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COMMUNICATION

Efficient unified synthesis of diverse bridged polycyclic scaffolds using a complexity-generating 'stitching' annulation approach

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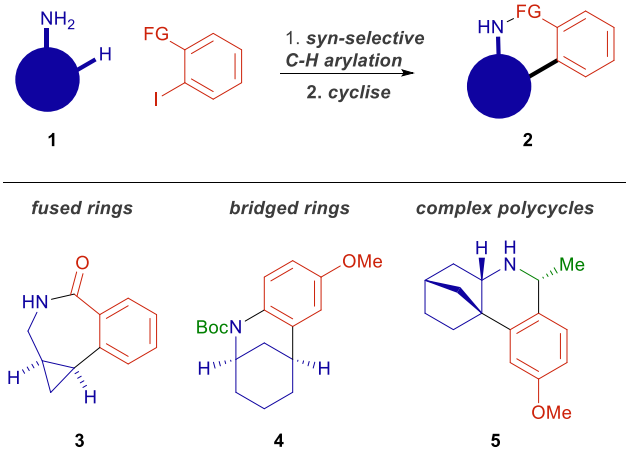
Regioselective and stereospecific directed C-H arylation of simple amine substrates, and cyclisation, delivered 30 diverse, three-dimensional scaffolds. The unified approach significantly expanded the range of bridged ring systems that contain both a nitrogen atom and an aromatic ring.

Small molecules continue to dominate our collective ability to treat disease and to understand biomedical mechanisms.[1] However, the efficient synthesis of diverse bioactive small molecules is an ongoing challenge. A narrow reaction toolkit has resulted in the uneven exploration of chemical space[2-5] and a focus on flatter and more lipophilic compounds,[6] despite these parameters correlating poorly with successful translation into marketed drugs.[7,8] As a result, the synthetic community has been challenged to develop synthetic methods that deliver compounds that align with drug-discovery needs.[9-11] Unified approaches have now been developed that enable diverse lead-like scaffolds[12] and sp^3-rich fragments[13] to be prepared.

The value of bridged ring systems in medicinal chemistry has increasingly been recognised, for example as isosteres of phenyl and piperidine rings;[14] and diverse bridged nitrogen-containing ring systems feature in FDA-approved drugs such as maraviroc (anti-HIV), varenicline (smoking cessation) and solfenacin (anti-muscarinic). We envisaged a unified approach to diverse sp^3-rich molecular scaffolds (Scheme 1), especially bridged scaffolds containing both a nitrogen atom and an aromatic ring. Only ~0.3% of building blocks within the ZINC database[15] of available compounds contain such a ring system.‡ Initially, key arylated



Scheme 1: Envisaged unified synthesis of diverse partially-saturated molecular scaffolds through C-H arylation/cyclisation 'stitching'.

intermediates would be prepared by amine-directed C-H (het)arylation of mono- or bicyclic amines **1**. Crucially, the directed nature of the activation enforces a *syn*-relationship between the amine and the introduced (het)aryl group, enabling subsequent cyclisations to yield alternative polycyclic scaffolds (→ **2**; e.g. **3** or **4**). Although many diversity-oriented approaches harness reactions that fuse a ring onto a pre-existing system,[12,13] the annulation of two cyclic ring systems (e.g. *via* benzyne chemistry[16]) is relatively rare. The possibility of rearrangement, in addition to cyclisation, (e.g. → **5**) would further increase scaffold diversity. Variation of the amine substrate, the introduced (het)aryl ring, and the cyclisation reaction, was expected to enable the synthesis of many diverse bridged molecular scaffolds.

Initially, we developed a toolkit of five cyclisation reactions using *exo*-2-aminonorbornane **6** as an exemplar starting material (Scheme 2). Arylation of **6** was achieved using a transient directing group (TDG) strategy.[17] C-H arylation with 3-iodoanisole and 2-iodobenzyl alcohol, followed by amine

