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Asymmetric 'Clip-Cycle' synthesis of 3-spiropiperidines†

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3-Spiropiperidines can be synthesized in up to 87% yield and 96 : 4 er using a two step 'Clip-Cycle' approach. The 'Clip' stage of this method is based on efficient and highly *E*-selective cross metathesis of *N*-Cbz-protected 1-amino-hex-5-enes with a thioacrylate. This is followed by the 'Cycle' step, in which an intramolecular asymmetric aza-Michael cyclization is promoted by a chiral phosphoric acid catalyst.

Introduction

Nitrogen-containing heterocycles are privileged structures in medicinal chemistry and present in a high percentage of FDA-approved pharmaceuticals.¹ Of these nitrogen-containing heterocycles, piperidine is the most abundant. Piperidines are common in biologically-active natural products and drugs,² making them a regular target for synthesis.³ Spirocyclic piperidines are also of wide interest, being found in an array of natural product structures, and recognised as desirable motifs in medicinal chemistry (Fig. 1).⁴ This interest is part of a broader drive to explore biologically active molecules with greater 3-dimensionality, as molecules with high '3D character' tend to occupy areas of chemical space that have been less well-explored (traditionally) in drug discovery.^{5,6} The advantages of such spirocyclic systems are that they are conformationally rigid and position hydrogen-bonding donor and acceptor atoms at well-defined positions for interaction with suitable protein receptors.⁵ They also offer the opportunity to develop novel intellectual property, through a richer diversification in chemical structure, beyond simple carbocyclic systems.

Contemporaneous with our work on the synthesis of racemic 2-spiropiperidines,⁷ a review article was published summarising methods for the synthesis of spiro-piperidines and describing their use in pharmaceutical molecules.^{4a} This review highlighted 3-spiropiperidines as being relatively under-represented structures, while 4-spiropiperidines are the most frequently synthesized in medicinal chemistry research programs.^{4a}

Thus, we decided to explore the development of a general strategy for the asymmetric synthesis of 3-spiropiperidines, based on our recently reported asymmetric 'Clip-Cycle' synthesis of pyrrolidines and tetrahydropyrans.⁸ The 'Clip-Cycle' approach had not been used to prepare piperidines prior to this study. We envisaged a synthesis based on "Clipping" a *N*-protected 1-amino-hex-5-ene with a thioacrylate *via* an alkene metathesis reaction, followed by the 'Cycle' step, where the *N*-protected amine undergoes aza-Michael cyclization catalysed by a chiral phosphoric acid (CPA) to yield enantio-enriched piperidines (Scheme 1). Advantages of this 'Clip-Cycle' approach are that both the metathesis and the aza-Michael reactions are catalytic, it enables the straightforward synthesis of a range of functionalized piperidines by changing the aminoalkane reagent, and that the thioester can be transformed into a variety of other functional groups under mild conditions post cyclisation. The successful realisation of this strategy is described herein, demonstrated by the enantioselective synthesis of ten thioester-containing 3-spiropiperidines, formed in yields up to 87%, with enantiomeric ratios up to 97 : 3.

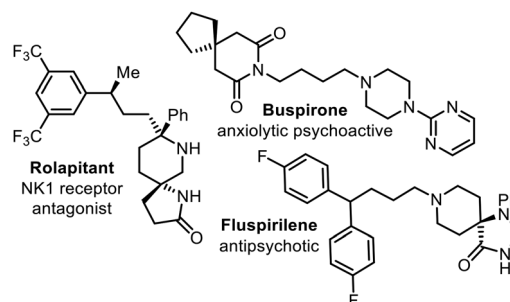


Fig. 1 Marketed spiro-piperidine-containing drugs.

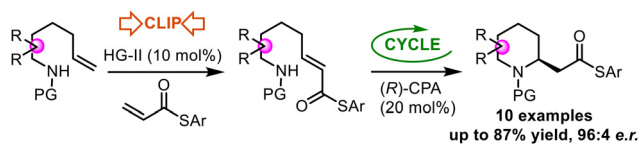
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‡ Deceased.





Scheme 1 Asymmetric 'Clip-Cycle' synthesis of 3-spiropiperidines.

