KEYNOTE (GREEN)

Escape from planarity in fragment-based drug discovery: A synthetic strategy analysis of synthetic 3D fragment libraries

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In fragment-based drug discovery (FBDD), there is a developing appreciation that 3D fragments could offer opportunities that are not provided by 2D fragments. This review provides an overview of the synthetic strategies that have been used to prepare 3D fragments, as discussed in 25 papers published from 2011 to mid-May 2020. Three distinct strategies are highlighted: (i) diversity-oriented synthesis; (ii) the synthesis and diversification of scaffolds; and (iii) computational design and synthesis (where 3D fragments were computationally enumerated and filtered on the basis of computationally generated 3D shape descriptors and other properties). We conclude that a workflow that combines computational design and one other strategy, together with a consideration of fragment properties, 3D shape and 'fragment sociability', could allow 3D fragments to feature more widely in fragment libraries and could facilitate fragment-to-lead optimisation.

Keywords: Fragment-based drug discovery; 3D; Fragment; Library; Synthesis

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Introduction

Fragment-based drug discovery (FBDD) is routinely employed in the toolkit of available methods for drug discovery.[1–4] To date, FBDD efforts have led to the approval of six drugs by the US Food & Drugs Administration (FDA) and to numerous clinical candidates.[5–13] One key factor in FBDD is the fragment library itself. The fragments within these libraries are designed to be of low complexity,[14] and their physicochemical properties typically follow the 'rule-of-three' (RO3) guidelines.[15] Historically, fragment libraries were dominated by sp^2-rich, planar, (hetero)aromatic, 2D fragments.[16] However, the landscape is changing and there is growing interest in, and justification for, the inclusion of 3D fragments in fragment libraries because they expand chemical space coverage and improve library diversity.[17,18] Although not directly concerned with 3D fragments, the papers on 'Escape from Flatland' by Lovering *et al.*[19,20] can be considered as a catalyst for activity in the general area of 3D fragments.[21] There are potential pros and cons associated with the use of 3D fragments. For example, the increased complexity of fragments may lead to lower hit rates.[14,22] Furthermore, there are challenges in the elaboration of 3D fragments to lead compounds, although recently developed synthetic methodology may provide opportunities.[23] By contrast, 3D fragments can offer better solubility than 2D fragments[24] and may be better starting points for challenging targets,[25,26] and they may also offer selectivity opportunities.[27]

In recent years, the FBDD community has issued a 'call to arms' to synthetic chemists in industry and academia to develop synthetic methods that will allow the efficient elaboration of a fragment hit to a lead compound, especially in 3D.[28–31] This has led to significant activity in the design and synthesis of 3D fragments. Less effort has been expended specifically in addressing the fragment-to-lead stage of the FBDD process, and Rees and co-workers[29] have recently coined the phrase 'fragment sociability' to define the growth vector suitability of fragments for evolution into a lead compound. The purpose of this review article is to summarise the synthetic strategies that have been used to prepare 3D fragments, as described in 25 recently published papers, and to provide some structural information on the wide range of 3D fragments that feature in synthetic 3D fragment libraries.[32–56] The review is separated into the three distinct strategies that have been utilised: (i) diversity-oriented synthesis (DOS); (ii) synthesis and diversification of scaffolds; and (iii) computational design and synthesis. Where appropriate, we consider the suitability of the synthetic methodology for fragment-to-lead generation. The key physicochemical parameters and a comparative 3D shape analysis of the 3D fragments generated from these synthetic studies are provided in our recently published companion article (covering the same 25 papers).[57]

Approach

For our analysis of synthetic strategies, we selected 25 recent publications, most of which are from the period 2015 to mid-May 2020, and all of which disclose organic molecules as fragments. The papers include the terms 'sp^3-rich fragment', 'shape-diverse fragment' or '3D fragment', or a variation thereof. The selected articles, the involved scaffolds, the key features and the synthetic strategies are summarised in Table 1 (where scaffolds highlighted in blue represent specific examples as there are so many different scaffolds in those papers that not all can be included).[32–56] Occasionally, the number of fragments listed in Table 1 differs from the total in the paper because of the selection criteria that were utilised in our analysis. Full details on the selection criteria, the identification of each synthesised 3D fragment structure, and the associated scaffold definition are provided in the accompanying properties article[57] and thus are not reproduced here. The synthetic chemistry utilised in the 25 publications can be separated into three main synthetic strategies: (i) diversity-oriented synthesis (DOS), in which a DOS approach was utilised and significant scaffold diversity was observed in the so-generated 3D fragments (Table 1, entries 1, 4, 8, 14, 17–20 and 24); (ii) synthesis and diversification of scaffolds, in which specific scaffolds were targeted with a particular piece of methodology and scaffolds were subsequently diversified using standard chemistry to generate a range of 3D fragments (Table 1, entries 2, 3, 5–7, 9, 11–13, 15, 21 and 23); and (iii) computational design and synthesis, in which 3D fragments were computationally enumerated and filtered in order to select specific 3D fragments for synthesis (Table 1, entries 10, 16 and 22). Exemplar structures of synthesised 3D fragments are provided in Figs. 1–4.