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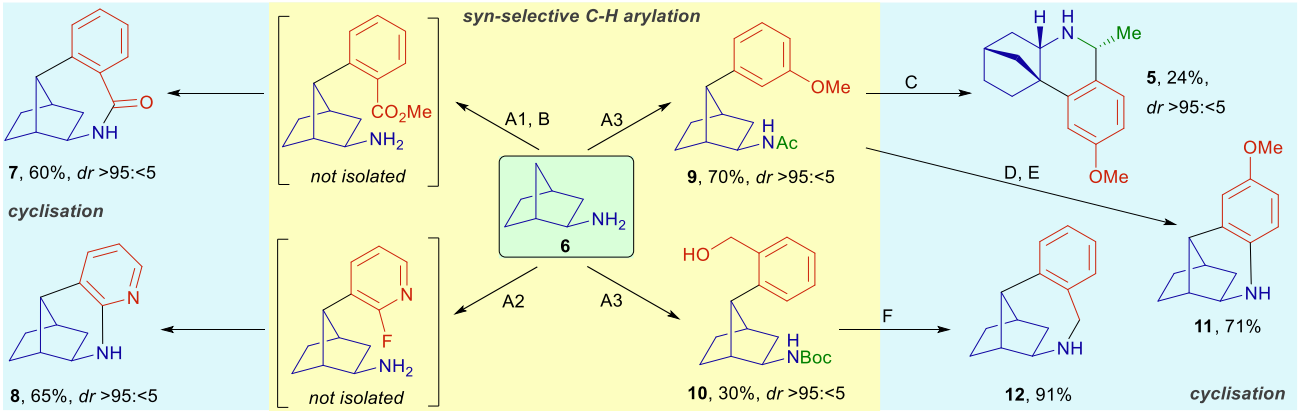
‡ Analysis of the ~1M "in stock" compounds with MW<350 revealed 2867 compounds that are based on 204 different bridged ring systems containing at least one nitrogen atom and aromatic ring.



Scheme 2: Synthesis of seven scaffolds (five bridged and two monoarylated) from *exo*-2-aminonorbornane **6**. Typical methods: A1: $Pd(OAc)_2$ (5 mol%), 2-hydroxynicotinaldehyde (10 mol%), methyl-2-iodobenzoate, AgTFA, HFIP:AcOH (19:1), 120 °C; A2: $Pd(OAc)_2$ (5 mol%), 2-chloro-6-hydroxybenzaldehyde (10 mol%), 2-hydroxy-5-trifluoromethylpyridine (25 mol%), 2-fluoro-3-iodopyridine, AgTFA, HFIP:AcOH (19:1), 120 °C then AcOH, 120 °C; A3: $Pd(OAc)_2$ (5 mol%), 2-hydroxynicotinaldehyde (10 mol%), Ar-I, AgTFA, HFIP:AcOH (19:1), 120 °C then Boc_2O or Ac_2O, NaOH, THF; B: NaOH, THF; C: $POCl_3$, MeCN, 100 °C then $NaBH_4$, MeOH; D: NBS, MeCN then $Pd(OAc)_2$ (5 mol%), *rac*-BINAP (7.5 mol%), Cs_2CO_3, toluene, 100 °C; E: HCl, EtOH, 80 °C; F: MsCl, Et_3N, DCM then TFA, DCM. See ESI† for full experimental details.

protection, gave **9** and **10** respectively as single regio- and diastereomers, while with aryl halides containing reactive electrophilic functionality allowed generation of polycyclic scaffolds in a single operation by one-pot C-H arylation/cyclisation.[18] Thus, use of methyl 2-iodobenzoate led to lactamisation to give benzazepinone **7** and 2-fluoro-3-iodopyridine underwent arylation/S_NAr sequence to give tetrahydroquinoxaline **8**. Cyclisation of **10**→**12** was effected by sulfonylation and nucleophilic substitution. The anisyl group in **9** was also exploited to effect further cyclisations: thus electrophilic bromination and intramolecular Buchwald-Hartwig coupling[19] allowed conversion of **9**→**11**. Remarkably, attempted Bischler-Napieralski cyclisation[20] of **9** resulted instead in rearrangement to give**,** after imine reduction, scaffold **5** as a single diastereomer, generating further structural diversity. Together, these cyclisation reactions enabled five diverse bridged scaffolds (**5**, **7**, **8**, **11** and **12**) to be prepared.

The reaction toolkit enabled a wide range of additional scaffolds to be prepared from alternative amine starting materials (Scheme 3). The required arylated intermediates were prepared using a TDG strategy where possible (→**13** and **14**); in other cases, C-H arylation was achieved using a picolinamide directing group (→ **16**, **19**, **21**, **23**, **25**, **26**, **28** and **29**).[21] Unfortunately, C-H arylation of 5-amino-2-azabicyclo[2.2.2]octane was not possible, with only unreacted starting material recovered from this reaction. However, the required arylated intermediate **32** was instead prepared *via* proline catalysed aza-Diels-Alder cycloaddition[22], followed by reductive amination and Boc protection.