Results and discussion

Initial optimisation studies focused on the *N*-Cbz-2-spirocyclohexylhex-5-ene substrate **1a** as a model for the formation of 3-spirocyclicpiperidines **4a–c** (Table 1). The *p*-tolyl thioester **2a** was chosen as the 'Clip'-partner, as it had been applied successfully in pyrrolidine formation.^{8a,b} For all of the optimisation studies, the 'Clip' product **3a–c** was first prepared using an alkene cross-metathesis protocol, using the Hoveyda-Grubbs Catalyst™ 2nd generation (reaction conditions are described in detail later; *vide infra* Scheme 3). The yields and *er* in Table 1 relate to the 'cycle' step, *i.e.* the conversion of alkenes **3a–c** into piperidines **4a–c**.

The reaction conditions identified as being successful for pyrrolidine synthesis previously^{8a} were examined first (Table 1, entries 1 and 2). It was initially disappointing to discover that

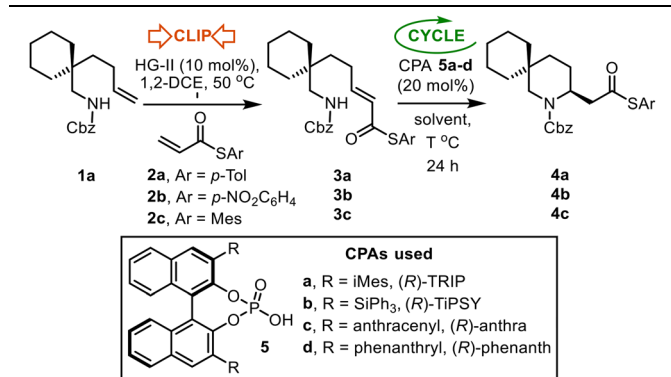
the yield of the piperidine **4a** was low. Under these conditions, the cyclisation step was sluggish, limiting overall product formation due to low conversion. Increasing the temperature to 100 °C did not result in a substantial improvement (entry 3), although it was encouraging that high enantioselectivities were observed at these elevated temperatures. To help drive the cyclisation reaction to completion, the aryl group of the thioester was changed to a *p*-nitrophenyl group (**2b**), with the idea being to increase the electrophilicity of the Michael-accepting motif. However, this structural change made little difference at 80 °C (entry 4). Extending the reaction time to 48 h (entry 5) resulted in an erosion in the enantiomeric ratio of piperidine **4b** and little change in product formation. When the reaction was run in octane at 100 °C, the reaction progressed further, and the yield of **4b** increased to 55% at the expense of the enantioselectivity (entry 6). We reasoned that the reduction in enantioselectivity at higher temperatures could be mitigated by using a bulkier thioester. Mesityl thioester **2c** was therefore investigated, and both the yield and the enantioselectivity increased using this substrate (*cf.* entries 3 and 7). Increasing the temperature further resulted in greater yields and only a slight drop in enantioselectivity (entry 8).

The next factor to be examined was the choice of chiral phosphoric acid (CPA) catalyst. Studies had initially employed only (*R*)-TRIP **5a** as the catalyst. The use of (*R*)-TiPSY **5b**, and (*R*)-phenanth **5d** both resulted in a reduction in enantioselectivity and yields. Although interestingly, the use of **5b** resulted in the opposite enantiomer being formed as the major product (entries 9 and 11). Catalyst (*R*)-anthra **5c**, was the most effective, forming piperidine **4c** in the highest yield so far of 67% and with excellent enantioselectivity 92 : 8 (entry 10). Subjecting the original test substrate **3a** to these reaction conditions with **5c** afforded **4a** in 80% yield and with an enantiomeric ratio of 93 : 7. Finally, the temperature was reduced to 80 °C to see if the conversion/yield and enantioselectivity could be conserved under these milder reaction conditions; this was indeed the case, with **4a** being formed in 78% yield with an enantiomeric ratio of 96 : 4. Note that Table 1 shows selected screening results only; for a more complete summary of the optimisation studies, see ESI Tables S1–S6.†

Next, attention turned to examining the scope of the reaction. To enable this, a series of *N*-Cbz-protected 1-amino-hex-5-ene substrates (**1a,d–k**) was prepared, starting from nitriles **6** using the three-step protocol summarised in Scheme 2. Full synthetic and characterisation details for all steps and products formed are described in the ESI.†

