Article:
Choi, A., Das, A., Meijer, A.J.H.M. orcid.org/0000-0003-4803-3488 et al. (2 more authors) (2024) Synthesis of enantioenriched spirocyclic 2-arylpiperidines via kinetic resolution. Organic & Biomolecular Chemistry, 22 (8). pp. 1602-1607. ISSN 1477-0520

https://doi.org/10.1039/d4ob00011k

Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/d4ob00011k

Received 3rd January 2024,
Accepted 23rd January 2024

DOI: 10.1039/d4ob00011k

rsc.li/obc

Synthesis of enantioenriched spirocyclic 2-arylpiperidines *via* kinetic resolution†

Anthony Choi,[a] Anjan Das,‡[a] Anthony J. H. M. Meijer,[a] Ilaria Proietti Silvestri[b] and Iain Coldham *[a]

Kinetic resolution of *N*-Boc-spirocyclic 2-arylpiperidines with spiro substitution at C-4 was achieved with high enantiomeric ratios using the chiral base *n*-BuLi/sparteine. Cyclopropanation or metallaphotoredox catalysis were used to access the piperidines, which could be further functionalised without loss of enantiopurity, highlighting their use as potential 3D fragments for drug discovery.

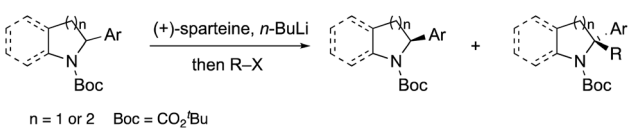
Introduction

Over many years, exploring 3D space within organic chemistry has been a fertile research area towards the development of new drugs and active pharmaceutial ingredients (APIs).[1–3] By introducing more 3D character into a molecule, it has been shown to improve the overall physical and chemical properties of a compound, making it more likely to be successful in drug discovery programs. Although there are many ways to introduce more 3D character into a structural motif, one of the simplest methods is by the replacement of sp^2 carbon centres with sp^3 carbon centres. In turn, this has led to an array of studies towards the synthesis of saturated ring systems such as pyrrolidines and piperidines. Furthermore, the addition of small, rigid ring systems, for example cyclopropane and cyclobutane rings, can provide beneficial properties, access new chemical space, and increase the novelty of a structure.

With the addition of more sp^3 carbon atoms into a molecule an important factor to consider is the ability to control the stereochemistry of these centres, in particular if the molecule of interest is to be biologically active. Overall, this has guided previous work we have reported that has involved controlling the stereochemistry of an alpha-carbon atom within a nitrogen-containing heterocycle, using the chiral base generated from *n*-BuLi and sparteine. By utilising this chiral base system, asymmetric deprotonation occurs at the alpha-carbon atom generating an organolithium intermediate. This intermediate can be trapped using an appropriate electrophile, generating a new stereocentre.[4] We have managed to successfully apply this chemistry in the form of kinetic resolution reactions on a variety of substrates including piperidines, tetrahydroquinolines, and indolines, obtaining excellent yields and enantioselectivities (Scheme 1).[5–10]

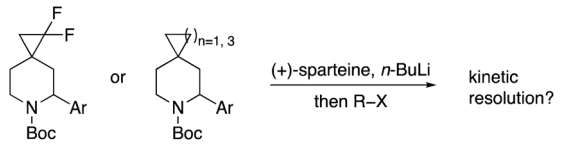
Recently our work has focused around developing molecular scaffolds by introducing a methylene functional group in the 4-position of a 2-arylpiperidine.[9] This work was highly successful, generating a range of enantioenriched compounds in good yields. In particular, the addition of the methylene synthetic handle was useful towards introducing new functional groups and structural motifs onto the piperidine core. For example, when exploring the scope for further functionalisation of the piperidines we were able to convert the methylene group into a carbonyl and hence, using DAST, a difluoro motif.

