
Article:
Rice, S, Cox, DJ, Marsden, SP orcid.org/0000-0002-2723-8954 et al. (1 more author) (2019) Unified synthesis of diverse building blocks for application in the discovery of bioactive small molecules. Tetrahedron, 75 (38). 130513. ISSN 0040-4020

https://doi.org/10.1016/j.tet.2019.130513

Unified synthesis of diverse building blocks for application in the discovery of bioactive small molecules

Scott Rice,[a,b] Daniel J. Cox,[c] Stephen P. Marsden[b] and Adam Nelson[a,b,*]

[a]Astbury Centre for Structural Molecular Biology, University of Leeds, Leeds, LS2 9JT, UK

[b]School of Chemistry, University of Leeds, Leeds, LS2 9JT, UK

[c]Redbrick Molecular, The Bioincubator, 40 Leavygreave Road, Sheffield, S3 7RD, UK

*Email: a.s.nelson@leeds.ac.uk

Abstract

The synthesis of large numbers of diverse molecular scaffolds with controlled molecular properties is a significant challenge in synthetic organic chemistry. A modular unified synthesis was developed, and was exploited in the synthesis of sixteen diverse three-dimensional scaffolds. The approach exploited two cyclisation precursors to be converted, using a toolkit of cyclisation reactions, into spirocyclic and fused-ring scaffolds. Remarkably, Pd-catalysed aminoarylation of substituted *N*-Boc-hex-5-enylamine cyclisation precursors to yield *N*-Boc piperidine-containing scaffolds was successful which was ascribed to a significant Thorpe–Ingold effect. Computational property analysis showed that the decorated scaffolds are shape-diverse, and enable diverse lead-like chemical space to be targeted.

Keywords

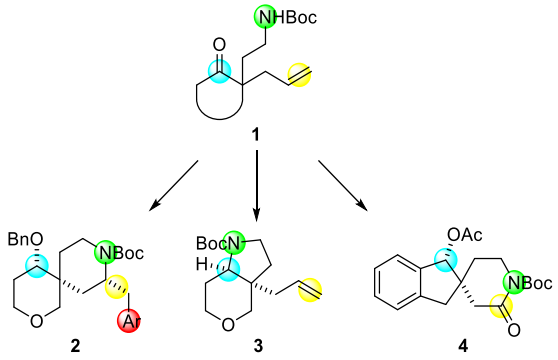
lead-oriented synthesis; molecular diversity; molecular scaffolds

Dedication

We dedicate this paper to Professor Steve Davies in recognition of his outstanding contribution to the fields of asymmetric and stereoselective synthesis.

Introduction

Controlling molecular properties is a challenge that is intrinsic to the discovery of useful bioactive molecules.[1] Yet, medicinal chemists have increasingly focused on flatter and more lipophilic compounds[2], despite these features correlating poorly with successful translation into marketed drugs.[3,4] This practice may stem, in part, from the poor availability of building blocks that have a high fraction of sp^3-hybrised carbons[5] and the narrow toolkit of reactions that currently dominates medicinal chemistry.[6-8] Recently, approaches have been developed that can deliver diverse molecules that align better with discovery needs.[1,9] In particular, unified approaches have been developed to synthesise many diverse molecular scaffolds that, on decoration, enable lead-like chemical space to be targeted.[10-16] Such scaffolds have been exploited, for example within the European Lead Factory, to produce screening libraries that target novel drug-relevant chemical space.[17,18] In addition, synthetic approaches have been developed to yield collections of useful shape-diverse fragments[19] for fragment-based drug discovery.[20-25]



Scheme 1: Overview of the envisaged unified synthetic approach

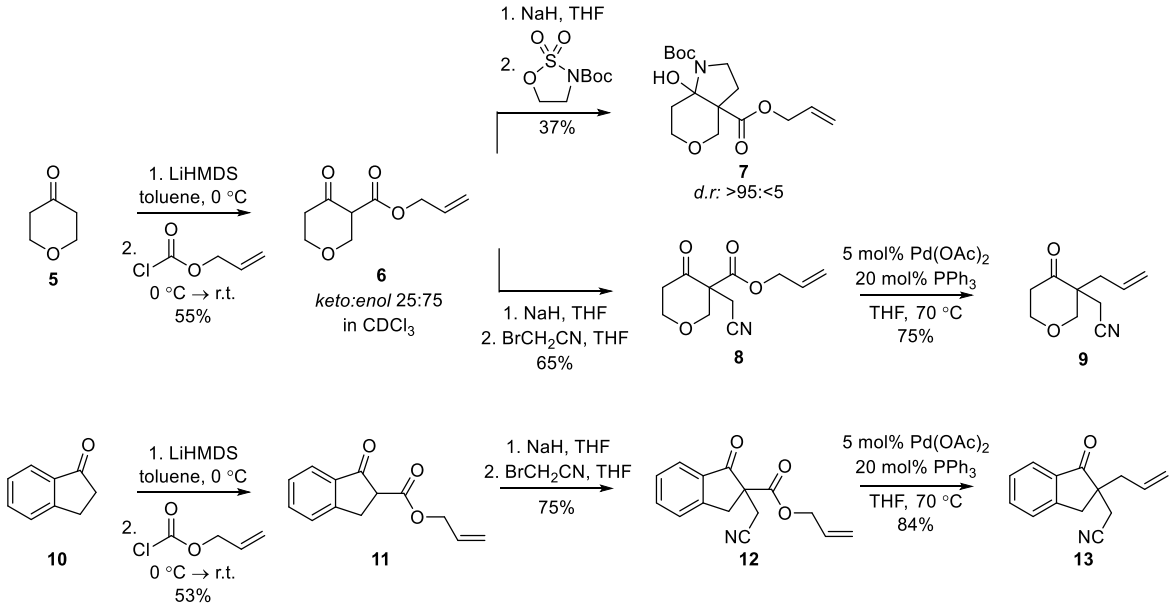
We recently developed a unified approach to lead-like scaffolds for CNS drug discovery that harnessed cyclisations of α-allyl α-aminomethyl carbonyl compounds; the approach yielded 30 diverse scaffolds with controlled molecular properties.[26] We recognised that this approach might be extended significantly *via* homologation of the cyclisation precursors, enabling a wider range of diverse scaffolds to be prepared. Cyclisation reactions involving different pairs of functional groups in the homologated precursors **1** would yield different ring system topologies (Scheme 1). For example, cyclisation between the *N*-Boc amine (green) and the terminal alkene (yellow) would give spirocyclic scaffolds (e.g. **2** and **4**) (in the case of **2**, with concomitant arylation (red)). Alternatively, fused-ring systems would be accessed by reaction between the *N*-Boc amine (green) and ketone (blue) groups (e.g. → **3**); or between the alkene (yellow) and the ketone (blue) groups. Furthermore, variation of