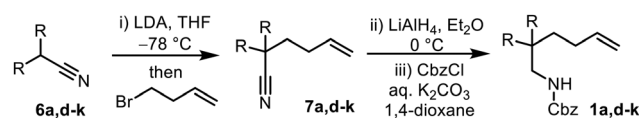
The resulting alkenes (**1a,d–k**) were then reacted with thioacrylate **2** in a cross metathesis reaction with the Hoveyda-

Table 1 Initial studies into the 'Clip-Cycle' formation of 3-spirocyclic piperidines **4a**, **4b** and **4c**



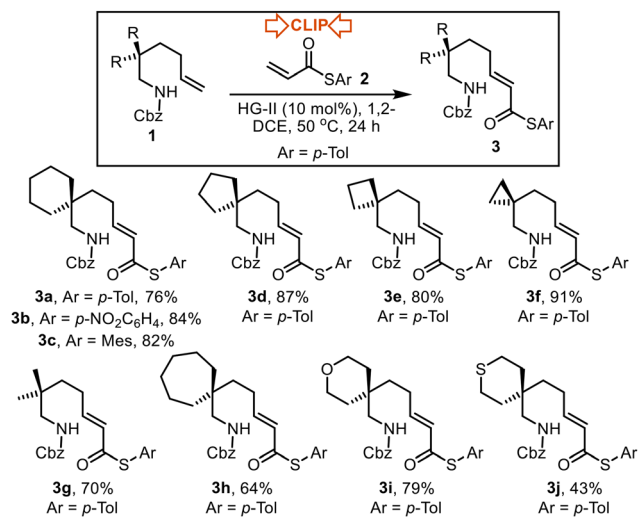
Entry	Substrate	CPA	Solvent/Temp (°C)	Yield (%)	<i>er</i> ^b
1	3a	5a	Cyclohexane/80	10	96 : 4
2 ^a	3a	5a	Cyclohexane/80	21	96 : 4
3	3a	5a	Octane/100	36	94 : 6
4	3b	5a	Cyclohexane/80	20	92 : 8
5 ^a	3b	5a	Cyclohexane/80	21	84 : 16
6	3b	5a	Octane/100	55	89 : 11
7	3c	5a	Octane/100	48	97 : 3
8	3c	5a	Octane/110	63	95 : 5
9	3c	5b	Octane/100	17	38 : 62
10	3c	5c	Octane/100	67	92 : 8
11	3c	5d	Octane/100	21	62 : 38
12	3a	5c	Octane/100	80	93 : 7
13	3a	5c	Cyclohexane/80	78	96 : 4

The reactions were run for 24 h with 20 mol% of the specified CPA catalyst in the specified solvent (0.02 M) unless stated. ^a Run for 48 h. ^b Determined by chiral stationary phase HPLC (see ESI† for details).



Scheme 2 Synthesis of *N*-Cbz-protected 1-amino-hex-5-ene starting materials.





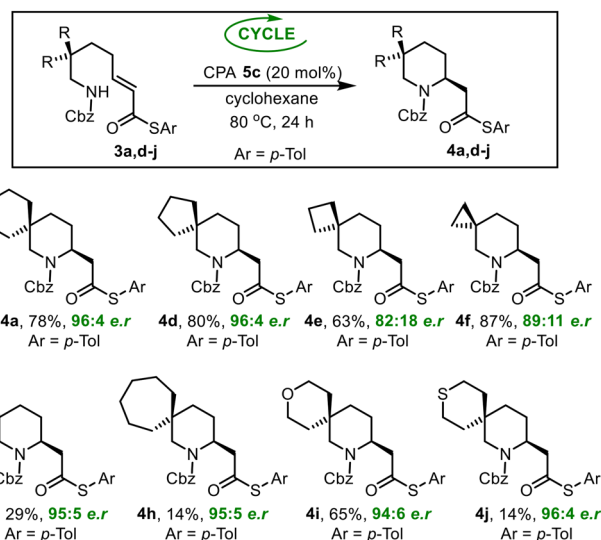
Scheme 3 'Clipping' 1-amino-hex-5-enes **1** with thioacrylates **2** using cross metathesis.

Grubbs Catalyst™ 2nd generation, in the 'Clip' phase of the overall 'Clip-Cycle'. Based on the optimisation results (Table 1) the *p*-toluene substituted thioester **2a** was chosen to take forward into the substrate scoping studies; products **3b** and **3c**, used in the earlier optimisation study, are also shown for completeness. The expected products **3a-j** were formed in 43–91% yields, as a single *E*-isomer in all cases (Scheme 3).