Over recent years fluorinated compounds have been of significant interest in medicinal chemistry. The combination of a conformationally locked cyclopropyl or difluorocyclopropyl unit could provide structures of interest as molecular building blocks due to their enhanced 3D character,[11] although few methods exist towards incorporating spirodifluorocyclopropanes into chiral, sp^3 rich structures.[12–14] We envisaged that, by carrying out kinetic resolution reactions on spirocyclic piperidines, we could apply asymmetric organolithium chemistry to more complex systems beyond simple nitrogen-contain-



Scheme 1 Generic kinetic resolution of *N*-boc-2-aryl cyclic amines.

[a]*Department of Chemistry, University of Sheffield, Sheffield S3 7HF, UK. E-mail: i.coldham@sheffield.ac.uk*
[b]*Liverpool ChiroChem, Heath Business & Technical Park, Runcorn WA7 4QX, UK*
†Electronic supplementary information (ESI) available. CCDC 2312678 and 2312679. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4ob00011k
‡New address: Department of Chemistry, SRM Institute of Science & Technology, Kattankulathur, Tamil Nadu 603203, India.



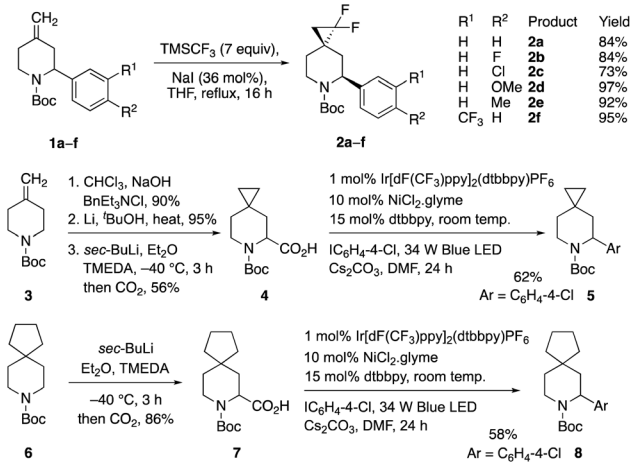
Scheme 2 Examples for kinetic resolution in this work.

ing heterocycles. We report here the synthesis of enantio-enriched spirocyclic 2-arylpiperidines *via* kinetic resolution using the chiral base generated from *n*-BuLi and (+)-sparteine (Scheme 2).

Results and discussion

We needed a robust and simple synthetic route to access a selection of spirocyclic compounds. Taking inspiration from literature methods,[15] the previously synthesised 4-methylene-2-aryl piperidines **1a–f**[9] were reacted with $TMSCF_3$ in the presence of sodium iodide to give the spirocyclic piperidines **2a–f** in good yields (Scheme 3). The addition of $TMSCF_3$ in excess was found to be beneficial to obtain the best yields of the desired spirocyclic piperidines. The reaction tolerated a selection of functional groups on the aryl ring including electron-donating and withdrawing moieties. In all cases the 2,4-*trans* configuration was isolated as the only diastereoisomer, which was confirmed by X-ray crystallography on piperidine **2d** (Fig. 1). The X-ray analysis also confirmed the expected axial orientation of the aryl group and hence equatorial orientation of the benzylic proton that needs to be removed in the kinetic resolution chemistry.

To prepare the corresponding unfluorinated cyclopropane, we initially attempted direct cyclopropanation with diiodomethane and Zn/Cu couple or Et_2Zn, but these were unsuccessful. Instead, we opted to carry out dichlorocyclopropanation with chloroform and sodium hydroxide on the parent piperidine **3** followed by reduction with lithium metal in *tert*-



Scheme 3 Synthesis of spirocyclic piperidines.