Strategies for the synthesis of 3D fragments

Strategy 1: Diversity-oriented synthesis

DOS, a synthetic strategy pioneered by Schreiber's group,[58] is defined as "a problem-solving technique for transforming a collection of simple and similar starting materials into a collection of more complex and diverse products".[59] As a synthetic approach, DOS provides a method for the exploration of structurally diverse chemical space and it can provide opportunities for the synthesis of compound libraries for drug discovery.[60] The structural diversity engendered by DOS can include skeletal, regiochemical, stereochemical and functional group appendage variations, which are typically incorporated by utilising a common synthetic route. The DOS approach has been used by a number of groups for the synthesis of 3D fragments (Table 1, entries 1, 4, 8, 14, 17–20 and 24; Fig. 1).

The Young group were the first to realise the potential of a DOS strategy for the generation of a 3D fragment collection, and they reported their first efforts in this area in 2011.[32] Utilising three common building blocks, which included pyrrolidines **1** and **2**, a build, couple and pair DOS approach was deployed to produce 35 3D fragments that all adhered to the RO3 (Fig. 1A, Young 1). Structural diversity was ensured by the use of different *N*-functionalisation approaches (e.g. sulphonamide/amide formation) together with ring-closing metathesis as the cyclisation methodology (with metathesis handles in different positions relative to each other). This afforded a series of 5–6, 5–7, 5–8 and 5–9 fused bicyclic and spirocyclic 3D fragments, such as **3** and **4**. The *trans*-diastereomer of **1** and the enantiomers of **1** and **2** were used to provide stereochemical diversity. Finally, in a stage termed the 'postpairing phase', some functional group interconversions, including ester hydrolysis and alkene hydrogenation, were

TABLE 1

Representative examples or generalised scaffold structures of the 3D fragment libraries analysed in this review, with the appropriate synthetic strategy (diversity-oriented synthesis, scaffold diversification or computational design).

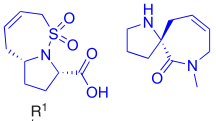
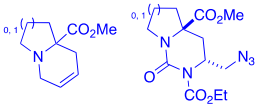
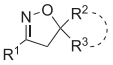
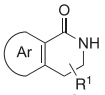
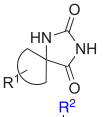
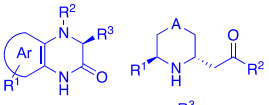
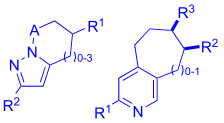
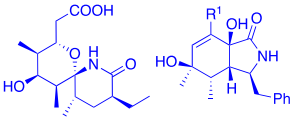
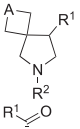
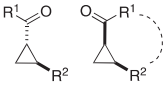
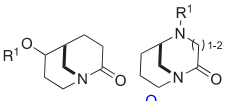
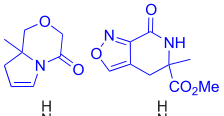
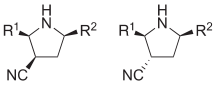
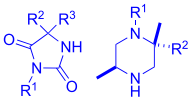
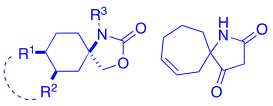
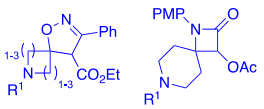
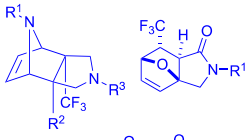
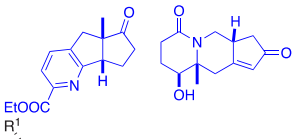
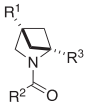
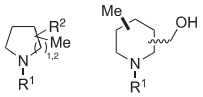
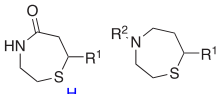
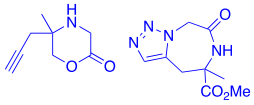
Entry	Research group[a]	Description[b]	(Exemplary) scaffold(s)[c]	Number of fragments[d] (and scaffolds)[e]	Synthetic strategy[f]
1	Young (Young 1)[32]	Spiro-/bicyclic pyrrolidines		44 (10)	Diversity-oriented synthesis
2	Bull (Bull 1)[33]	*N*-arylated 2-imidazolines		21 (1)	Scaffold diversification
3	Bull (Bull 2 and 3)[34,35]	2-(aryl-sulfonyl)oxetanes		16 and 24 (1 and 1)	Scaffold diversification
4	Nelson and Marsden (Nelson 1)[36]	Mono-/bi-/tricyclic heteroaliphatic rings		22 (22)	Diversity-oriented synthesis
5	Willand (Willand 1)[37]	2-isoxazolines		21 (7)	Scaffold diversification
6	Rees[38]	Dihydroisoquinolones		26 (4)	Scaffold diversification
7	Willand[g] (Willand 2)[39]	Spirohydantoins		25 (11)	Scaffold diversification
8	Young and Hung (Young 2)[40]	Substituted (bicyclic) heterocycles		86 (23)	Diversity-oriented synthesis
9	Spring (Spring 1)[41]	Partially saturated bicyclic heteroaromatics		43 (13)	Scaffold diversification
10	Lizos[42]	Natural product-like fragments		15 (6)	Computational design
11	Mykhailiuk[43]	Spiro-/bicyclic heterocycles		44 (4)	Scaffold diversification
12	Bull (Bull 4)[44]	Substituted cyclopropanes		50 (2)	Scaffold diversification
13	Nelson and Marsden (Nelson 2)[45]	Twisted bicyclic lactams		22 (3)	Scaffold diversification
14	Spring and Mateu (Spring 2)[46]	Bi-/spirocyclic heterocycles with quaternary carbon atoms		40 (27)	Diversity-oriented synthesis
15	Garner and Cox[47]	Trisubstituted pyrrolidines		24 (1)	Scaffold diversification
16	Bayliss, Warriner, Nelson[h] (Nelson 3)[48]	Polysubstituted heterocycles		20 (5)	Computational design
17	Spring and Mateu (Spring 3)[49]	Substituted spirocycles		30 (10)	Diversity-oriented synthesis