the cyclic precursor **1** would enable variation of the existing ring system in the scaffolds: for example, the THP in **2** and **3**, and the indane in **4**. Herein we describe the successful realisation of this strategy, leading to the production of 16 novel lead-like scaffolds.

Results and Discussion

Synthesis of α-cyanomethyl ketone intermediates

We synthesised the β-keto ester **6** by reaction of the lithium enolate of **5**, prepared by treatment with LiHMDS, with allyl chloroformate as in our previous study.[26] In order to introduce a Boc-protected 2-aminoethyl group, we initially investigated the reaction of the enolate of the β-keto ester **6**, prepared by treatment with sodium hydride, with the cyclic sulfamidate.[27] However, although the alkylation was successful, the product existed exclusively as hemiaminal **7** which proved not to be susceptible to palladium-catalysed[28] decarboxylative allylation. We therefore investigated alkylation of the enolate of the β-keto ester **6** with an alternative electrophile, bromoacetonitrile; the corresponding alkylated product **8** was obtained in 65% yield. Pd-catalysed decarboxylative allylation[28] (5 mol% $Pd(OAc)_2$, 20 mol% PPh_3, THF, 70 °C) then gave the required cyclisation precursor **9** in 75% yield. The cyclisation precursor **13** was similarly prepared from 1-indanone **10** with similar or better yields for the three steps.