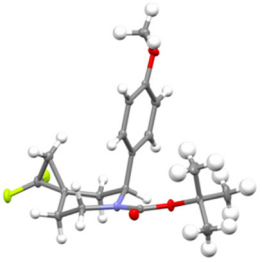


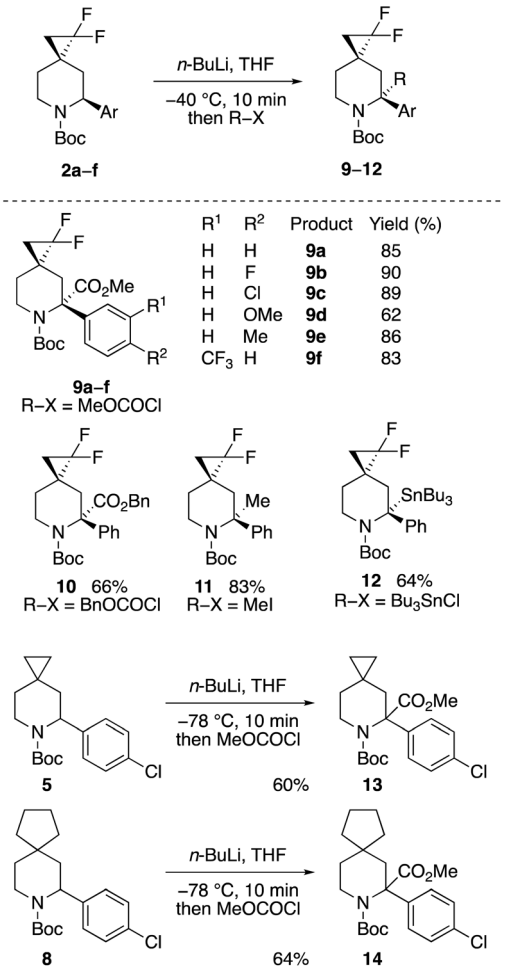
Fig. 1 Single crystal X-ray structure of (±)-**2d**.

BuOH. Subsequent proton abstraction and carboxylation gave the acid **4** that was subjected to metallaphotoredox catalysis[16,17] with coupling to 1-chloro-4-iodobenzene to give the piperidine **5**. This chemistry provides an alternative approach to the preparation of such 2-aryl substituted compounds. In the same way, the piperidine **6** was subjected to proton abstraction and carboxylation to give the acid **7**, followed by photocatalysis with coupling to 1-chloro-4-iodobenzene to give the piperidine **8** (other aryl derivatives should also be accessible[16]).

Racemic lithiation–trapping studies were carried out on the spirocyclic piperidines. By using reaction conditions based on previous work,[9] piperidine **2a** was treated with *n*-BuLi at −40 °C in THF. After 10 minutes the organolithium intermediate could be trapped with MeOCOCl to give the quenched product **9a** in 85% yield. This compound was formed as a single diastereomer which was assumed to be a result of retention based on the known reactions of chiral 2-lithiopiperidines.[18]

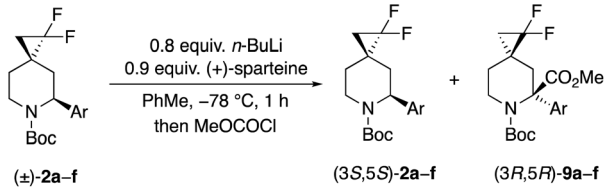
By applying the same conditions to the remaining substrates, the corresponding methyl ester derivatives **9b–f** could be isolated. From the results, it seems that electron-withdrawing groups on the 2-aryl substituent such as 4-fluoro and 4-chloro gave the best yields of the ester products (**9b** and **9c**). In comparison, a slightly lower yield (62%) for ester **9d** was obtained with the electron-donating 4-methoxy group. The lithiation tolerated a 4-methyl and 3-trifluoromethyl group to give compounds **9e** and **9f** with good yields. In addition, the electrophile scope was expanded to include benzyl chloroformate, iodomethane, and tributyltin chloride to give products **10–12** respectively. The substrate scope could be expanded to include piperidines **5** and **8**, allowing the synthesis of spirocyclic piperidines **13** and **14** (Scheme 4).