Cyclisation of the arylated intermediates **13**, **14**, **16**, **23**, **26**, **29** and **32** using a Buchwald-Hartwig reaction, if necessary after regioselective bromination, successfully yielded seven additional cyclised scaffolds (**4**, **15**, **17**, **24**, **27**, **31** and **33**). Bischler-Napieralski cyclisation, and imine reduction, provided two more cyclised scaffolds (**16**→**18** and **29**→**30**). Additionally, lactamisation of the ester-containing arylated intermediates yielded scaffolds **3** and **20**, and cyclisation by S_NAr reaction yielded scaffold **22**. Here, cyclisation by S_N2 reaction was not exploited as it would have yielded similar scaffolds to those prepared by Bischler-Napieralski cyclisation.

Overall, the unified approach enabled 30 sp^3-rich scaffolds to be prepared: 17 cyclised scaffolds as well as 13 arylated intermediates. Scaffold diversity was assessed by iterative simplification of the deprotected scaffolds to reveal eight different parental monocyclic frameworks derived from the 23 unique molecular frameworks at the graph-node-bond level (Fig. 1).[23] This analysis revealed significant structural diversity at each level of hierarchy, demonstrating that the scaffolds are not closely-related derivatives. Further analysis using LLAMA (Lead Likeness And Molecular Analysis)[24] showed that the scaffolds are both significantly shape-diverse and three-dimensional

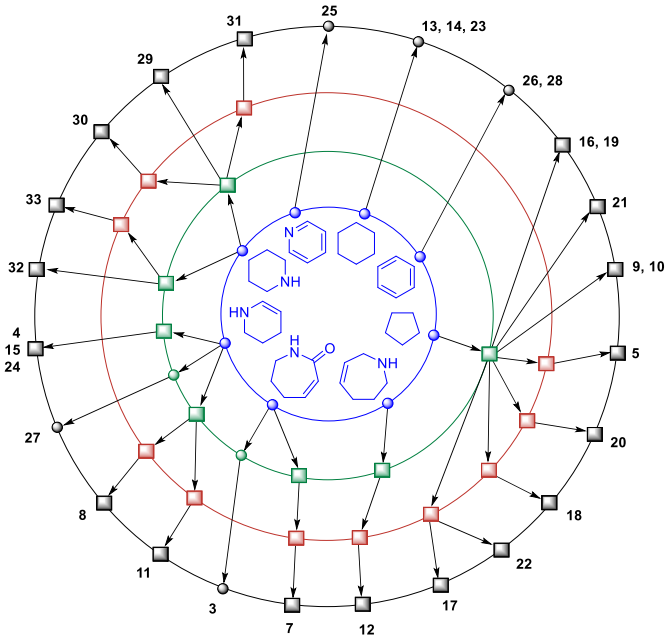
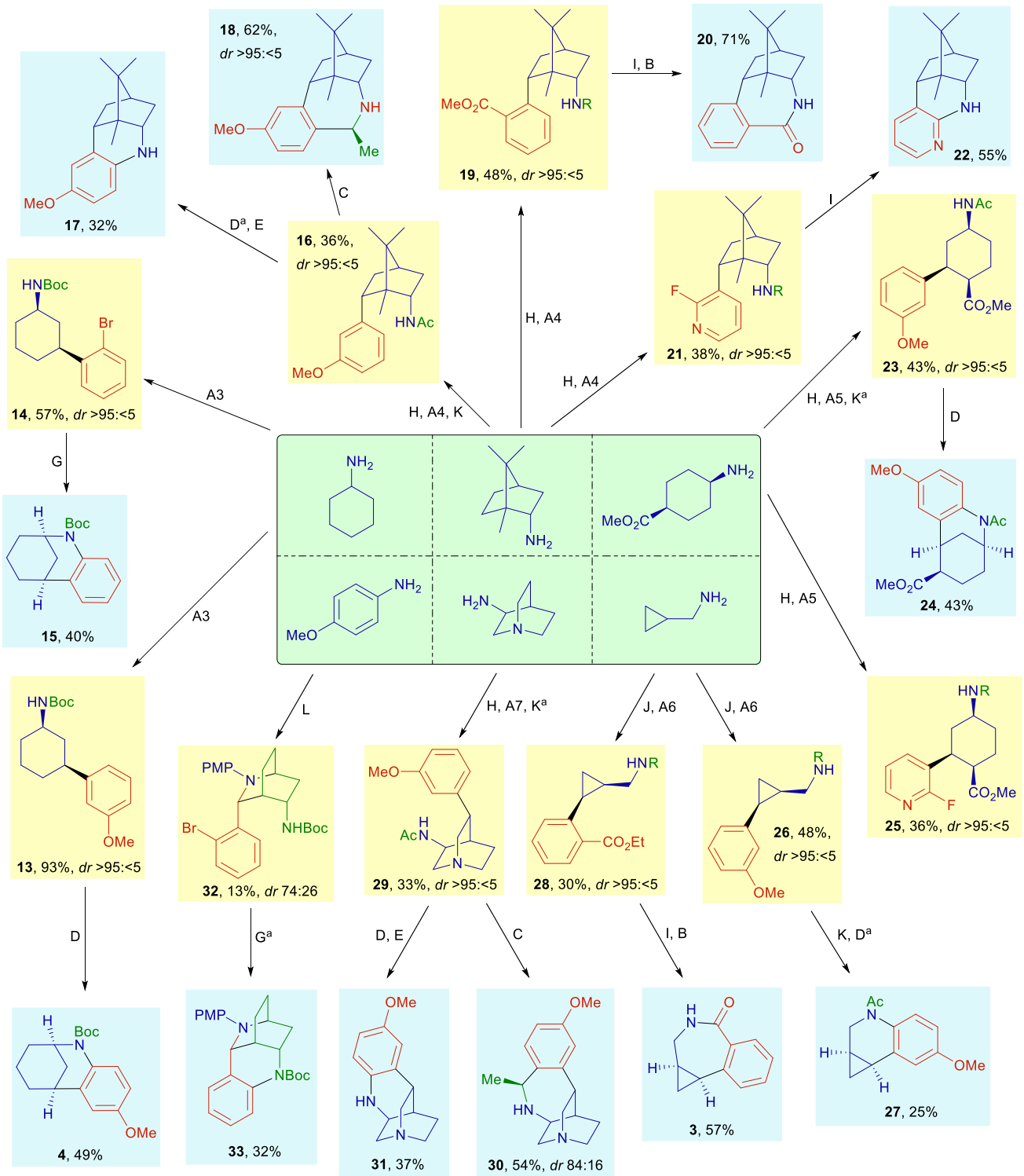