TABLE 1 (*CONTINUED*)

Entry	Research group[a]	Description[b]	(Exemplary) scaffold(s)[c]	Number of fragments[d] (and scaffolds)[e]	Synthetic strategy[f]
18	Spring (Spring 4)[50]	Heterocyclic spirocycles		9 (9)	Diversity-oriented synthesis
19	Clausen[i,51]	Fluorinated fragments		102 (33)	Diversity-oriented synthesis
20	Spring (Spring 5)[52]	Natural product-inspired fragments		38 (20)	Diversity-oriented synthesis
21	Cox and Cox (Cox)[53]	Bridged pyrrolidines		56 (1)	Scaffold diversification
22	O'Brien[54]	Pyrrolidines and piperidines		56 (2)	Computational design
23	Pomerantz[55]	1,4-thiazepan(on)es		32 (2)	Scaffold diversification
24	Spring (Spring 6)[56]	(Fused) heterocycles with quaternary carbon atoms		40 (4)	Diversity-oriented synthesis

[a]For clarity, the research groups are referred to by the corresponding author(s)/group leader. If multiple publications arise from the same group, they are numbered according to their publication date and this notation (in brackets) is used in the figures. [b]General description of the scaffold(s). [c]Structures of the disclosed scaffold(s). Where possible, all scaffolds were generalised into one structure (black). In cases where all scaffolds cannot be summarised, the structures that are shown are exemplary and coloured blue. IUPAC rules for depicting relative and absolute stereochemistry were followed. [d]Number of fragments disclosed; for cases in which mixtures of diastereomers are present, both compounds are included. [e]Number of distinct scaffolds comprising the fragment library, according to the rules described in the main text. [f]Synthetic strategy is defined in the main text. [g]Two compounds are omitted from our data set for Willand 2 (entry 7) as conformations for compounds **2 g** and **2 h** could not be generated from the publication. [h]Purchased compounds for Nelson 3 (entry 16) are not included in this review. [i]Only compounds that passed the authors' quality controls are included for Clausen (entry 19).

carried out in order to expand the functional group diversity of the library (Fig. 1A, exemplar 3D fragments).

A related DOS strategy, which included a wider range of creatively conceived cyclisation modes, was described by Nelson, Marsden and co-workers in 2015.[36] Although these workers set out to provide a systematic entry to structurally diverse lead-like scaffolds, the synthesised compounds clearly fit into the RO3 and 3D fragment space, and thus are included in this review article. Thus, starting from trifunctionalised saturated heterocycles exemplified by azetidine **5** and pyrrolidine **6**, *N*-functionalisation and different cyclisation reactions were used to generate 3D fragments such as **7** (via a Heck reaction) and **8** (via iodine-mediated cyclisation and azide displacement of the iodide) (Fig. 1B, Nelson 1). Other cyclisation modes, such as hydantoin or lactam formation and ring-closing metathesis, have been implemented. The study also included two other amino acid derivatives, a piperazine and an acyclic system, which ultimately delivered a set of 22 different scaffolds (Fig. 1B, exemplar 3D fragments).

