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C(sp³)-H arylation to construct all-*syn* cyclobutane-based heterobicyclic systems: a novel fragment collection†

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All-*syn* fused cyclobutanes remain an elusive chemotype and thus present an interesting synthetic challenge. Herein, we report the successful application of Pd-catalysed C(sp³)-H arylation of cyclobutane compounds to generate all-*syn* heterobicyclic fragments using an innovative ‘inside-out’ approach. Through this strategy we generate a virtual collection of 90 fragments, which we demonstrate to have enhanced three-dimensionality and superior fragment-like properties compared to existing collections.

Fragment-based drug discovery (FBDD) has emerged as a powerful approach to generate new medicines, as demonstrated by the recent clinical approvals of vemurafenib, venetoclax and ribociclib, along with many candidates currently under clinical evaluation.^{1,2} Despite this promise, progress in FBDD is slowed by problems associated with the overrepresentation of “flat” aromatic compounds and dearth of sp³-rich fragments containing chiral centres in commercial screening libraries.³ Advancement of fragment hits along the pipeline is further hampered by the challenges of synthetically elaborating hit fragments (through growing, linking or merging), often due to the absence of readily available “exit vectors” on fragments of interest, or inability to incorporate new three-dimensional (3D) elements such as stereocentres in a straightforward manner.^{4,5} Thus, the development of novel methodologies to construct saturated and stereochemically enriched fragment scaffolds in new areas of chemical space is of utmost importance to alleviate these hurdles.⁶ In particular, it has been noted that strategic application of direct C-H functionalisation chemistries has the potential to significantly streamline these issues.⁷

Aryl-substituted cyclobutanes and small, fused cyclobutane-heterobicyclic systems constitute prevalent structural entities

within pharmaceuticals and natural products (Fig. 1A).^{8–10} Undeniably, this moiety therefore presents an attractive core ring for a fragment-based library, further evidenced by its small size (four heavy atoms) and potential to act as a constrained heterocycle mimic from a medicinal chemistry perspective.¹¹

Fig. 1 (A) Cyclobutane-containing natural products and pharmaceuticals. (B) Previous work on ‘outside-in’ construction of heterobicyclic systems. (C) Recent application of Pd-catalysed C-H arylation for construction of an all-*syn* azabicyclo[3.2.0]heptane scaffold. (D) This work, ‘inside-out’ approach to several all-*syn* heterobicyclic fragments.

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Consequently, the construction of cyclobutane-containing bicyclic structures has been the subject of longstanding interest. Commonly, the bicycle is built by constructing the cyclobutane ring *via* inter- or intramolecular [2+2] reactions, which we term the 'outside-in' strategy (Fig. 1B). Intramolecular photochemical [2+2] reactions of tethered 1,6-diene substrates have been frequently employed¹² for this purpose. These strategies, however, remain generally limited to the formation of (hetero)bicyclo[3.2.0]heptane scaffolds, proceed with variable levels of efficiency and provide *anti*-diastereoselectivity (anti-relationship between the fused heterocycle and substituents on the cyclobutane) that can be heavily dependent on the specific substrates employed. Intra- and intermolecular cyclobutane syntheses proceeding *via* photoredox-type catalytic cycles have also afforded access to certain fused cyclobutane substitution patterns,¹³ but are often limited in scope and proceed with modest to high *anti*-diastereoselectivity.

Despite this substantial precedent, a general strategy for the construction of all-*syn*, fused cyclobutane–heterobicyclo[*n*.2.0] systems remains elusive. A solution to this problem would represent a significant synthetic advance, particularly in the realm of FBDD, which calls for synthetic solutions to fragment synthesis ideally in numerous 3D arrangements.