Attention then turned to the 'Cycle' phase, using the optimised conditions for cyclisation (Table 1, entry 13). Substrates containing a carbocyclic spirocycle all worked well; homologues **4a-d** were each formed in good yield and *er* using the standard protocol (Scheme 4). To test whether the carbocycle provides a benefit to cyclisation, a dimethylated substrate **3g** was also tested for comparison. In this case the isolated yield was much lower (29%), although notably the *er* (95:5) remained high. Larger carbocyclic product **4h** and thioether spirocycle **4j** were each formed in lower yield also, again with the *er* high. Cyclic ether containing spirocycle **4i** was formed in much better yield, with the *er* also high. In the three lower yielding examples (**4g,h,j**) the majority of the mass balance was accounted for by unreacted starting material. As the *er* was high in all three cases, we expect that further optimisation would allow these products to be isolated in higher yield, by optimising the conditions to increase the reaction conversion (*e.g.* using conditions similar to those in Table 1, entry 12).§

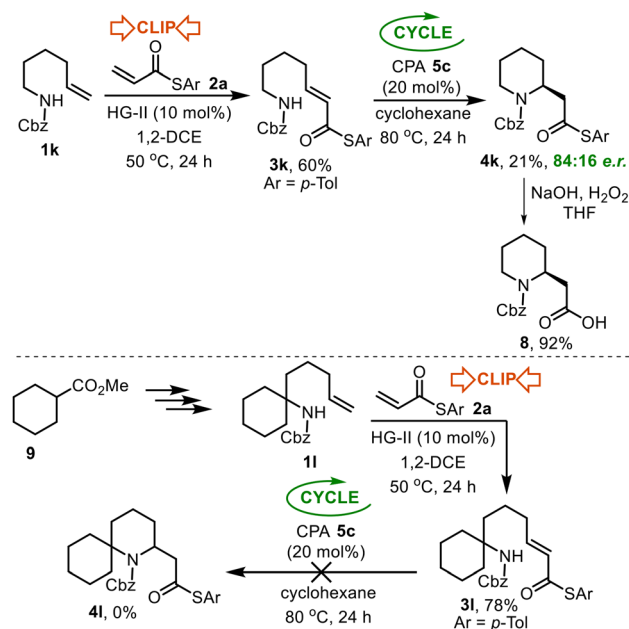
To assign the absolute stereochemistry of the products formed, the 'Clip-Cycle' approach was used to prepare piperidine **4k** without a spirocyclic moiety. The yield was low in this

§ Unfortunately, the development of the 'Clip-Cycle' approach will not continue in York as Prof Paul A. Clarke passed away in November 2023. This manuscript is therefore presented for the scientific record, and to disclose value of this new piperidine forming method. Other researchers interested in continuing to study 'Clip-Cycle' reactivity based on the results described herein are strongly encouraged.



Scheme 4 Asymmetric cyclisation of alkenes **3** to form enantio-enriched piperidines **4**. Enantiomeric ratios were determined by chiral stationary phase HPLC (see ESI† for details).

case, but the *er* was found to be in line with the spirocyclic derivatives; attempts to improve the outcome of this reaction using other CPA catalysts were unsuccessful (see ESI, Table S6†). Hydrolysis to carboxylic acid **8** enabled assignment of the *S*-stereochemistry shown, by measuring its optical rotation and comparing to literature data for the known *R*-enantiomer.⁹ This allowed for the assignment of the absolute stereochemistry of all other substrates described in this manuscript, by analogy (Scheme 5). The major enantiomer



Scheme 5 'Clip-Cycle' synthesis of **4k** and hydrolysis to **8** to confirm the absolute stereochemistry and the unsuccessful attempted synthesis of 2-spiropiperidine **4l**.



formed was the same as that produced in the preceding pyrrolidine- and tetrahydropyran-forming variants of the method, and hence the enantioselectivity can be explained using the models previously established.^{8a,c}

We also attempted the synthesis of 2-spiropiperidine **4l** using the 'Clip-Cycle' approach. In this case, the 'Clip' step proceeded as expected, with alkenes **1l** and **2a** undergoing efficient cross metathesis to form **3l** in good yield. However, **3l** did not react under the optimised cyclisation conditions, likely due to the increase in steric bulk adjacent to the protected amine inhibiting the aza-Michael step; unreacted **3l** was recovered.