Fig.1: Hierarchical scaffold tree highlighting the eight parental monocyclic frameworks (blue) related to the 30 (deprotected) scaffolds prepared *via* the unified approach. Bridged (square) and non-bridged (circle) frameworks are indicated.



Scheme 3: Twenty-three additional scaffolds (twelve cyclised and eleven monoarylated) prepared from alternative amine substrates. Typical methods (see also Scheme 2): A4: $Pd(OAc)_2$ (5 mol%), $CuBr_2$ (10 mol%), Ar-I, CsOAc, ^{t}AmOH, 140 °C; A5: $Pd(OAc)_2$ (10 mol%), Ar-I, Ag_2CO_3, 2,6-dimethylbenzoic acid, DMF, 120 °C; A6: $Pd(OAc)_2$ (5 mol%), Ar-I, PivOH, K_2CO_3, toluene, 130 °C; A7: $Pd(OAc)_2$ (15 mol%), 3-iodoanisole, Ag_2CO_3, PivOH, DMF, 100 °C; G: $Pd(OAc)_2$ (5 mol%), *rac*-BINAP (7.5 mol%), Cs_2CO_3, toluene, 100 °C; H: Picolinic acid, CDI, DMF; I: Zn/HCl, THF; J: Picolinic acid, $POCl_3$, Et_3N, DCM; K: Zn/HCl, THF then NaOH, Ac_2O, THF; L: 2-bromobenzaldehyde, cyclohexenone, *rac*-proline (30 mol%), MeCN:H_2O (9:1), 35 °C then sat. NH_3/MeOH, $Ti(O^iPr)_4$, $NaBH_4$ then Boc_2O, NaOH, THF. See ESI† for full experimental details. [a]See ESI† for details of method variations. R = 2-pyridylcarbonyl.

(see ESI†). The shape diversity was assessed by comparison with ~90,000 randomly selected compounds from the ZINC database.[12f] This analysis confirmed the high shape diversity of the scaffolds (Fsp^3: $\mu = 0.56$) in comparison with the randomly-selected commercially-available compounds (Fsp^3: $\mu = 0.33$). All of the cyclised (deprotected) scaffolds were novel and, indeed, only two of the (deprotected) arylated intermediates (**13** and **28**) were found as substructures of building blocks in the ZINC database.‡,[15] Additionally, the scaffolds were virtually decorated with a selection of medicinally-relevant capping groups, and the resulting compounds were shown to be shape-diverse, three-dimensional and largely lead-like (see ESI†).