The directed, Pd-catalysed C–H arylation reaction first reported by Daugulis in 2005¹⁴ has now been established as a reliable approach for the stereocontrolled construction of 1,2-*syn* vicinal stereocentres. This methodology has been extensively utilised for the stereocontrolled C–H arylation of medicinally relevant heterocycles, such as azetidines,^{15a} and pyrrolidinones.^{15b–d} Functionalisation of cyclobutanes under this manifold has been reported in several natural product total syntheses beginning with Baran's synthesis of the piperarborenines in 2011,¹⁶ psiguadial B¹⁷ as well as scopiariusicide.¹⁸ Outside of total synthesis applications, studies focused on the synthesis of functionalised cyclobutanes using this methodology have been reported, however, the elaboration into more complex fragments remains limited. Work by the Yu group has detailed the selective formation of all-*syn* cyclobutyl carboxylic acids and ketones using both conventional and transient directing groups.¹⁹ Recently, Sanford and co-workers reported an elegant approach to *syn*-arylated alicyclic amines *via* directed, Pd-catalysed transannular C–H arylation (Fig. 1C),²⁰ including a single example of highly *syn*-selective C–H arylation of the cyclobutane ring in an azabicyclo[3.2.0]heptane system.

Inspired by these pioneering efforts, we envisioned the general construction of all-*syn* heterobicyclo[*n*.2.0] fragment systems could be accomplished by exploiting this chemistry using an approach we term the 'inside-out' strategy (Fig. 1D). We proposed directed Pd-catalysed C–H arylation on a cyclobutane core, followed by heterocycle formation utilising the latent carboxylic acid oxidation state (accessed *via* directing group removal) and a proximal heteroatom-containing substituent. Herein, we report the successful realization of this vision towards a novel, sp³-enriched collection of all-*syn* heterobicyclic fragments in a manner that is stereochemically complementary to most 'outside-in' approaches.

Our studies commenced with the construction of a suitable cyclobutane-containing substrate to facilitate exploration of the

Fig. 2 Synthetic sequence to access the all-*syn* cyclobutane core substrate and initial C–H arylation result.

C–H functionalisation reaction (Fig. 2). Several directing groups have been employed for this purpose, including 2-(methylthio)-aniline (2-MTA),^{16,21,22} and 8-aminoquinoline,^{17,23} among others.^{24,25} In particular, the 2-MTA directing group was selected for this study due to its reported ease of removal, an important factor to enable the downstream derivatisations envisioned. Furthermore, despite its apparent potential during use in the piperarborenine B and scopiariusicide A syntheses, the aryl-iodide scope under a 2-MTA directing group had yet to be systematically explored for cyclobutane C–H arylation on other substrates. Thus, arylation precursor 3 was synthesized in four steps from a commercially available anhydride. Next, we were gratified to find that subjecting of 3 and 4-iodoanisole (2 equiv.) to C–H arylation conditions reported by Baran and coworkers¹⁶ resulted in a good yield of arylated product 4 with excellent diastereoselectivity.

Finding the C–H arylation conditions fit for purpose, exploration of the aryl-iodide scope began (Fig. 3). The reaction revealed a broad tolerance of electron-rich (4, 5) and electron-poor functional groups (6–15) at both the *para*- and *meta*-positions of the arene. Although the literature suggests that *ortho*-substitution typically is not tolerated in this type of chemistry,²³ the use of 2-nitro-4-methoxy-iodobenzene furnished product 16 in 50% yield, providing a useful amine precursor. Incorporation of some pharmaceutically important heterocycles could also be accomplished (17, 18). Interestingly, when 1,4-diiodobenzene was employed as the arene, bis-cyclobutanated product 19 was isolated as the major product. Collectively, these examples demonstrate the utility of the cyclobutane C–H bond as a vector for fragment synthesis. Moreover, the broad range of functional groups incorporated could serve as polar or lipophilic pharmacophores, or as vectors for fragment growth or modification.

With these key precursors in hand, we next sought to explore our proposed approach to all-*syn* heterobicyclo[*n*.2.0] systems (Fig. 4). To begin, fused butyrolactone–cyclobutane fragment 20 was produced *via* Boc protection of 4 followed by desilylation with TBAF, resulting in direct lactonisation and displacement of the directing group. This cascade represents an attractive and mild method for directing group removal, which often requires harsh conditions that could epimerise a sensitive stereotriad. This sequence could be readily applied to other arylated products to afford butyrolactones 21–23 (see ESI† for details). Gratifyingly, a single crystal X-ray structure of lactone 20 confirmed the all-*syn* configuration. Satisfied by this

Fig. 3 Scope of Pd-catalysed C–H arylation reaction. Reagents and conditions: **3** (1 equiv.), Ar–I (2 equiv.), Pd(OAc)₂ (0.1 equiv.), PivOH (1 equiv.), Ag₂CO₃ (1 equiv.), HFIP (0.2 M), 75 °C, 24 h. DG = 2-(methylthio)-aniline.