To further showcase the utility of DOS in 3D fragment synthesis, Young and colleagues reported the use of a DOS approach to generate three different classes of 3D fragments, and highlighted the potential of the DOS method for facilitating the elaboration of 3D fragments to form more potent compounds.[40] The 3D fragment member library comprised a total of 86 5–6, 5–7, 5–8 and 5–9 fused bicyclic and spirocyclic 3D fragments (from their earlier work,[32] Fig. 1A), a set of 2,6-disubstituted piperazine 3D fragments (whose synthesis was subsequently reported in full[61]), and benzofused piperazinone 3D fragments such as **10** (Fig. 1C, Young 2). In each case, the build, couple and pair DOS approach was employed. For example, starting from the S_NAr-enabled nitro-substituted pyridinyl fluoride **9**, S_NAr with an amino ester and subsequent nitro reduction and lactamization delivered piperazinone **10** and other exemplar fragments (Fig. 1C). The 3D piperazinone fragments showed up as hits in fragment screening against glycogen synthase kinase β3 (GSK β3); the subsequent elaboration follow-up work to produce a high-affinity binding compound was straightforward due to the simplicity and versatility of this DOS approach.

The Spring group has been very active in applying DOS methodology to the construction of 3D fragment libraries and have introduced several clever approaches to generate a wide range of diverse scaffolds (Fig. 1D and 1F–H, Spring 2–6).[46,49,50,52,56] Their first contribution, which was published in 2018, focused on a DOS approach to a 40-member library of *N*-substituted quaternary carbon-containing 3D fragments.[46] The