Conclusion

In summary, the efficacy of the 'Clip-Cycle' approach for 3-spiropiperidine synthesis has been validated, with ten 3-spiropiperidine products generated in yields up to 87% yield. The 'Clip' step proceeds smoothly, with the Hoveyda-Grubbs Catalyst™ 2nd generation used to promote cross metathesis of *N*-Cbz-protected 1-amino-hex-5-enes with thioacrylates. The 'Cycle' step is best promoted by a chiral phosphoric acid catalyst (*R*)-anthra **5c**, to afford the 3-spiropiperidine products in up to 97:3 er. The synthesis of a non-spirocyclic piperidine was also completed, to enable the assignment of absolute stereochemistry.

This study represents the first report of the 'Clip-Cycle' method being used to prepare piperidines. Having validated its efficacy for 3-spiropiperidine synthesis, we anticipate that similar 'Clip-Cycle' strategies will also allow the preparation of a much wider range of functionalised, biologically important piperidines. §

Author contributions

Synthetic studies were done by S.R and C.J.M. The project was conceived, designed and led by P.A.C. The paper was written by W.P.U. and I.J.S.F., with contributions from S.R.

Data availability

The data supporting this article have been included as part of the Supplementary Information ESI. †

Conflicts of interest

There are no conflicts to declare.

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References

- 1 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.
- 2 (a) M. Prashad, H.-Y. Kim, Y. Lu, D. Har, O. Repic, T. J. Blacklock and P. Giannousis, *J. Org. Chem.*, 1999, **64**, 1750–1753; (b) N. Shankaraiah, R. A. Pilli and L. S. Santos, *Tetrahedron Lett.*, 2008, **49**, 5098–5100; (c) M. Baumann and I. R. Baxendale, *Beilstein J. Org. Chem.*, 2013, **9**, 2265–2319; (d) X.-N. Cao, X.-M. Wan, F.-L. Yang, K. Li, X.-Q. Hao, T. Shao, X. Zhu and M.-P. Song, *J. Org. Chem.*, 2018, **83**, 3657–3668; (e) S. P. Chavan, D. B. Kalbhor and R. G. Gonnade, *Tetrahedron*, 2021, **80**, 131773; (f) J. C. Anderson, E. Bouvier-Israel, C. D. Rundell and X. Zhang, *Tetrahedron*, 2021, **78**, 131821.
- 3 (a) P. S. Watson, B. Jiang and B. Scott, *Org. Lett.*, 2000, **2**, 3679–3681; (b) L. Zhou, D. W. Tay, J. Chen, G. Y. C. Leung and Y.-Y. Yeung, *Chem. Commun.*, 2013, **49**, 4412–4414; (c) P. A. Clarke, A. V. Zaytsev and A. C. Whitwood, *Tetrahedron Lett.*, 2007, **48**, 5209–5212; (d) P. A. Clarke, A. V. Zaytsev, T. W. Morgan, A. C. Whitwood and C. Wilson, *Org. Lett.*, 2008, **10**, 2877–2880; (e) M. A. Larsen, E. T. Hennessy, M. C. Deem, Y. H. Lam, J. Sauri and A. C. Sather, *J. Am. Chem. Soc.*, 2020, **142**, 726–732; (f) J. Garcia, J. Eichwald, J. Zesiger and T. K. Beng, *RSC Adv.*, 2022, **12**, 309–318; (g) S. Fustero, S. Monteagudo, M. Sánchez-Roselló, S. Flores, P. Barrio and C. del Pozo, *Chem. – Eur. J.*, 2010, **16**, 9835–9845; (h) R. R. Mittapalli, S. J. J. Guesné, R. J. Parker, W. T. Klooster, S. J. Coles, J. Skidmore and A. P. Dobbs, *Org. Lett.*, 2019, **21**, 350–355; (i) H. Liu, D. Su, G. Cheng, J. Xu, X. Wang and Y. Hu, *Org. Biomol. Chem.*, 2010, **8**, 1899–1904; (j) S. G. Davies, A. M. Fletcher, J. A. Lee, P. M. Roberts, A. J. Russell, R. J. Taylor, A. D. Thomson and J. E. Thomson, *Org. Lett.*, 2012, **14**, 1672–1675; (k) H. Kawabata, T. Hirama, T. Yanagisawa, K. Sato, N. Kogure, M. Kitajima and H. Takayama, *Org. Lett.*, 2019, **21**, 7982–7986; (l) E. C. Carlson, L. K. Rathbone, H. Yang, N. D. Collett and R. G. Carter, *J. Org. Chem.*, 2008, **73**, 5155–5158.
- 4 (a) S. D. Griggs, N. Thompson, D. T. Tape and P. A. Clarke, *Org. Biomol. Chem.*, 2018, **16**, 6620; (b) T. M. McQueen and S. D. Griggs, *Tetrahedron Lett.*, 2021, **65**, 152752; (c) L. Zhou, F. Yuan, Y. Zhou, W. Duan, M. Zhang, H. Deng and L. Song, *Tetrahedron*, 2018, **74**, 3761–3769; (d) A. A. Peshkov, A. A. Peshkov, A. Makhmet, O. Bakulina, E. Kanov, R. Gainetdinov, V. A. Peshkov, M. Krasavin and L. N. Gumilyov, *Synthesis*, 2022, **54**, 2604–2615; (e) A. A. Peshkov, O. Bakulina, D. Dar'in, G. Kantin, A. Bannykh, V. A. Peshkov and M. Krasavin, *Eur. J. Org.*