Having established that the spirocyclic piperidines were able to undergo successful lithiation–trapping, the kinetic resolution of these compounds was investigated using the chiral base system of *n*-BuLi/(+)-sparteine. Initial reaction conditions considered for the kinetic resolution of piperidine **2a** used 0.8 eq. of *n*-BuLi and 0.9 eq. (+)-sparteine at −78 °C for 1 h followed by addition of MeOCOCl. After purification by column chromatography, the piperidine (3*S*,5*S*)-**2a** was isolated in 41% yield with a high enantiomer ratio (er) of 97 : 3. The corresponding methyl ester (3*R*,5*R*)-**9a** was isolated with a yield of 49% and er 86 : 14 (Scheme 5 and Table 1). Repeating the



Scheme 4 Racemic lithiation–trapping studies.

same conditions on the 4-fluoro derivative **2b** gave similar results: 41% yield for the recovered piperidine (3*S*,5*S*)-**2b**, accompanied by an excellent er (99 : 1). When applying the same reaction conditions to the 4-chloro derivative **2c** we encountered problems with stirring the reaction mixture. To overcome this, the reaction was carried out at a higher dilution (0.13 M) with an additional 0.2 eq. of *n*-BuLi and (+)-sparteine. After quenching the reaction, the recovered starting material (3*S*,5*S*)-**2c** was isolated in a good yield of 41% with an er of 94 : 6. These reaction conditions were applied to the remaining substrates, except for the *p*-MeO derivative **2d**, which was more sluggish to lithiate. After adding 1.5 eq. of *n*-BuLi and 1.6 eq. of (+)-sparteine to spirocyclic piperidine **2d** at −78 °C, and quenching the reaction with MeOCOCl, the piperidine (3*S*,5*S*)-**2d** was obtained in low yield (19%) but with a satisfactory er of 90 : 10. Kinetic resolution of piperidine **2e** occurred smoothly to give the recovered starting material (3*S*,5*S*)-**2e** in a good yield of 43% with 92 : 8 er. Applying these same conditions to the 3-trifluoromethyl derivative **2f** resulted in a lower yield (34%) of the piperidine (3*S*,5*S*)-**2f** with a slightly lower er (88 : 12) (Table 1). In each case, none of the diastereoisomer of



Scheme 5 Kinetic resolution studies with piperidines **2** (see Table 1).

Table 1 Results of kinetic resolution with piperidines **2**

Starting material	Recovered **2**	Product **9**
2a[a]	(3*S*,5*S*)-**2a** 41% er 97:3	(3*R*,5*R*)-**9a** 49% er 86:14
2b[a]	(3*S*,5*S*)-**2b** 41% er 99:1	(3*R*,5*R*)-**9b** 57% er 76:24
2c[b]	(3*S*,5*S*)-**2c** 41% er 94:6	(3*R*,5*R*)-**9c** 54% er 79:21
2d[c]	(3*S*,5*S*)-**2d** 19% er 90:10	(3*R*,5*R*)-**9d** 72% er 62:38
2e[b]	(3*S*,5*S*)-**2e** 43% er 92:8	(3*R*,5*R*)-**9e** 47% er 84:16
2f[b]	(3*S*,5*S*)-**2f** 34% er 88:12	(3*R*,5*R*)-**9f** 59% er 72:28

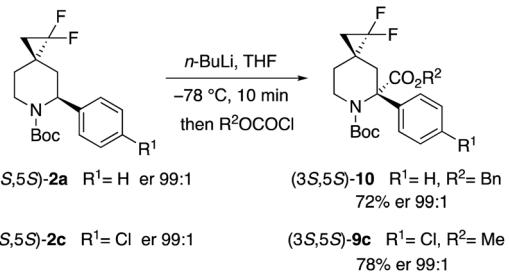
[a] Reaction molarity 0.25 M. [b] Reaction molarity 0.13 M using 1.0 *n*-BuLi and 1.1 (+)-sparteine. [c] Reaction molarity 0.13 M using 1.5 *n*-BuLi and 1.6 (+)-sparteine.

the 5,5-disubstituted products **9a–f** was detected by HPLC or NMR spectroscopy, indicating configurational stability of the intermediate organolithium. The lower er for these products fits with almost complete lithiation of the 3*R*,5*R* enantiomer of **2a–f** and only partial lithiation of the 3*S*,5*S* enantiomer.