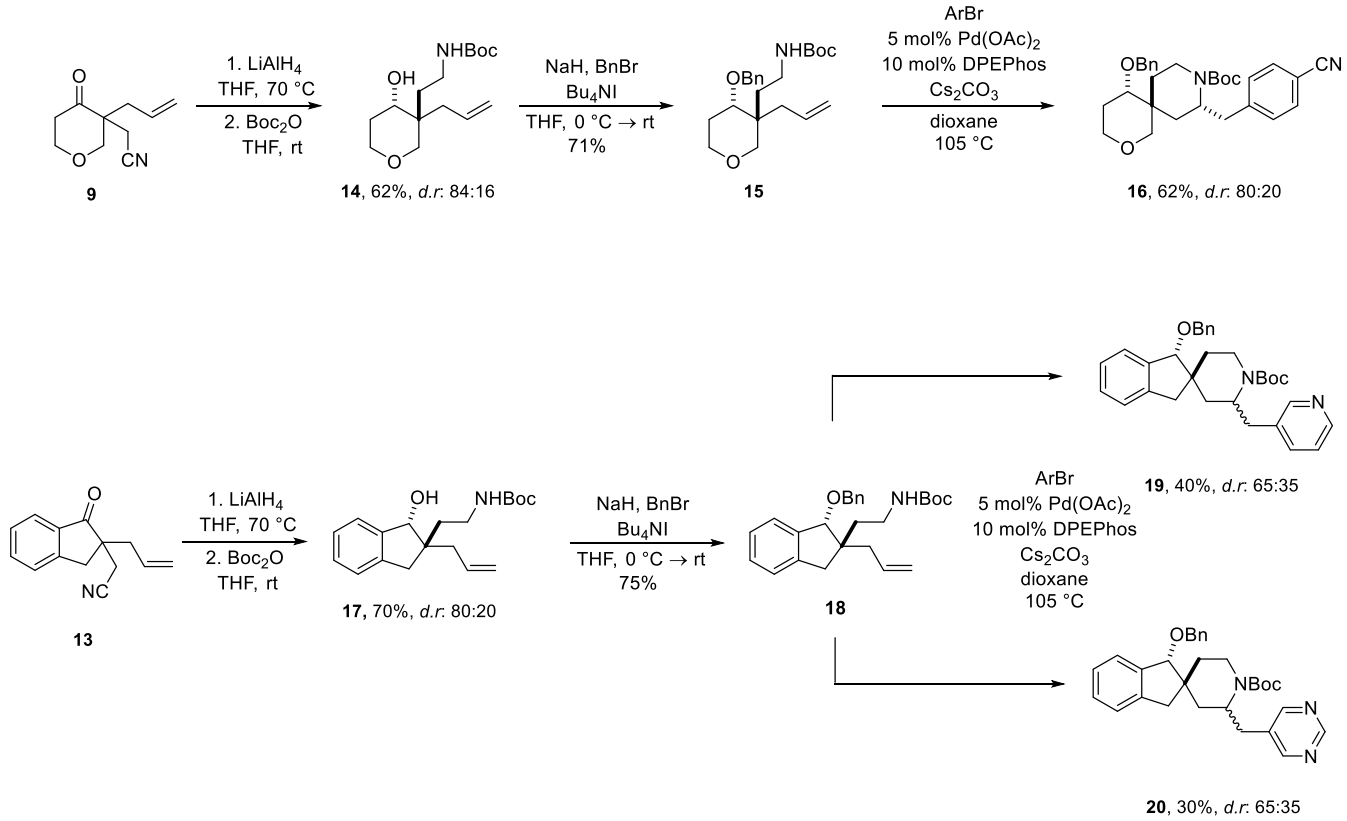


Scheme 2: Preparation of the α-cyanomethyl ketone intermediates **9** and **13**

Synthesis of spirocyclic piperidines by Pd-catalysed aminoarylation

Attention then turned to the development of cyclisation reactions for the introduction of new rings into product scaffolds. We have previously found Pd-catalysed aminoarylation[29-31] of *N*-Boc pent-4-en-amines to be a valuable reaction for the synthesis of functionalised pyrrolidines.[13,17,26,32] However, the synthesis of the corresponding Boc-protected piperidines is not well known, perhaps because Heck reaction competes with cyclisation.[33] The synthesis of piperidines by aminoarylation is, however, possible with *N*-phenyl or *N*-tosyl hex-5-en-amines as substrates.[33] Nonetheless, we decided to reinvestigate the synthesis of *N*-Boc piperidines by Pd-catalysed aminoarylation because the subsequent deprotection would likely be more straightforward than removal of an *N*-phenyl or *N*-tosyl group.

Initially, we prepared the required substrates for the cyclisation reaction (Scheme 3). Thus, treatment of the cyanoketones **9** and **13** with $LiAlH_4$ gave, after Boc protection, the amino alcohols **14** and **17** with good diastereoselectivity. The proposed configuration of the major diastereomeric product **14** was consistent with the observation of a diagnostic interaction in its NOESY spectrum (Figure 1), as well as the configuration of subsequent derivatives (see Scheme 6). Delivery of the reducing agent to the ketone *via* coordination to the amine is consistent with the observed diastereoselectivity (Figure 1). In both cases, the mixture of diastereomers obtained was taken directly forward for benzyl protection. Treatment of the alcohols **14** and **17** with NaH, and reaction with benzyl bromide in the presence of Bu_4NI, gave the corresponding protected derivatives **15** and **18** as single diasteromers



Scheme 3: Synthesis of spirocyclic piperidines by Pd-catalysed aminoarylation

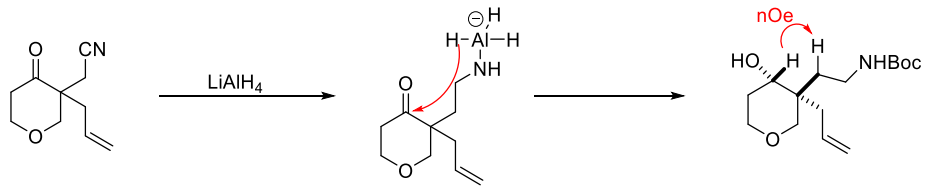


Figure 1: Stereochemical outcome of the reduction of the ketone **9**

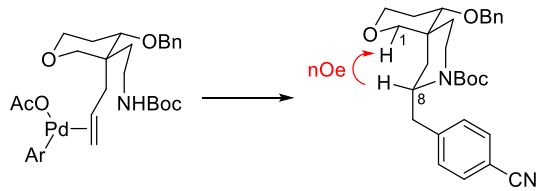
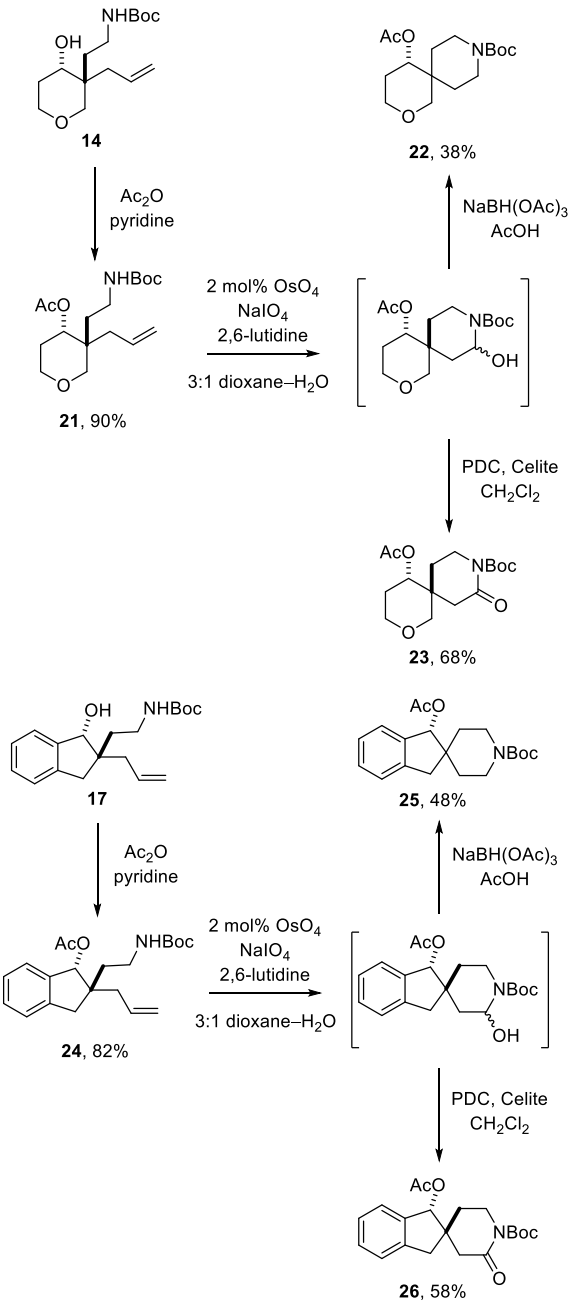