- Chem.*, 2021, 1726–1731; (f) L. A. Martinez-Alsina, J. C. Murray, L. M. Buzon, M. W. Bundesmann, J. M. Young and B. T. O'Neill, *J. Org. Chem.*, 2017, **82**, 12246–12256; (g) M.-C. Yang, C. Peng, H. Huang, L. Yang, X.-H. He, W. Huang, H.-L. Cui, G. He and B. Han, *Org. Lett.*, 2017, **19**, 6752–6755; (h) H. E. Askey, J. D. Grayson, J. D. Tibbetts, J. C. Turner-Dore, J. M. Holmes, G. Kociok-Kohn, G. L. Wrigley and A. J. Cresswell, *J. Am. Chem. Soc.*, 2021, **143**, 15936–15945.
- 5 For perspective on the exploration of 3D space in medicinal chemistry, see:(a) E. M. Carreira and T. C. Fessard, *Chem. Rev.*, 2014, **114**, 8257; (b) A. W. Hung, A. Ramek, Y. Wang, T. Kaya, J. A. Wilson, P. A. Clemons and D. W. Young, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 6799; (c) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257; (d) W.-Y. Siau and J. W. Bode, *J. Am. Chem. Soc.*, 2014, **136**, 17726; (e) K. B. Sippy, D. J. Anderson, W. H. Bunnelle, C. W. Hutchins and M. R. Schrimpf, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 1682.
- 6 For the synthesis and properties of bioactive spirocycles, see:(a) K. Heisinger, D. Dar'in, E. Proschak and M. Krasavin, *J. Med. Chem.*, 2021, **64**, 150–183; (b) S. J. Chambers, G. Coulthard, W. P. Unsworth, P. O'Brien and R. J. K. Taylor, *Chem. – Eur. J.*, 2016, **22**, 6496; (c) A. Ding, M. Meazza, H. Guo, J. W. Yang and R. Rios, *Chem. Soc. Rev.*, 2018, **47**, 5946–5996.
- 7 S. D. Griggs, N. Thompson, D. T. Tape, M. Fabre and P. A. Clarke, *Org. Biomol. Chem.*, 2018, **16**, 6663–6674.
- 8 (a) C. J. Maddocks, K. Ermanis and P. A. Clarke, *Org. Lett.*, 2020, **22**, 8116–8121; (b) C. J. Maddocks and P. A. Clarke, *Tetrahedron*, 2021, **78**, 131789; (c) K. Alomari, N. S. P. Chakravarthy, B. Duchadeau, K. Ermanis and P. A. Clarke, *Org. Biomol. Chem.*, 2022, **20**, 1181–1185.
- 9 E. C. Carlson, L. K. Rathbone, H. Yang, N. D. Collett and R. G. Carter, *J. Org. Chem.*, 2008, **73**, 5155–5158.