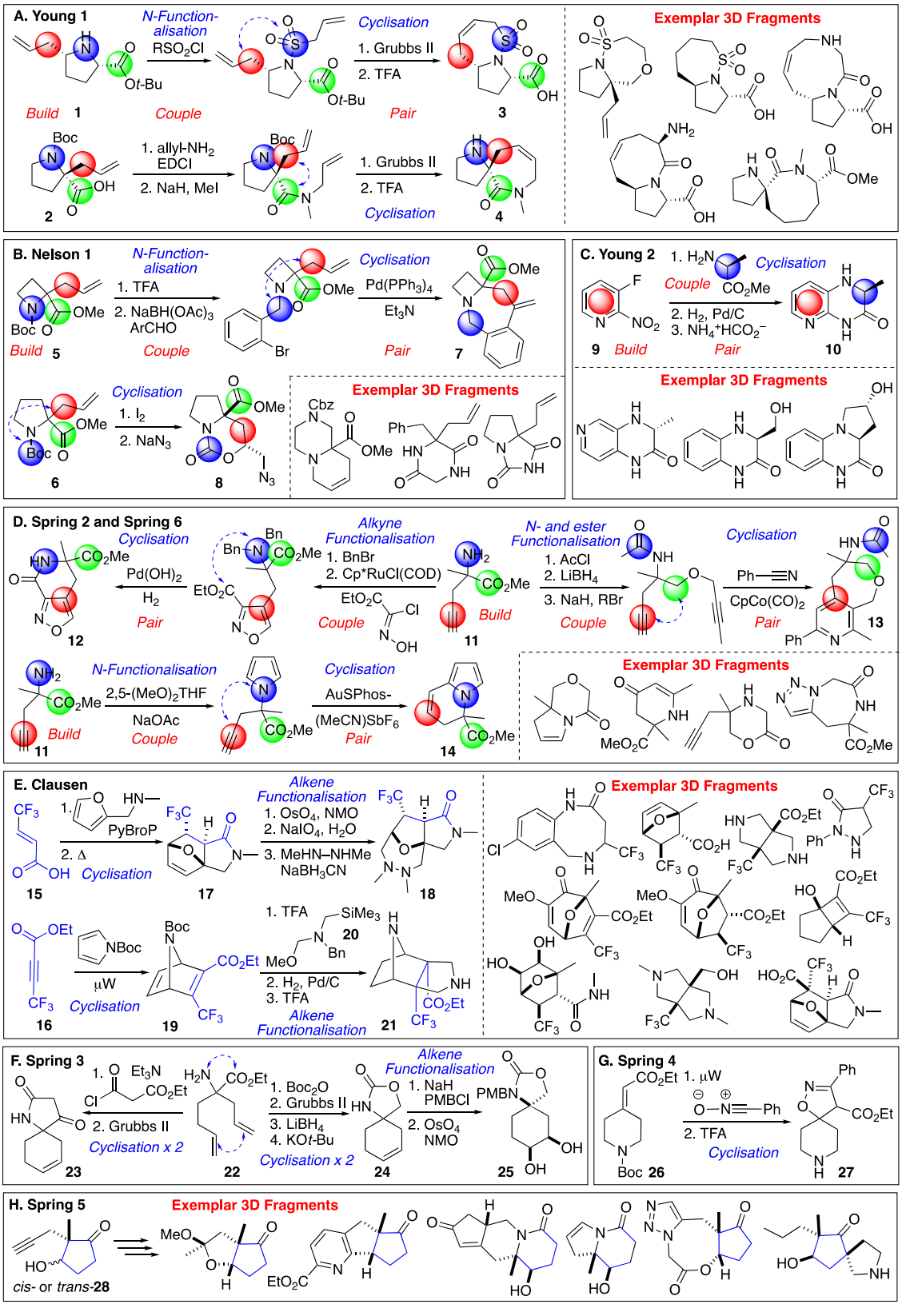


FIGURE 1
Synthesis of 3D fragments using diversity-oriented synthesis (DOS).

DOS build, couple and pair approach utilised a wide array of reactions and delivered 27 different scaffolds from just one starting material, α-methyl-α-propargyl amino ester **11** (Fig. 1D, Spring 2). For example, *N*-dibenzylation of trifunctionalised amino ester **11**, subsequent Ru-mediated cycloaddition of a chloro-oxime, and debenzylation/lactamization generated 3D fragment **12**. Alternatively, *N*-acylation, ester functionalisation and a co-induced [2 + 2 + 2] cyclotrimerisation with benzonitrile delivered **13**. In another DOS sequence, *N*-functionalisation of **11** was accomplished using a Paal-Knorr pyrrole synthesis from which Au-catalysed cyclisation afforded 3D fragment **14**. This DOS approach delivered 40 structurally diverse 3D fragments (Fig. 1D, exemplar 3D fragments). This 40-member 3D fragment library is available at the Diamond XChem X-ray crystallographic screening facility. To highlight this opportunity, Spring and co-workers recently reported the X-ray crystallographic screening of these 40 DOS-derived 3D fragments against three different protein targets (*P. aeruginosa* Penicillin Binding Protein 3 (PBP3), CFI_{25} and Activan A).[56] At least one X-ray-characterised hit was identified for each protein and, in each case, the rapid generation of 10–14 new, structure-guided, elaborated fragment analogues was possible. This produced an additional library of 38 3D fragments, and the modular nature of the synthetic work that underpinned the initial DOS library meant that fragment elaboration was quick and straightforward.

In 2020, Clausen and co-workers disclosed a DOS approach to generate 115 trifluoromethyl-containing, natural product-like 3D fragments, 'The 3F Library', which were designed for structural diversity and to facilitate rapid ^{19}F-based NMR spectroscopic screening (Fig. 1E, Clausen).[51] This library is the most extensive published collection of 3D fragments that has been deliberately designed and synthesised to date. Starting from six trifluoromethylated α,β-unsaturated esters or acids such as **15** and **16**, cycloaddition and Michael addition-initiated cyclisations were used to construct nine distinct 3D scaffolds. From there, a range of subsequent functionalisations, such as hydrogenation, further cycloaddition and alkene oxidation/cleavage, was used to generate the 115 3D fragments which, impressively, covered 67 distinct frameworks (Fig. 1E, exemplar 3D fragments). The two syntheses depicted in Fig. 1E are illustrative. Amide formation of α,β-unsaturated acid **15** with a furfuryl amine and subsequent intramolecular Diels-Alder reaction gave **17**, which was oxidatively derivatised to hydrazine **18** (after double reductive amination). An intermolecular Diels-Alder reaction between alkyne ester **16** and *N*-Boc pyrrole gave **19**, which underwent a [3 + 2] cycloaddition with an azomethine ylide generated from **20** and *N*-deprotections to deliver **21**. The 115-member 3D fragment library was constructed using related transformations. Of note, 102 fragments passed quality control (QC) analysis and were screened against four proteins (p70S6K1, p38, BACE1 and DC-SIGN) by ^{19}F NMR spectroscopy to give 30 hits. This is a particularly encouraging hit rate of 3–11% for each protein. Of note, eight of the nine scaffold classes featured in these hits, and most hits were validated by a second assay.