Figure 2: Stereochemical outcome of Pd-catalysed aminoarylation

We investigated the Pd-catalysed aminoarylation of the functionalised substrates **15** and **18**. Remarkably, treatment of the benzyl-protected substrates **15** and **18** with an aryl bromide, 5 mol% $Pd(OAc)_2$, 10 mol% DPEPhos

and caesium carbonate in dioxane at 105 ^{o}C gave the required spiro-fused piperidines **16**,**19** and **20** with moderate to good diastereoselectivity. We found that protection of the alcohol was necessary as aminoarylation with the corresponding alcohols **14** and **17** failed to yield any cyclised product and instead gave a complex mixture of products. The configuration of the major diastereomer of **16** was determined by observation of a diagnostic NOESY correlation (Figure 2). The stereochemical outcome is consistent with cyclisation *via* a conformation in which the benzyloxy group is equatorial, with the developing exocyclic substituent equatorial on the forming ring. Given the limited literature prognosis for the cyclisation of *N*-Boc-hex-5-enylamines *via* aminoarylation, we envisaged that the success of this cyclisation may be, in part, due to the Thorpe–Ingold effect.[34] In order to determine if the geminal disubstitution of the chain was key for cyclisation, we investigated the aminoarylation of *N*-Boc ahex-5-en-1-ylamine (i.e. a model unsubstituted compound) under identical reaction conditions; no reaction was observed, suggesting that the Thorpe–Ingold effect is significant for the successful synthesis of *N*-Boc piperidines **16**, **19** and **20** with aminoarylation cyclisations

Synthesis of other spirocyclic scaffolds

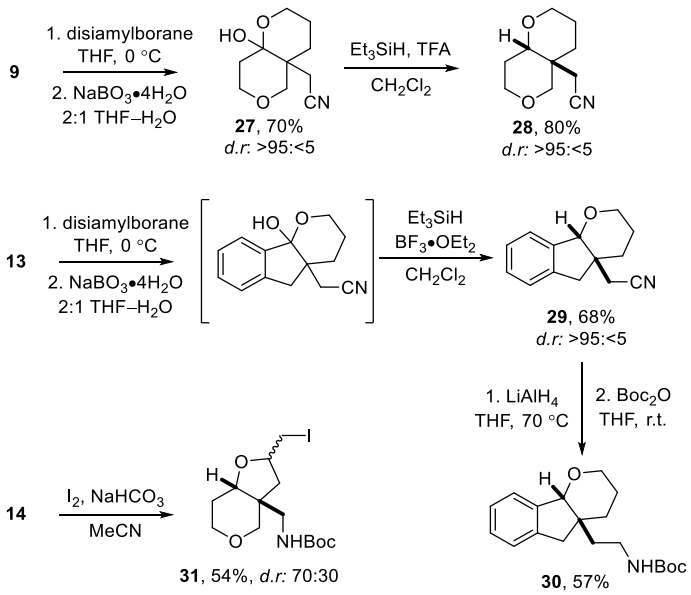


Scheme 4: Synthesis of other spirocyclic scaffolds

Alternative cyclisation chemistries of these polyfunctional molecules facilitate the synthesis of different spirocyclic scaffolds from the cyclisation precursors **9** and **13** (Scheme 4). Treatment of the alcohols **14** and **17** with acetic anhydride in pyridine gave the corresponding acetylated derivatives **21** and **24** in excellent yield. Lemieux–Johnson oxidative cleavage[35] of the alkenes **21** and **24** gave, after cyclisation, the hemiaminal intermediates, which after reaction with $NaBH(OAc)_3$ in acetic acid, gave the spirocyclic amines **22** and **25**. Alternatively, oxidation of the hemiaminal intermediate with PDC gave the spirocyclic lactams **23** and **26**.