success, the formation of other heterobicyclo[*n*.2.0] frameworks from butyrolactone **20**, were then explored. Pleasingly, reduction of lactone **20** proceeded in straightforward manner to afford diol **24**. Subsequent treatment of **24** with triphosgene and pyridine afforded the [5.2.0] 1,3-dioxepane-2-one scaffold **25**. Alternatively, reacting **24** with Tf₂O and pyridine furnished tetrahydrofuran-containing [3.2.0] scaffold **26**. Next, the pyrrolidine-containing [3.2.0] scaffold **27** was constructed by conversion of **24** to a ditosylate followed by heating with benzylamine. Finally, direct opening of lactone **20** with hydrazine followed by Curtius rearrangement afforded cyclic urethane-containing [4.2.0] system **28**.

To explore the potential properties of this collection, we created a virtual library of 90 scaffolds using our demonstrated aryl scope (4–19) on each of the final five heterobicyclic scaffolds (**20**, **25–28**) and the diol (**24**, see ESI† for enumerated products). Cheminformatic analysis was performed, comparing this library to the commercially available Maybridge Rule-of-three (Ro3) core collection²⁶ and representative scaffolds from the ChEMBL database (see ESI† for details).²⁷ The all-*syn* collection demonstrated Ro3 compliance similar to or more favourable than both libraries. Importantly, the all-*syn* library also exhibited significantly higher complexity metrics (Fsp³, number of chiral centres, and percent of compounds out of 'flatland') than the libraries used for comparison. Collectively, these results show that the small molecules produced using the

A. Directing group removal and lactonisation.

B. Divergent modification of butyrolactone 18 to other heterobicyclic fragments.

Fig. 4 Arylation products were modified in a divergent manner to generate five fused-heterobicyclic scaffolds in a variety of ring sizes. Reagents and conditions: (a) Boc₂O, DMAP, NEt₃, THF, reflux; (b) TBAF, THF, 0 °C to RT; (c) LiAlH₄, THF, 0 °C to RT, 96%; (d) triphosgene, pyridine, THF, 0 °C, 66%; (e) Tf₂O, pyridine, RT, 85%; (f) TsCl, pyridine, 53%. (g) BnNH₂, reflux, 51%; (h) (i) hydrazine hydrate, MeOH, RT. (ii) NaNO₂, HCl, THF/H₂O, 0 °C. 51% over 2 steps.

approach outlined in this work can be maximally complex without sacrificing good fragment-like properties (Table 1).

There remains a demand for the development of novel methodologies to construct new biologically relevant scaffolds to seed pharmaceutical research. This study has demonstrated that the strategic application C–H arylation of a cyclobutane-containing moiety can enable the synthesis of a collection of

Table 1 Mean values for *in silico* library generated by the matrix of scaffold and substrate scope. Colour scale: green (within ideal range and/or optimally complex), yellow (slightly outside of the ideal range or moderately complex), red (far outside ideal range, or minimally complex)

	Parameter	Ideal Range	This Work	ChEMBL	Maybridge
Complexity	Fsp ³	-	0.48	0.41	0.29
	# Chiral	-	3	0.38	0.15
	% out of 'flatland'	-	94%	48%	28%
Fragment Rule of 3	MW	140 - 230	229	270	182
	AlogP	0 - 2	2.14	3.26	1.92
	HBA	<3	2.93	3.14	1.86
	HBD	<3	0.67	1.00	0.99
	HAC	10 to 16	16	20	13

all-*syn* heterobicyclo[*n*.2.0] containing fragments. This 'inside-out' synthetic approach is complementary to 'outside-in' approaches relying on [2+2] cycloaddition chemistry for construction of the cyclobutane core, and furnishes fragment precursors in a stereochemically distinct fashion. Cheminformatic analysis of the products compared to commercially available fragments and structurally similar molecules with known biological activity shows the all-*syn* products to be substantially more complex while maintaining good fragment-like properties. Overall, this work demonstrates the power of merging synthetic strategy, new synthetic methodology, and fragment design principles to facilitate the construction of novel and complex fragments.