The kinetic resolution chemistry was extended to the other spirocyclic derivatives **5** and **8** (Scheme 6). Both substrates were successful with only 0.6 equivalents of *n*-BuLi and 0.8 equivalents of (+)-sparteine. The enantioenriched piperidines (*S*)-**5** and (*S*)-**8** were recovered together with the quenched products (*R*)-**13** and (*R*)-**14** with high selectivities.

To probe the scalability of the reaction, the kinetic resolution was performed using 2 g of piperidine **2a** (Scheme 7). Although a lower yield of 33% was obtained for (3*S*,5*S*)-**2a** this was accompanied with an excellent er of 99 : 1 and importantly, the (+)-sparteine ligand could be recovered through acid-base extraction of the crude product. The (+)-sparteine was isolated in 85% recovery after purification, which was then used in another large-scale kinetic resolution reaction with piperidine **2c** (1 g). Applying the same reaction conditions gave a similar result where a low yield of 25% was obtained for (3*S*,5*S*)-**2c** with a very high er of 99 : 1. The yields of these reactions could potentially be improved with further optimisation (to reduce the amount of **9** and increase the amount of **2**). Overall, this demonstrated that (+)-sparteine could be recycled and reused successfully without any detrimental loss in enantioselectivity of the recovered starting materials.

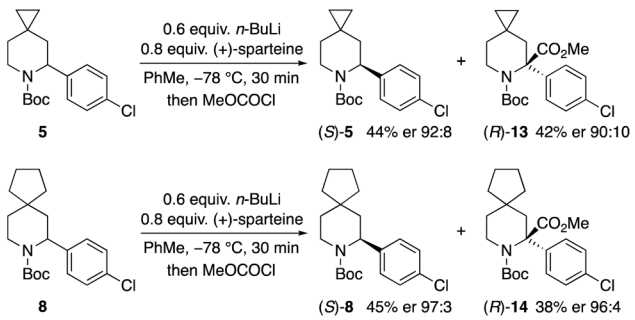
To demonstrate the potential use of the enantioenriched compounds, further transformations were carried out on (3*S*,5*S*)-**2a** (er 99 : 1) and (*S*)-**2c** (er 99 : 1). Lithiation of (3*S*,5*S*)-**2a** and (3*S*,5*S*)-**2c** at −78 °C, followed by the addition of BnOCOCl or MeOCOCl gave enantioenriched esters (3*S*,5*S*)-**10** and (3*S*,5*S*)-**9c** in good yields. Furthermore, the high er of 99 : 1 was retained from both starting materials (Scheme 8).



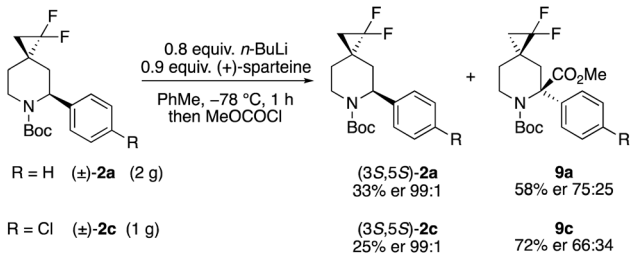
Scheme 8 Lithiation–trapping of enantioenriched **2a** and **2c**.

With ester (3*S*,5*S*)-**10** the addition of HCl in dioxane successfully gave the boc-deprotected compound (3*S*,5*S*)-**15** as the hydrochloride salt. In contrast, when ester (3*S*,5*S*)-**10** was subjected to hydrogenolysis conditions carboxylic acid (3*S*,5*S*)-**16** was isolated instead. Overall, this demonstrates that an orthogonal deprotection strategy could be successfully applied to compounds such as (3*S*,5*S*)-**10** to provide synthetic handles and allow for further potential functionalisation (Scheme 9).