Synthesis of fused scaffolds

We also investigated the synthesis of a range of fused ring systems by linking the ketone and the alkene in the precursors **9** and **13** (Scheme 5). Treatment of **9** with disiamylborane, and then sodium perborate, gave the hemiacetal **27** as a single diastereomer.[26] Reduction of the hemiacetal **27**, by treatment with Et_3SiH and TFA, gave the fused scaffold **28** as a single diastereomer in excellent yield. The configuration of the *cis*-fused bicycle **28** was determined by observation of a diagnostic NOESY correlation (Figure 3). The high diastereoselectivity of the reduction may be explained in terms of attack of the reducing agent from the *exo* face of the intermediate bicyclic oxocarbenium ion. In a similar vein, hydroboration-oxidation of **13**, and reduction of the resulting hemiacetal, gave the corresponding scaffold **29** as a single diastereomer (68% yield over 2 steps). $LiAlH_4$ reduction of **29**, followed by Boc protection, gave the building block **30** in 57% yield. Alternatively, treatment of **14** with iodine and sodium bicarbonate in acetonitrile gave the corresponding fused scaffold **31** as a 70:30 mixture of diastereomers in 54% yield.



Scheme 5: Synthesis of fused molecular scaffolds

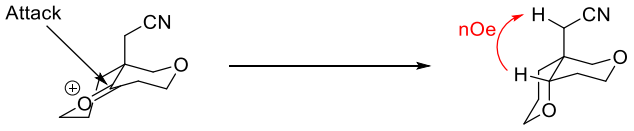
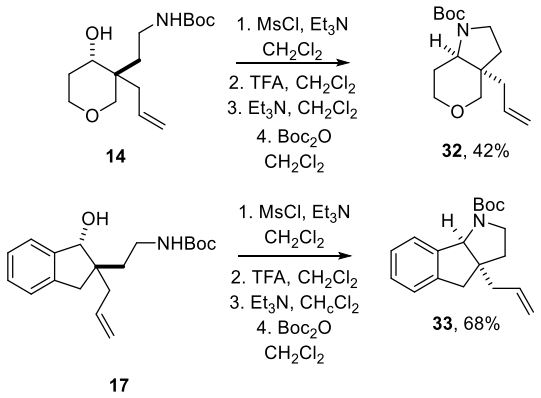


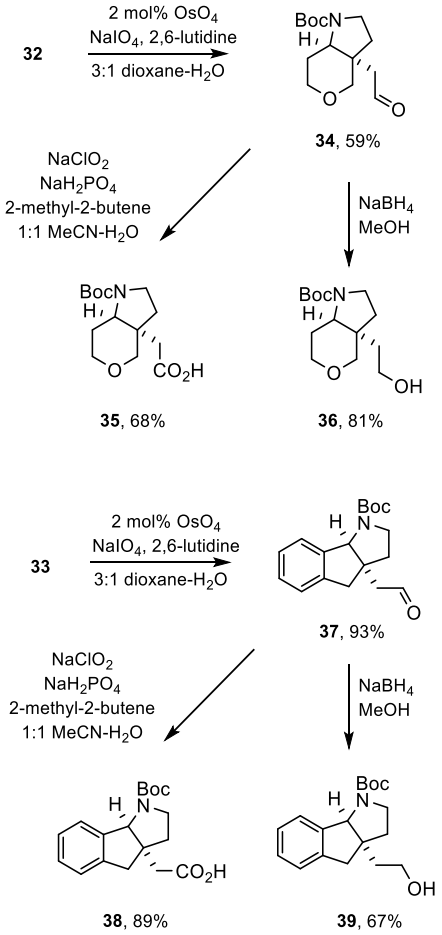
Figure 3: Stereochemical outcome of the reduction of an oxocarbenium ion intermediate



Scheme 6: Synthesis of fused ring pyrrolidines

We envisaged that alternative fused scaffolds might be prepared *via* intramolecular substitution. Thus, mesylation of the alcohols **14** and **17** was followed by Boc deprotection and triethylamine-induced cyclisation; Boc reprotection gave the fused pyrrolidines **32** and **33** in moderate to good yield over 4 steps (Scheme 6). The successful outcome of this cyclisation also validates the previous stereochemical assignment of the corresponding alcohols **14** and **17** as the alternative diastereomer would likely not cyclise efficiently due to strain in *trans*-fused pyrrolidines.

We demonstrated that the allyl substituents in the fused pyrrolidines **32** and **33** could be converted into more useful functional groups for subsequent elaboration (Scheme 7). Thus, Lemieux–Johnson oxidative cleavage[35] gave the corresponding aldehydes **34** and **37**. Subsequent Pinnick oxidation[36] ($NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, 1:1 MeCN–H_2O, rt) of the aldehydes **34** and **37** gave the corresponding carboxylic acids **35** and **38**. Alternatively, reduction of the aldehydes **34** and **37** by treatment with sodium borohydride gave the corresponding primary alcohols **36** and **39**.