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X-ray crystallographic data for 20 has been deposited at the CCDC (deposition number 1986749).†

Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 C. W. Murray, D. R. Newell and P. Angibaud, *MedChemComm*, 2019, **10**, 1509–1511.
- 2 D. A. Erlanson, S. W. Fesik, R. E. Hubbard, W. Jahnke and H. Jhoti, *Nat. Rev. Drug Discovery*, 2016, **15**, 605–619.
- 3 J. A. Johnson, C. A. Nicolaou, S. E. Kirberger, A. K. Pandey, H. Hu and W. C. K. Pomerantz, *ACS Med. Chem. Lett.*, 2019, **10**, 1648–1654.
- 4 C. W. Murray and D. C. Rees, *Angew. Chem., Int. Ed.*, 2016, **11**, 488–492.
- 5 S. L. Kidd, T. J. Osberger, N. Mateu, H. F. Sore and D. R. Spring, *Front. Chem.*, 2018, **6**, 460.
- 6 For recent examples in this field see: (a) Y. Wang, J.-Y. Wach, P. Sheehan, C. Zhong, C. Zhan, R. Harris, S. C. Almo, J. Bishop, S. J. Haggarty, A. Ramek, K. N. Berry, C. O'Herin, A. N. Koehler, A. W. Hung and D. W. Young, *ACS Med. Chem. Lett.*, 2016, **7**, 852–856; (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**, 6799–6804; (c) E. Lenci, R. Innocenti, G. Menchi and A. Trabocchi, *Front. Chem.*, 2018, **6**, 522; (d) E. Lenci, A. Rossi, G. Menchi and A. Trabocchi, *Org. Biomol. Chem.*, 2017, **15**, 9710–9717; (e) E. Lenci, G. Menchi, A. Guarna and A. Trabocchi, *J. Org. Chem.*, 2015, **80**, 2182–2191; (f) R. A. Croft, M. A. J. Dubois, A. J. Boddy, C. Denis, A. Lazaridou, A. S. Voisin Chiret, R. Bureau, C. Choi, J. J. Mousseau and J. A. Bull, *Eur. J. Org. Chem.*, 2019, 5385–5395; (g) D. Foley, R. Doveston, I. Churcher, A. Nelson and S. P. Marsden, *Chem. Commun.*, 2015, **51**, 11174–11177; (h) H. Hassan, S. P. Marsden and A. Nelson, *Bioorg. Med. Chem.*, 2018, **26**, 3030–3033; (i) J. Mayol-Llinàs, W. Farnaby and A. Nelson, *Chem. Commun.*, 2017, **53**, 12345–12348; (j) A. R. Hanby, N. S. Troelsen, T. J. Osberger, S. L. Kidd, K. T. Mortensen and D. R. Spring, *Chem. Commun.*, 2020, **56**, 2280–2283.
- 7 D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson and A. Wood, *Nat. Chem.*, 2018, **10**, 383–394.
- 8 R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845–5859.
- 9 I.-L. Tsai, F.-P. Lee, C.-C. Wu, C.-Y. Duh, T. Ishikawa, J.-J. Chen, Y.-C. Chen, H. Seki and I.-S. Chen, *Planta Med.*, 2005, **71**, 535–542.
- 10 Y. Liu, T. Yang, H. Li, M. H. Li, J. Liu, Y. T. Wang, S. X. Yang, J. Zheng, X. Y. Luo, Y. Lai, P. Yang, L. M. Li and Q. Zou, *Br. J. Pharmacol.*, 2013, **168**, 632–643.
- 11 P. R. Verhoest, C. Proulx-Lafrance, M. Corman, L. Chenard, C. J. Helal, X. Hou, R. Kleiman, S. Liu, E. Marr, F. S. Menniti, C. J. Schmidt, M. Vanase-Frawley, A. W. Schmidt, R. D. Williams, F. R. Nelson, K. R. Fonseca and S. Liras, *J. Med. Chem.*, 2011, **54**, 7602–7620.
