process. Iodine has also been used, along with an excess of peroxide co-oxidant, for the formation of enaminyl sulfones using simple acyclic amines and sulfinates.

Oxidative β-C–H sulfonylation of cyclic amines†

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

Scheme 1  (a) The C–H functionalization of piperidines, and (b) this work: the preparation cyclic enaminyl sulfones.
salts as starting materials. 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 enaminy sulfones were obtained in only poor yields and selectivities.

Both of these reports focus mostly on acyclic amine substrates and propose that an intermediary amine attacks an electrophilic sulfonyl species. Our previous work showed evidence of proceeding via an iminium/enamine pathway, thus we speculated that formation of cyclic enaminy 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 β-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 α-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 of 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 enaminy 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 enaminy sulfone 2a

| Entry | Equiv. p-TolSO₂Na | Oxidant | Reaction conditions | % 2a
|-------|------------------|---------|--------------------|-------|
| 1     | 3                | NIS     | RT, 0.5 h actv, 3 h, 2:1 THF: water, 5 eq. NaHCO₃ | 43    |
| 2     | 3                | NIS     | RT, 0.5 h actv, 3 h, 2:1 DMSO: water, 5 eq. NaHCO₃ | 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                | I₂      | 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, N₂, dark | 81    |
| 8     | 3                | NIS     | RT, 0.5 h actv, 2 h, THF, N₂, dark | 95    |
| 9     | 3                | NIS     | RT, 0.5 h actv, 2 h, 2-MeTHF, N₂, dark | 65    |
| 10    | 1.5              | NIS     | RT, 0.5 h actv, 2 h, THF, N₂, dark | 90    |
| 11    | 1.5*             | NIS     | RT, 0.5 h actv, 2 h, THF, N₂, dark | 71    |

*Reaction conditions: 1a (1.0 eq.), oxidant (4.0 eq.), solvent, 0.5 h, then p-TolSO₂Na, solvent (0.063 M), 2 h. *°% conversion to 2a was measured by 1H NMR analysis of the crude material against 3,4,5-trichloropyridine as an internal standard. °actv refers to the pre-stirring of oxidant with 1a. *THF contained 250 ppm BHT radical inhibitor. °THF was inhibitor-free. *p-TolSO₂Li was used as the sulfinate salt instead. *P-Tol = para-tolyl.
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 sulfinates (2i–l) also performed well, although a lower conversion was observed for the 2-pyridyl sulfinate. Non-aryl sulfinates failed to provide the targeted enamyl sulfones, with the only exceptions being the use of sodium cyclopropylsulfinate and sodium styrylsulfinate, which provided enamyl 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 arylmethylsulfinyl 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 enamyl sulfones. The presence of a methyl-substituent on the framework of the piperidine ring steered sulfonylation 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 sulfonylation 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 medicinally relevant compounds; enamyl sulfone 4o is derived from oxidative sulfonylation 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 2 Variation of the sulfinate reaction component

Table 3 Variation of the amine reaction component

*a Isolated yields shown; values in parentheses show conversion to product as measured by 1H NMR analysis of crude product mixture using an internal standard. † 71% NMR conversion observed when TolSO2Li was used. ‡ 2.0 equivalents of RSO2Na was used.

*a Isolated yields shown; values in parentheses show conversion to product as measured by 1H NMR analysis of crude product mixture using an internal standard. † 3.0 equivalents of p-TolSO2Na was used and DMSO as the reaction solvent. Tol = para-tolyl.
TEMPO has some precedent in related iodine/sulfinate reaction systems,\textsuperscript{ae} thus a radical pathway could not be completely excluded at this stage.

However, a radical clock experiment with 3p provided a mixture of 4p\textsuperscript{a} and 4p\textsuperscript{b}, 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 \textit{via} a radical-mediated pathway. The light and air-sensitivity of the reaction is indicative of formation of a sulfonyl iodide \textit{in situ}, which are known to be unstable in the presence of light and oxygen.\textsuperscript{13} This accounts for the poorer results observed for aliphatic and hetereoaromatic sulfonyl halides have been known to be unstable.\textsuperscript{14} 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 enaminyl sulfones, their use in synthesis has not been well explored.\textsuperscript{15} 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 enaminyl sulfone products obtained in this study as templates for further diversification (Scheme 3). Selective reduction of the enamine could be achieved under acidic silane conditions,\textsuperscript{16} affording saturated system 5 in an excellent 91% yield. Alternatively, hydrogenation over Pd/C using Zn/HCl in CO\textsubscript{2}ware 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,\textsuperscript{17} and for the introduction of synthetic handles for subsequent chemical transformations.\textsuperscript{18} 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). Desulfonation of 11b could be achieved using magnesium in methanol,\textsuperscript{19} 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 β to the amine was achieved using an arylidonium salt in the presence of a copper catalyst,29 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.21

Conclusions
In conclusion, we have developed a straightforward process for the β-C–H functionalization of piperidines. The reactions combine piperidines and sodium sulfinites, under the action of NIS, to provide enaminyl sulfone products. The process is achieved under mild conditions, and shows good functional group tolerance. We also establish that the resultant cyclic enaminyl 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.

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References
1 (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.
2 T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal and S. W. Krksa, Chem. Soc. Rev., 2016, 45, 546–576.
3 (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) A. Mitchell, A. Peschliuli, N. Lefevre, L. Meerpoel and B. U. W. Maes, Chem.–Eur. J., 2012, 18, 10092–10142.
4 (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.
5 (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.
6 (a) N. Simpkins, Sulfones in Organic Synthesis, Pergamon Press, Oxford, 1st edn, 1993; (b) N. S. Simpkins, Tetrahedron, 1990, 46, 6951–6984.
7 (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) T. 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.
8 (a) B. P. Bandgar, S. V. Bettigeri and J. Phopase, Org. Lett., 2006, 8, 2105–2108; (b) S. Cavali, 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. Chiapanichayakul, K. Korvorapan, M. Pohnakot, 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.
9 (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.