Spring and co-workers have reported the synthesis of 3D fragments that contain a rigid spirocyclic scaffold motif (Fig. 1F,G, Spring 3–4).[49,50] Two different DOS strategies were utilised in constructing the 3D fragments. One approach started with dialkene-containing amino esters such as **22** and used different amino-ester cyclisation modes in tandem with ring-closing metathesis.[49] For example, decarboxylative Dieckmann cyclisation of **22** and subsequent ring-closing metathesis produced spirocyclic lactam **23**. By contrast, starting from **22**, ring-closing metathesis, reduction and carbamate formation gave **24**; subsequent *N*-protection and alkene dihydroxylation delivered **25** (Fig. 1F). Ultimately, using different tether lengths to attach the alkene and other alkene functionalisation reactions, 28 3D spirocyclic fragments (with 5–5, 5–6, 6–6, 5–7 ring systems) were generated using this DOS approach. The other approach to spirocyclic 3D fragments developed in the Spring group used [3 + 2] cycloadditions.[50] As a representative example, the cycloaddition of nitrile oxides with heterocyclic α,β-unsaturated esters **26** generated isoxazole 3D fragment **27** after Boc removal. A few other examples were reported and nine distinct 3D fragments were produced. As was the case for Clausen's 3D fragment library, natural product-likeness was the inspiration behind a 3D fragment library designed and synthesised by Spring and co-workers (Fig. 1H, Spring 5).[52] The DOS approach utilised a range of cyclisation modes starting from diastereomeric trifunctional propargyl ketones *cis*- or *trans*-**28**, and produced a library of 38 3D fragments (20 distinct frameworks, containing bicyclic and tricyclic fused systems as well as spirocycles) (Fig. 1H, exemplar 3D fragments).

Strategy 2: Synthesis and diversification of scaffolds

The use of a particular synthetic methodology to construct specific scaffolds and, typically, subsequent functional group diversification has been widely exploited for the synthesis of 3D fragments (Table 1, entries 2, 3, 5–7, 9, 11–13, 15, 21 and 23; Figs. 2 and 3). Cycloaddition reactions have been particularly popular for 3D fragment synthesis because they generate rigid cyclic scaffolds and they can be carried out in a modular fashion. Furthermore, such reactions often generate sp^3 stereocentres and increase complexity, starting from much simpler, accessible materials. Nevertheless, other bespoke synthetic methodologies have been applied to the synthesis of 3D fragment libraries and these are collected together below as 'miscellaneous' methodologies. An attractive feature of the synthesis and diversification of scaffolds approach is that, because the scaffolds are based on a specific synthetic methodology, they are very well-suited to subsequent fragment elaboration and fragment-to-lead optimisation.

Synthesis of 3D fragments using cycloaddition reactions

The Willand group has reported two different cycloaddition approaches for the synthesis of spirocyclic 3D fragments.[37,39] The first approach used 1,3-dipolar cycloaddition between different 1,1-disubstituted alkenes and generated nitrile oxides, which furnished 2-isoxazoline spirocycles such as **29** (Fig. 2A, Willand 1).[37] The nitrile oxides were produced *in situ* by elimination of chloro-oximes prepared from aldehyde-derived oximes using N-chlorosuccinimide (NCS). Three different oximes and several 1,1-disubstituted alkenes were used, and this enabled the generation of 21 3D fragments that were based on the 2-isoxazoline