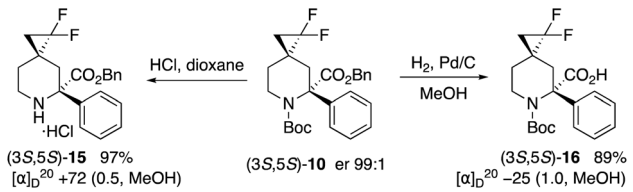
The stereochemistry of (3*S*,5*S*)-**9c** was confirmed by single crystal X-ray analysis (Fig. 2). The high Flack parameter of 0.023 was consistent with a single mirror image of this compound. Unlike the 5-monosubstituted piperidine **2d** (Fig. 1), the structure of the piperidine core was not in a chair conformation but in a boat shape. To investigate this further, density functional theory (DFT) calculations were performed to deter-



Scheme 6 Kinetic resolution studies with piperidines **5** and **8**.



Scheme 7 Scale-up of the kinetic resolution.



Scheme 9 Deprotection of enantioenriched ester **10**.

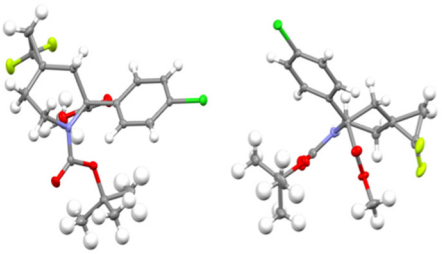


Fig. 2 Two representations of the single crystal X-ray structure of (3S,5S)-**9c**.

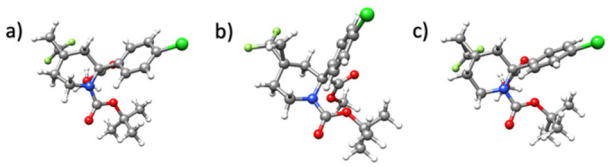


Fig. 3 Optimised geometries of (3S,5S)-**9c** in THF solution.

mine the relative energies between the different conformations of (3*S*,5*S*)-**9c**.

Using the B3LYP-D3BJ functional with the def2-TZVP basis set (B3LYP-D3BJ//def2-TZVP)[19–21] as implemented in Gaussian09,[22] optimisation of the structure of (3*S*,5*S*)-**9c** gave the boat conformation shown in Fig. 3a. Subsequent optimisation of the two chair conformations of (3*S*,5*S*)-**9c**, where the *p*-chlorophenyl group could adopt an axial or equatorial position gave the structures shown in Fig. 3b and c respectively. The lower energy of the two chair conformations was where the *p*-chlorophenyl group was in the axial position ($\Delta G \approx 2.5$ kJ mol^{-1} at 298 K) which agreed with previous work.[23] A closer inspection of this axial chair conformation indicated an unfavourable interaction between the CH_2 of the cyclopropane ring and the *p*-chlorophenyl group. However, within the equatorial chair conformation another potential unfavourable interaction between the CF_2 of the cyclopropane ring and the methyl ester group was possible. Consequently, the axial and equatorial chair conformations were higher in energy than the optimised boat conformation of (3*S*,5*S*)-**9c** by 1.2 kJ mol^{-1} and 3.7 kJ mol^{-1}, respectively. Therefore, (3*S*,5*S*)-**9c** adopting a boat conformation appeared to minimise unfavourable interactions between the cyclopropane ring and the substituents attached to the α-carbon position of the piperidine core, making it the preferred conformation, agreeing with the X-ray crystallography results.

Conclusions

In summary, we have demonstrated by using the base *n*-BuLi and the chiral ligand (+)-sparteine that kinetic resolution by deprotonation of 2-arylpiperidines can be successfully extended to include spirocyclic systems, including those with a gem-difluoro motif. Excellent yields and high enantiomer ratios can be obtained even when reactions are performed on multigram scales. This allows the preparation of highly enantioenriched piperidines with multiple points of substitution. The tetrasubstituted piperidines were found to prefer a boat conformation and this was confirmed by X-ray analysis and DFT studies. Further reactions on the enantioenriched compounds can be performed without any loss in enantiopurity to access substituted spirocyclic piperidines, which have the potential to be used as molecular building blocks in academia and industry.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

We acknowledge support for this research from the EPSRC (Grant No. EP/R024294/1), the Royal Society (Short Industry Fellowship SIF\R2\202031), the Royal Society–SERB (Newton International Fellowship NIF\R1\191853), and the University of Sheffield. We thank Craig Robertson for the single-crystal X-ray analyses and Benjamin Partridge for access to chiral HPLC equipment. We acknowledge the Faculty of Science mass spectrometry service at the University of Sheffield. For the purpose of open access, the author has applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript version arising.