To conclude, our unified synthetic approach enabled the preparation of 30 diverse and three-dimensional scaffolds. 22 of these scaffolds were based on bridged ring systems containing both a nitrogen atom and an aromatic ring, significantly expanding on the 204 such ring systems currently in the ZINC database.‡ The scaffolds were prepared from commercially available starting materials in a total of 45 synthetic steps (i.e. 1.5 steps per scaffold), illustrating the efficiency of the unified approach. We envisage that the resulting diverse scaffolds will be exploited to broaden the chemical space that is explored within drug discovery programmes. We thank EPSRC (EP/N025652/1) and Redbrick Molecular for funding.

Conflicts of interest

Redbrick Molecular markets diverse building blocks for applications in drug discovery.

References

1 (a) E. V. Gurevich and V. V. Gurevich, *Handb. Exp. Pharmacol*., 2014, **219**, 1; (b) C. J. Gerry and S. L. Schreiber, *Nat. Rev. Drug Discov.*, 2018, **17**, 333.

2 S. D. Roughley and A. M. Jordan, *J. Med. Chem.,* 2011, **54**, 3451.

3 J. Boström, D. Brown, R. Young and G. Keserü, *Nat. Rev. Drug. Discov*., 2018, **17**, 709.

4 D. Brown and J. Boström, *J. Med. Chem.*, 2015, **59**, 4443.

5 S. R. Langdon, N. Brown and J. Blagg, *J. Chem. Inf. Model.*, 2011, **51**, 2174.

6 W. P. Walters, J. Green, J. R. Weiss, and M. A. Murcko, *J. Med. Chem*., 2011, **54**, 6405.

7 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752.

8 D. A. Smith, B. C. Jones, D. K. Walker, *Med. Res. Rev.*, 1996, **16**, 243.

9 F. W. Goldberg, J. G. Kettle, T. Kogej, M. W. D. Perry and N. P. Tomkinson, *Drug Discovery Today*, 2015, **20**, 11.

10 A. Nadin, C. Hattotuwagama and I. Churcher, *Angew. Chem. Int. Ed.*, 2012, **51**, 1114.

11 C. W. Murray and D. C. Rees, *Angew. Chem. Int. Ed.*, 2016, **55**, 488.

12 (a) M. Lüthy, M. Wheldon, C. Haji-Cheteh, M. Atobe, P. Bond, P. O'Brien, R. Hubbard and I. Fairlamb, *Bioorg. Med. Chem.*, 2015, **23**, 2680; (b) D. Foley, P. Craven, P. Collins, R. Doveston, A. Aimon, R. Talon, I. Churcher, F. von Delft, S. P. Marsden and A. Nelson, *Chem. Eur. J.*, 2017, **23**, 15227; (c) J. Mayol-Llinas, W. Farnaby and A. Nelson., *Chem. Commun.*, 2017, **53**, 12345; (d) R. G. Doveston, P. Tosatti, M. Dow, D. J. Foley, H. Y. Li, A. J. Campbell, D. House, I. Churcher, S. P. Marsden and A. Nelson, *Org. Biomol. Chem.*, 2015, **13**, 859; (e) S. M. Wales, E. G. Merisor, H. V. Adcock, C. A. Pearce, I. R. Strutt, W. Lewis, D. Hamza and C. J. Moody, *Chem. Eur. J.*, 2018, **24**, 8233; (f) D. J. Foley, R. G. Doveston, I. Churcher, A. Nelson and S. P. Marsden, *Chem. Commun*, 2015, **51**, 11174.