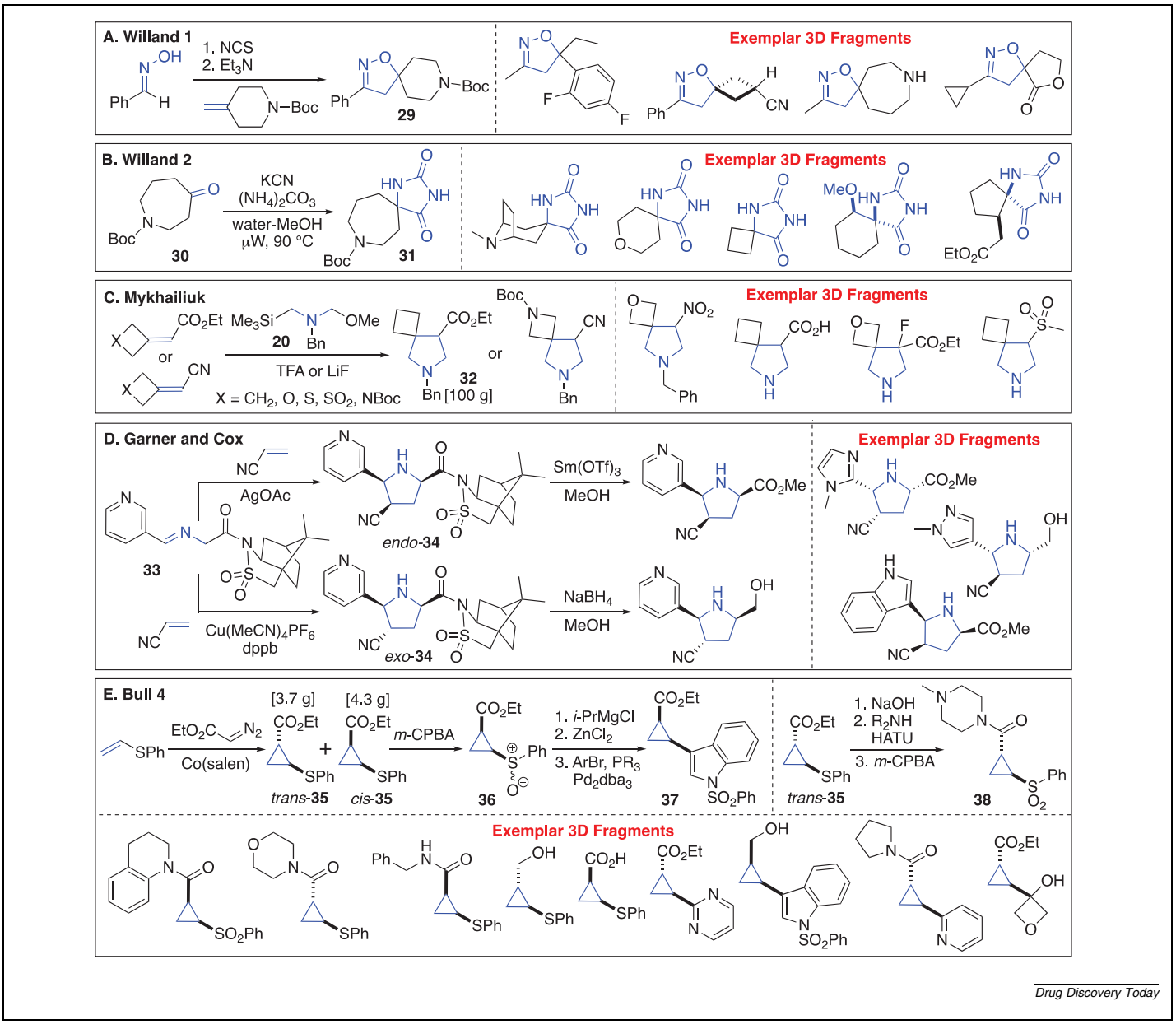


FIGURE 2
Synthesis of 3D fragments using scaffold diversification: cycloaddition reactions.

spirocyclic motif (Fig. 2A, exemplar 3D fragments). Subsequently, Willand and co-workers described the one-step conversion of cyclic ketones (e.g. **30**) into spirohydantoins (e.g. **31**) upon reaction with ammonium carbonate and potassium cyanide (Fig. 2B, Willand 2).[39] Variation of the cyclic ketone and subsequent hydantoin functionalisation produced 27 distinct spirohydantoin 3D fragments (Fig. 2B). Of note, 39 out of 48 3D fragments from both of these libraries had a solubility of $\geq$ 0.8 mM in aqueous phosphate pH 7.4-buffered saline solution.

In 2017, during work aimed at exploring building blocks with 3D vectors, Mykhailiuk and co-workers reported the synthesis of an attractive set of pyrrolidine 3D fragments containing the 6-azaspiro[4.3]alkane scaffold.[43] The pyrrolidine ring was crafted using a [3 + 2] cycloaddition between an azomethine ylide generated from **20** and 4-membered ring-containing α,β-unsaturated esters and nitriles (and other electron-withdrawing groups) (Fig. 2C, Mykhailiuk). The robust methodology was amenable to scale-up, and a 100-g batch of cyclobutylpyrrolidine **32** was prepared. A set of 20 *N*-benzyl spirocyclic pyrrolidine variations was subsequently prepared. A related methodology was described by Juhl and co-workers around the same time.[62] In similar work, Garner, Cox and co-workers utilised the [3 + 2] cycloaddition of azomethine ylides derived from imines such as **33** and acrylonitrile in the synthesis of a set of 48 3D pyrrolidine fragments (Fig. 2D, Garner and Cox).[47] Notably,