Scheme 7: Conversion of the scaffolds **32** and **33** into carboxylic acid and alcohol derivatives

Analysis of potential value in drug discovery applications

The molecular properties and shape diversity of the final library of 16 scaffolds were analysed using LLAMA (Lead-Likeness And Molecular Analysis; www.llama.leeds.ac.uk), a computational tool developed to analyse libraries derived from scaffolds.[37] The 16 synthesised (unprotected) scaffolds were decorated virtually with either one or two capping groups (Figure 4). The undecorated scaffolds library generally had molecular properties that were appropriate for application as fragments in fragment-based lead discovery (i.e. 140 < *MW* < 300; *c*logP < 2) (Figure 5, Panel A).[19] Crucially, none of the Murcko frameworks[38] of the scaffolds were found as substructures in a random 2% sample of the ZINC database[39] of commercially-available compounds. Furthermore, the scaffolds had significant shape diversity and three-dimensionality.[40]

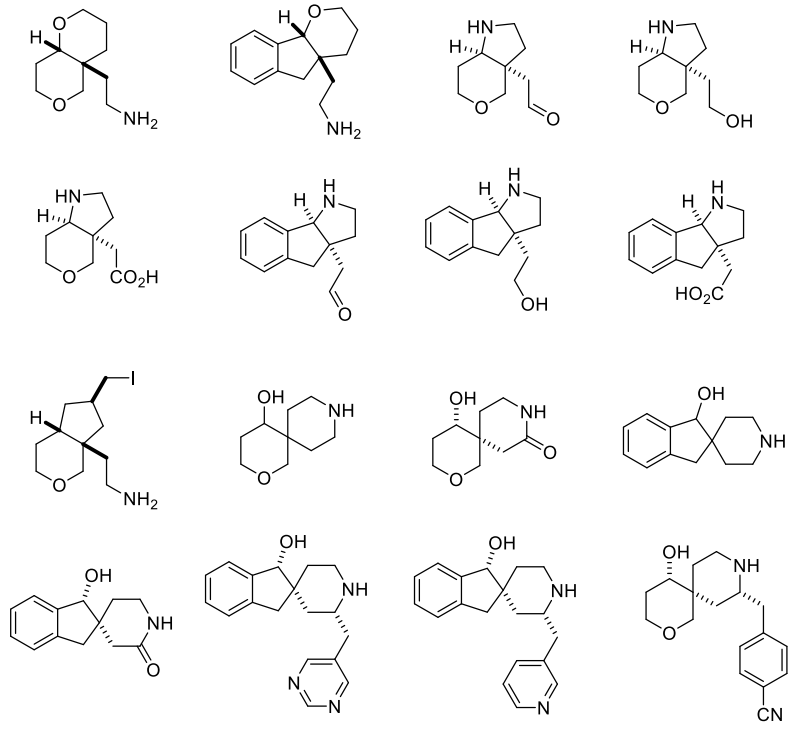
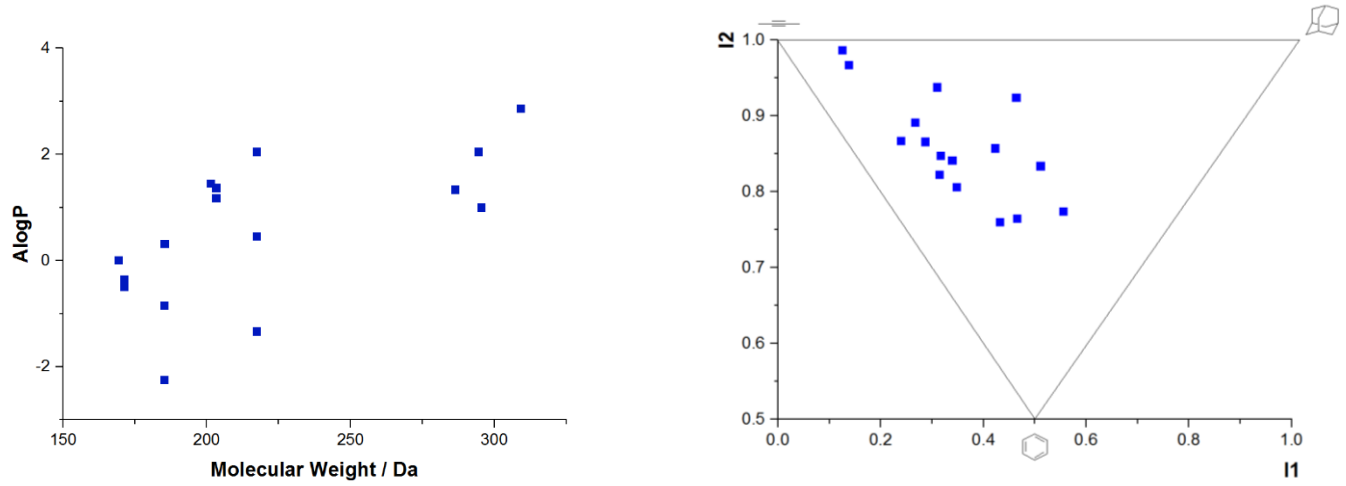