References

1 I. Proietti Silvestri and P. J. J. Colbon, *ACS Med. Chem. Lett.*, 2021, **12**, 1220.
2 H. F. Klein, D. J. Hamilton, I. J. P. de Esch, M. Wijtmans and P. O'Brien, *Drug Discovery Today*, 2022, **27**, 2484.
3 D. J. Hamilton, T. Dekker, H. F. Klein, G. v Janssen, M. Wijtmans, P. O'Brien and I. J. P. de Esch, *Drug Discovery Today: Technol.*, 2020, **38**, 77.
4 K. Kasten, N. Seling and P. O'Brien, *Org. React.*, 2019, **100**, 255.
5 E. J. Cochrane, D. Leonori, L. A. Hassall and I. Coldham, *Chem. Commun.*, 2014, **50**, 9910.
6 N. Carter, X. Li, L. Reavey, A. J. H. M. Meijer and I. Coldham, *Chem. Sci.*, 2018, **9**, 1352.
7 A. Choi, A. El-Tunsi, Y. Wang, A. J. H. M. Meijer, J. Li, X. Li, I. Proietti Silvestri and I. Coldham, *Chem. – Eur. J.*, 2021, **27**, 11670.
8 A. El-Tunsi, N. Carter, S.-H. Yeo, J. D. Priest, A. Choi, C. M. Kobras, S. Ndlovu, I. Proietti Silvestri, A. K. Fenton and I. Coldham, *Synthesis*, 2022, **54**, 355.
9 A. Choi, A. J. H. M. Meijer, I. Proietti Silvestri and I. Coldham, *J. Org. Chem.*, 2022, **87**, 8819.
10 S.-H. Yeo, A. Choi, S. Greaves, A. J. H. M. Meijer, I. Proietti Silvestri and I. Coldham, *Chem. – Eur. J.*, 2023, **29**, e202300815.
11 K. Hiesinger, D. Dar'in, E. Proschak and M. Krasavin, *J. Med. Chem.*, 2021, **64**, 150.
12 P. S. Nosik, A. O. Gerasov, R. O. Boiko, E. Rusanov, S. v Ryabukhin, O. O. Grygorenko and D. M. Volochnyuk, *Adv. Synth. Catal.*, 2017, **359**, 3126.
13 R. M. Bychek, V. v Levterov, I. v Sadkova, A. A. Tolmachev and P. K. Mykhailiuk, *Chem. – Eur. J.*, 2018, **24**, 12291.
14 A. Gerasov, G. A. Dolgonos, A. Y. Mandzhulo, A. Ryabitsky, V. Fetyukhin, O. Lukin and A. Shivanyuk, *Synthesis*, 2020, **52**, 1015.
15 O. v Hryshchuk, A. O. Varenyk, Y. Yurov, Y. O. Kuchkovska, A. v Tymtsunik and O. O. Grygorenko, *Eur. J. Org. Chem.*, 2020, 2217.
16 A. Das, A. Choi and I. Coldham, *Org. Lett.*, 2023, **25**, 987.

17 Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle and D. W. C. MacMillan, *Science*, 2014, **345**, 437.
18 D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham and A. Sanderson, *J. Am. Chem. Soc.*, 2010, **132**, 7260.
19 F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, 2005, **7**, 3297.
20 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.
21 S. Grimme, S. Ehrlich and L. Goerigk, *J. Comput. Chem.*, 2011, **32**, 1456.
22 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09, Revision E.01*, Gaussian, Inc., Wallingford CT, 2009.
23 N. S. Sheikh, D. Leonori, G. Barker, J. D. Firth, K. R. Campos, A. J. H. M. Meijer, P. O'Brien and I. Coldham, *J. Am. Chem. Soc.*, 2012, **134**, 5300.