- 12 (a) S. Poplata, A. Tröster, Y. Q. Zou and T. Bach, *Chem. Rev.*, 2016, **116**(17), 9748–9815; (b) G. Steiner, R. Munschaner, G. Klebe and L. Siggel, *Heterocycles*, 1995, **40**, 319–330; (c) A. V. Denisenko, T. Druzhenko, Y. Skalenko, M. Samoilenko, O. O. Grygorenko, S. Zozulya and P. K. Mykhailiuk, *J. Org. Chem.*, 2017, **82**, 9627–9636; (d) T. Bach, C. Krüger and K. Harms, *Synthesis*, 2000, 305–320; (e) D. A. Fort, T. J. Wolterling, A. M. Alker and T. Bach, *J. Org. Chem.*, 2014, **79**, 7152–7161; (f) S. C. Coote and T. Bach, *J. Am. Chem. Soc.*, 2013, **135**, 14948–14951; (g) S. C. Coote, A. Pöthig and T. Bach, *Chem. – Eur. J.*, 2015, **21**, 6906–6912.
- 13 (a) M. A. Ischay, M. E. Anzovino, J. Du and T. P. Yoon, *J. Am. Chem. Soc.*, 2008, **130**(39), 12886–12887; (b) M. A. Ischay, Z. Lu and T. P. Yoon, *J. Am. Chem. Soc.*, 2010, **132**(25), 8572–8574; (c) L. Ackermann, A. Althammer and S. Fenner, *Angew. Chem., Int. Ed.*, 2009, **48**, 201–204; (d) A. E. Hurtley, Z. Lu and T. P. Yoon, *Angew. Chem., Int. Ed.*, 2014, **53**, 8991–8994.
- 14 V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154–13155.
- 15 (a) M. Maetani, J. Zoller, B. Melillo, O. Verho, N. Kato, J. Pu, E. Comer and S. L. Schreiber, *J. Am. Chem. Soc.*, 2017, **139**, 11300–11306; (b) D. Antermite, D. P. Affron and J. A. Bull, *Org. Lett.*, 2018, **20**, 3948–3952; (c) D. P. Affron and J. A. Bull, *Eur. J. Org. Chem.*, 2016, 139–149; (d) D. Antermite and J. A. Bull, *Synthesis*, 2019, 3171–3204.
- 16 W. R. Gutekunst and P. S. Baran, *J. Am. Chem. Soc.*, 2011, **133**, 19076–19079.
- 17 L. M. Chapman, J. C. Beck, L. Wu and S. E. Reisman, *J. Am. Chem. Soc.*, 2016, **138**, 9803–9806.
- 18 M. Zhou, X.-R. Li, J.-W. Tang, Y. Liu, X.-N. Li, B. Wu, H.-B. Qin, X. Du, L.-M. Li, W.-G. Wang, J.-X. Pu and H.-D. Sun, *Org. Lett.*, 2015, **17**, 6062–6065.
- 19 (a) K.-J. Xiao, D. W. Lin, M. Miura, R.-Y. Zhu, W. Gong, M. Wasa and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**(22), 8138–8142; (b) L.-J. Xiao, K. Hong, F. Luo, L. Hu, W. R. Ewing, K.-S. Yeung and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2020, **59**, 2–9.
- 20 J. Topczewski, P. Cabrera, N. Saper and M. S. Sanford, *Nature*, 2016, **531**, 220–224.
- 21 R. A. Panish, S. R. Chintala and J. M. Fox, *Angew. Chem., Int. Ed.*, 2016, **55**, 4983–4987.
- 22 J. L. Hu, L. W. Feng, L. Wang, Z. Xie, Y. Tang and X. Li, *J. Am. Chem. Soc.*, 2016, **138**, 13151–13154.
- 23 R. Parella, B. Gopalakrishnan and S. A. Babu, *J. Org. Chem.*, 2013, **78**, 11911–11934.
- 24 M. Virelli, W. Wang, R. Kuniyil, J. Wu, G. Zanon, A. Fernandez, J. Scott, M. Vendrell and L. Ackermann, *Chem. – Eur. J.*, 2019, **25**, 12712–12718.
- 25 W. R. Gutekunst and P. S. Baran, *J. Org. Chem.*, 2014, **79**, 2430–2452.
- 26 N. Mateu, S. L. Kidd, L. Kalash, H. F. Sore, A. Madin, A. Bender and D. R. Spring, *Chem. – Eur. J.*, 2018, **24**, 13681–13687.
- 27 I. Colomer, C. J. Empson, P. Craven, Z. Owen, R. G. Doveston, I. Churcher, S. P. Marsden and A. Nelson, *Chem. Commun.*, 2016, **52**, 7209–7212.