Figure 4: Scaffolds used for the computational analysis using LLAMA

A



B

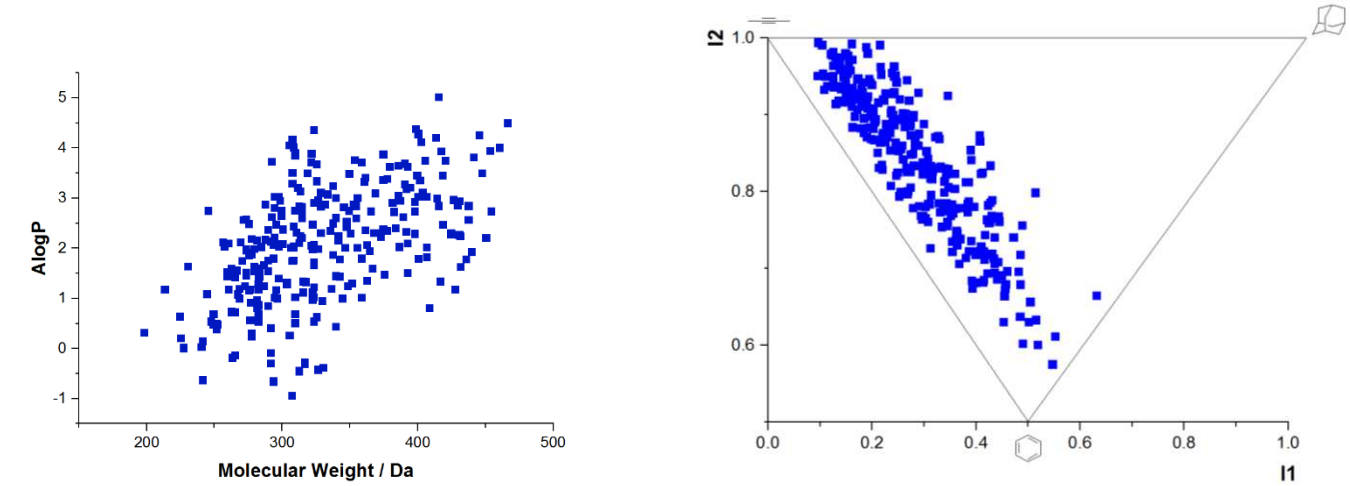


Figure 5: Molecular properties and shape diversity of scaffolds (Figure 4) and derivatives. Panel A: Undecorated scaffolds. Panel B: Compounds obtained by virtual decoration of the scaffolds with one capping group.

Decoration of the scaffolds using a selection of medicinally-relevant capping groups was also undertaken to enable an assessment of lead-likeness (Figure 5, Panel B). Firstly, the lead-likeness of the virtual scaffold library was analysed and it was found that about 60% of the decorated compounds lie in lead-like chemical space. Secondly, a PMI plot of the decorated scaffolds was generated, which confirmed that many of these lead-like compounds also showed significant shape diversity. The fraction of sp^3-hybridised carbons (Fsp^3) in the decorated scaffolds was also analysed, as previously it was shown that compounds with more Fsp^3 character correlates strongly with success in drug discovery.[3] This has led to the recent drive for the efficient preparation more three-dimensional lead-like

compounds. The mean Fsp^3 of the decorated scaffold library was found to be 0.58 which shows significantly higher Fsp^3 in comparison with a random sample from the ZINC database (0.33), thus highlighting the success of our synthetic approach in preparing decorated scaffold libraries with higher Fsp^3 than most commercially available compounds.

Conclusion

In conclusion, we have successfully demonstrated a highly modular synthetic approach to prepare sixteen diverse three-dimensional scaffolds. Our approach involved the synthesis of cyclisation precursor compounds that contained a range of reaction handles that could be reacted together to prepare the diverse scaffold library. We were able to successfully develop and utilise a toolkit of cyclisation reactions to prepare range of spirocyclic and fused-ring scaffolds from just two precursor compounds. This scaffold library, through computational analysis, has been shown to have ideal molecular and chemical properties needed for both fragment elaboration and lead-like scaffold synthesis.

Acknowledgments

We thank Redbrick Molecular and EPSRC (EP/N025652/1) for funding, and Andy Hogben for useful discussions.

References

1. D. Foley, A. Nelson and S. P. Marsden, *Angew. Chem. Int. Ed.*, 2016, **55**, 13650-13657.
2. W.P. Walters, J. Green, J.R. Weiss, and M. A. Murcko, *J. Med. Chem*. 2011, **54**, 6405-6416.
3. F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.,* 2009, **52**, 6752-6756.
4. D. A. Smith, B. C. Jones, D. K. Walker, *Med. Res. Rev.* 1996, **16**, 243−266.
5. J. Kettle and D. Wilson, *Drug Discovery Today*, 2016, **21**, 1596-1608.
6. S. D. Roughley and A. M. Jordan, *J. Med. Chem.,* 2011, **54**, 3451-3479.
7. J. Boström, D. Brown, R. Young and G. Keserü, *Nat. Rev. Drug. Discov*., 2018, **17**, 709-727.
8. D. Brown and J. Boström, *J. Med. Chem.*, 2015, **59**, 4443-4458.
9. A. Nadin, C. Hattotuwagama and I. Churcher, *Angew. Chem. Int. Ed.*, 2012, **51**, 1114-1122.