13 (a) F. K. Morgan, I. A. Hollingsworth, J. A. Bull, *Chem. Commun.*, 2014, **50**, 5203; (b) D. Twigg, N. Kondo, S. Mitchell, W. Galloway, H. Sore, A. Madin and D. Spring, *Angew. Chem. Int. Ed.*, 2016, **55**, 12479; (c) A. R. Hanby, N. S. Troelsen, T. J. Osberger, S. L. Kidd, K. T. Mortensen and D. Spring, *Chem. Commun.*, 2020, **56**, 2280; (d) A. W. Hung, A. Ramek, Y. Wang, T. Kaya, J. A. Wilson, P. A. Clemons and D. W. Young, *Proc. Natl. Acad. Sci.*, 2011, **108**, 6799; (e) N. S. Troelsen, E. Shanina, D. Gonzalez-Romero, D. Danková, I. S. A. Jensen, K. J. Śniady, F. Nami, H. Zhang, C. Rademacher, A. Cuenda, C. H. Gotfredsen and M. H. Clausen, *Angew. Chem. Int. Ed.*, 2020, **59**, 2204; (f) R. Zhang, P. J. McIntyre, P. M. Collins, D. J. Foley, C. Arter, F. von Delft, R. Bayliss, S. Warriner and A. Nelson, *Chem. Eur. J.*, 2019, **25**, 6831; (g) N. Luise and P. G. Wyatt, *Chem. Eur. J.*, 2018, **24**, 10443.

14 (a) A. F. Stepan, C. Subramanyam, I. V. Efremov, J. K. Dutra, T. J. O'Sullivan, K. J. DiRico, W. S. McDonald, A. Won, P. H. Dorff, C. E. Nolan, S. L. Becker, L. R. Pustilnik, D. R. Riddell, G. W. Kauffman, B. L. Kormos, L. Zhang, Y. Lu, S. H. Capetta, M. E. Green, K. Karki, E. Sibley, K. P. Atchison, A. J. Hallgren, C. E. Oborski, A. E. Robshaw, B. Sneed and C. J. O'Donnell, *J. Med. Chem*., 2012, **55**, 3414; (b) X. Zheng, P. Bauer, T. Baumeister, A. J. Buckmelter, M. Caligiuri, K. H. Clodfelter, B. Han, Y.-C. Ho, N. Kley, J. Lin, D. J. Reynolds, G. Sharma, C. C. Smith, Z. Wang, P. S. Dragovich, A. Oh, W. Wang, M. Zak, J. Gunzner-Toste, G. Zhao, P.-W. Yuen and K. W. Bair, *J. Med. Chem.*, 2013, **56**, 4921.

15 J. J. Irwin, T. Sterling, M. M. Mysinger, E. S. Bolstad and R. G. Coleman, *J. Chem. Inf. Model.*, 2012, **52**, 1757.

16 A. V. Dubrovskiy, N. A. Markina and R. C. Larock, *Org. Biomol. Chem.*, 2013, **11**, 191.

17 Y. Wu, Y.-Q. Chen, T. Liu, M. D. Eastgate and J.-Q. Yu, *J. Am. Chem. Soc.*, 2016, **138**, 14554.

18 Y.-Q. Chen, Z. Wang, Y. Wu, S. R. Wisniewski, J. X. Qiao, W. R. Ewing, M. D. Eastgate and J.-Q. Yu, *J. Am. Chem. Soc.*, 2018, **140**, 17884.

19 A. S. Guram, R. A. Rennels and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 1995, **34**, 1348.

20 A. Bischler and B. Napieralski, *Ber. Dtsch. Chem. Ges.*, 1893, **26**, 1903.

21 (a) C. E. Coomber, L. Benhamou, D.-K. Bučar, P. D. Smith, M. J. Porter and T. D. Sheppard, *J. Org. Chem.*, 2018, **83**, 2495; (b) D. H. O' Donovan, P. Aillard, M. Berger, A. de la Torre, D. Petkova, C. Knittl-Frank, D. Geerdink, M. Kaiser and N. Maulide, *Angew. Chem. Int. Ed.*, 2018, **57**, 10737; (c) B. F. Van Steijvoort, N. Kaval, A. A. Kulago and B. U. W. Maes, *ACS Catal.*, 2016, **6**, 4486; (d) D. S. Roman and A. B. Charette, *Org. Lett.*, 2013, **15**, 4394.

22 P. J. Coleman, J. D. Schreier, A. J. Roecker, S. P. Mercer, G. B. McGaughey, C. D. Cox, G. D. Hartman, C. M. Harrell, D. R. Reiss, S. M. Doran, S. L. Garson, W. B. Anderson, C. Tang, T. Prueksaritanont, C. J. Winrow and J. J. Renger, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 4201.

23 A. Schuffenhauer, P. Ertl, S. Roggo, S. Wetzel, M. A. Koch and H. Waldmann, *J. Chem. Inf. Model.*, 2007, **47**, 47.

24 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; LLAMA is available at www.llama.leeds.ac.uk.