10. (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**, 2680-2694. (b) A. V. Borisov A.V., Voloshchuk V.V., Nechayev M.A. and Grygorenko O.O., *Synthesis*, 2013, **45**, 2413-2416. (c) Ryabukhin S.V., Panov D.M., Granat D.S., Ostapchuk E.N., Kryvoruchko D.V. and Grygorenko O.O., *ACS Comb. Sci.*, 2014, **163**, 146-153. (d) Chambers S.J., Coulthard G., Unsworth W.P., O'Brien P. and Taylor R.J.K., *Chem. Eur. J*, 2016, **22**, 6496-6500.
11. 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**, 15227-15232.
12. J. D. Firth, P. G. E. Craven, M. Lilburn, A. Pahl, S. P. Marsden and A. Nelson, *Chem. Commun.*, **52**, 9837-9840.
13. R. Doveston, P. Tosatti, M. Dow, D. Foley, H. Li, A. Campbell, D. House, I. Churcher, S. P. Marsden and A. Nelson, *Org. Biomol. Chem.*, 2015, **13**, 859-865.
14. D. Foley, R. Doveston, I. Churcher, A. Nelson and S. P. Marsden, *Chem. Commun.*, 2015, **51**, 11174-11177.
15. T. James, P. MacLellan, G. Burslem, I. Simpson, J. Grant, S. Warriner, V. Sridharan and A. Nelson, *Org. Biomol. Chem.*, 2014, **12**, 2584-2591.
16. T. James, I. Simpson, J. Grant, V. Sridharan and A. Nelson, *Org. Lett.*, 2013, **15**, 6094-6097.
17. R. Morgentin, M. Dow, A. Aimon, G. Karageorgis, T. Kalliokoski, D. Roche, S. P. Marsden and A. Nelson, *Drug Discovery Today*, 2018, **23**, 1578-1583.
18. A. Karawajczyk, F. Giordanetto, J. Benningshof, D. Hamza, T. Kalliokoski, K. Pouwer, R. Morgentin, A. Nelson, G. Müller, A. Piechot and D. Tzalis, *Drug Discovery Today*, 2015, **20**, 1310-1316.
19. N. Palmer, T. M. Peakman, D. Norton and D. C. Rees, *Org. Biomol. Chem.*, 2016, **14**, 1599-1610.
20. S. Haftchenary, S. D. Nelson Jr., L. Furst, S. Dandapani, S. J. Ferrara, Ž. V. Bošković, S. F. Lazú, A. M. Guerrero, J. C. Serrano, D. K. Crews, C. Brackeen, J. Mowat, T. Brumby, M. Bauser, S. L. Schreiber and A. J. Phillips, *ACS Comb. Sci.,* 2016, **18**, 569-574.
21. F. K. Morgan, I. A. Hollingsworth, J. A. Bull, *Chem. Commun.*, 2014, **50**, 5203-5205.
22. J. D. Firth, P. G. E. Craven, M. Lilburn, A. Pahl, S. P. Marsden and A. Nelson, *Chem. Commun.*, **52**, 9837-9840.

23. D. Twigg, N. Kondo, S. Mitchell, W. Galloway, H. Sore, A. Madin and D. Spring, *Angew. Chem. Int. Ed.*, 2016, **55**, 12479-12483.
24. A. Hung, A. Ramek, Y. Wang, T. Kaya, J. Wilson, P. Clemons and D. Young, *Proc. Natl. Acad. Sci. USA*, 2011, **108**, 6799-6804.
25. O. Davis, R. Croft and J. Bull, *Chem. Commun.*, 2015, **51**, 15446-15449.
26. J. Mayol-Llinas, W. Farnaby and A. Nelson., *Chem. Commun.*, 2017, **53**, 12345-12348.
27. T. Moss, B. Alonso, D. Fenwick and D. Dixon, *Angew. Chem. Int. Ed.*, 2009, **49**, 568-571.
28. Y. Numajiri, B. P. Pitchett, K. Chiyoda and B. M. Stoltz, *J. Am. Chem. Soc.*, 2015, **137**, 1040-1043.
29. J. Wolfe and D. Schultz, *Synthesis*, 2012, **44**, 351-361.
30. M. Bertrand and J. Wolfe, *Tetrahedron*, 2005, **61**, 6447-6459.
31. D. Mai and J. Wolfe, *J. Am. Chem. Soc.*, 2010, **132**, 12157-12159.
32. P. Craven, A. Aimon, M. Dow, N. Fleury-Bregeot, R. Guilleux, R. Morgentin, D. Roche, T. Kalliokoski, R. Foster, S. P. Marsden and A. Nelson, *Bioorg. Med. Chem.*, 2015, **23**, 2629-2635.
33. T. Jepsen, M. Larsen and M. Nielsen, *Tetrahedron*, 2010, **66**, 6133-6137.
34. M. E. Jung and G. Piizzi, *Chem. Rev.*, 2005, **105**, 1735–1766.
35. W. Yu, Y. Mei, Y. Kang, Z. Hua, and Z. Jin, *Org. Lett.*, 2004, **6**, 3217-3219.
36. B.S. Bal, W.E. Childers Jr, H.W Pinnick, *Tetrahedron*, 1981, **37**, 2091-2096.
37. I. Colomer, C. Empson, P. Craven, Z. Owen, R. Doveston, I. Churcher, S.P. Marsden and A. Nelson, *Chem. Commun.*, 2016, **52**, 7209-7212.
38. G. Bemis and M. Murcko, *J. Med. Chem.*, 1996, **39**, 2887-2893.
39. J.J. Irwin, T. Sterling, M.M. Mysinger, E.S. Bolstad, R.G. Coleman, *J. Chem. Inf. Model.*, 2012, **52**, 1757-1768.
40. J. Meyers, M. Carter, N. Mok and N. Brown, *Future Med. Chem.*, 2016, **8**, 1753-1767.