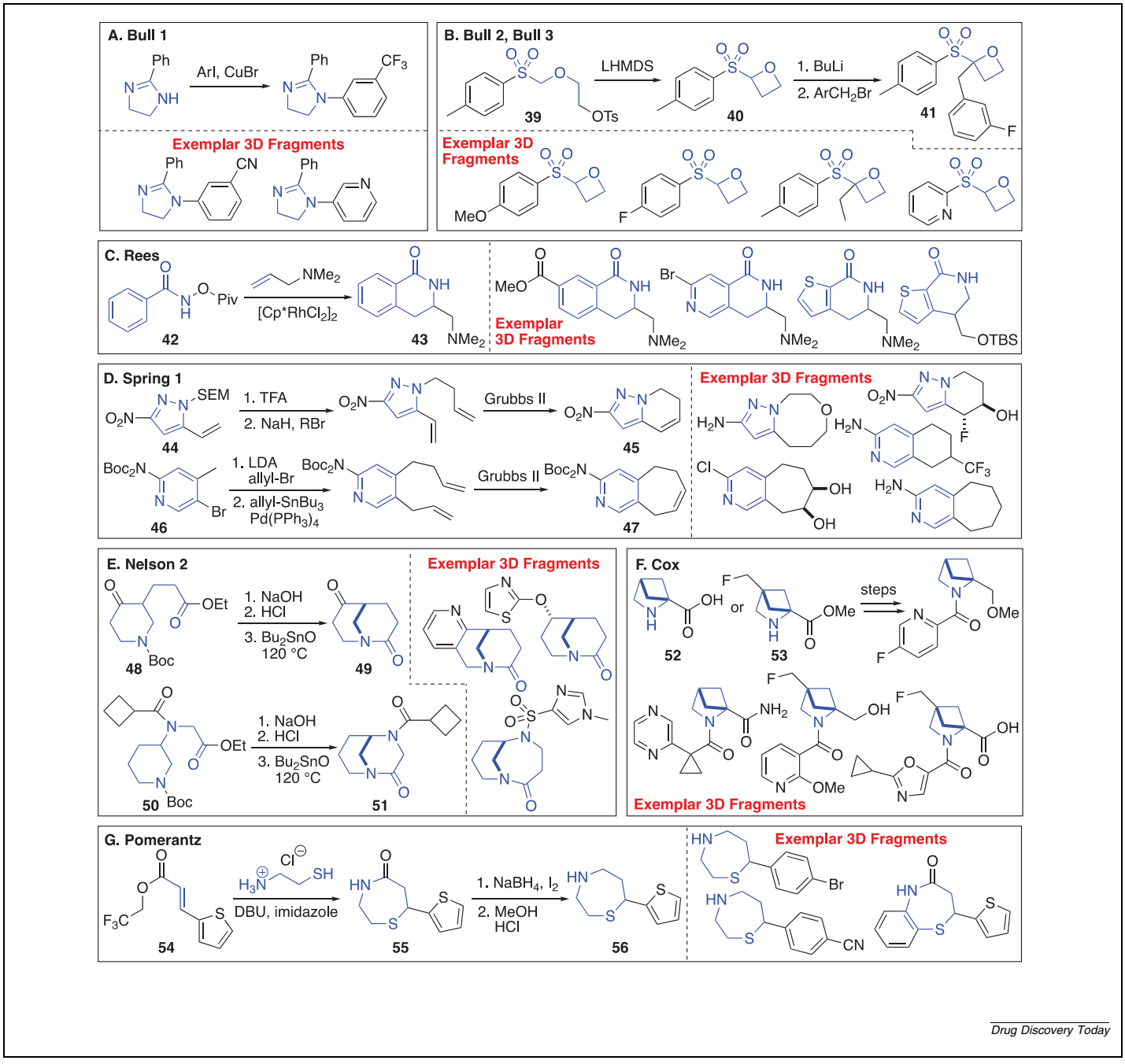


FIGURE 3
Synthesis of 3D fragments using scaffold diversification: bespoke methodology.

the use of Oppolzer's camphorsultam chiral auxiliary allowed access to enantiomerically pure fragments. Complementary access to different diastereomers was possible using Ag(I) or Cu (I) catalysis, which gave pyrrolidine *endo*-**34** or *exo*-**34**, respectively. Two different methods for removing the chiral auxiliary were deployed, enabling the production of pyrrolidine ester and hydroxymethyl 3D fragments. The use of six different heteroaryl groups gave rise to 48 3D fragments (24 distinct 3D fragments in each of the two enantiomeric series) (Fig. 2D, exemplar fragments).

The Bull group utilised two cyclopropane-containing bifunctional building blocks, *trans*- and *cis*-**35**, in conjunction with wide-ranging diversification reactions to prepare a variety of 3D fragments (Fig. 2E, Bull 4).[44] The cyclopropane building blocks *trans*- and *cis*-**35** were prepared from phenylvinyl sulphide and ethyl diazoacetate using a co-catalysed cyclopropanation reaction. The 3D fragments were then generated by diversifying the sulphide and ester synthetic handles. For example, oxidation of *cis*-**35** to a sulfoxide **36** and sulfoxide-magnesium exchange generated a Grignard reagent that could be directly trapped with electrophiles or subjected to transmetallation-Negishi cross-

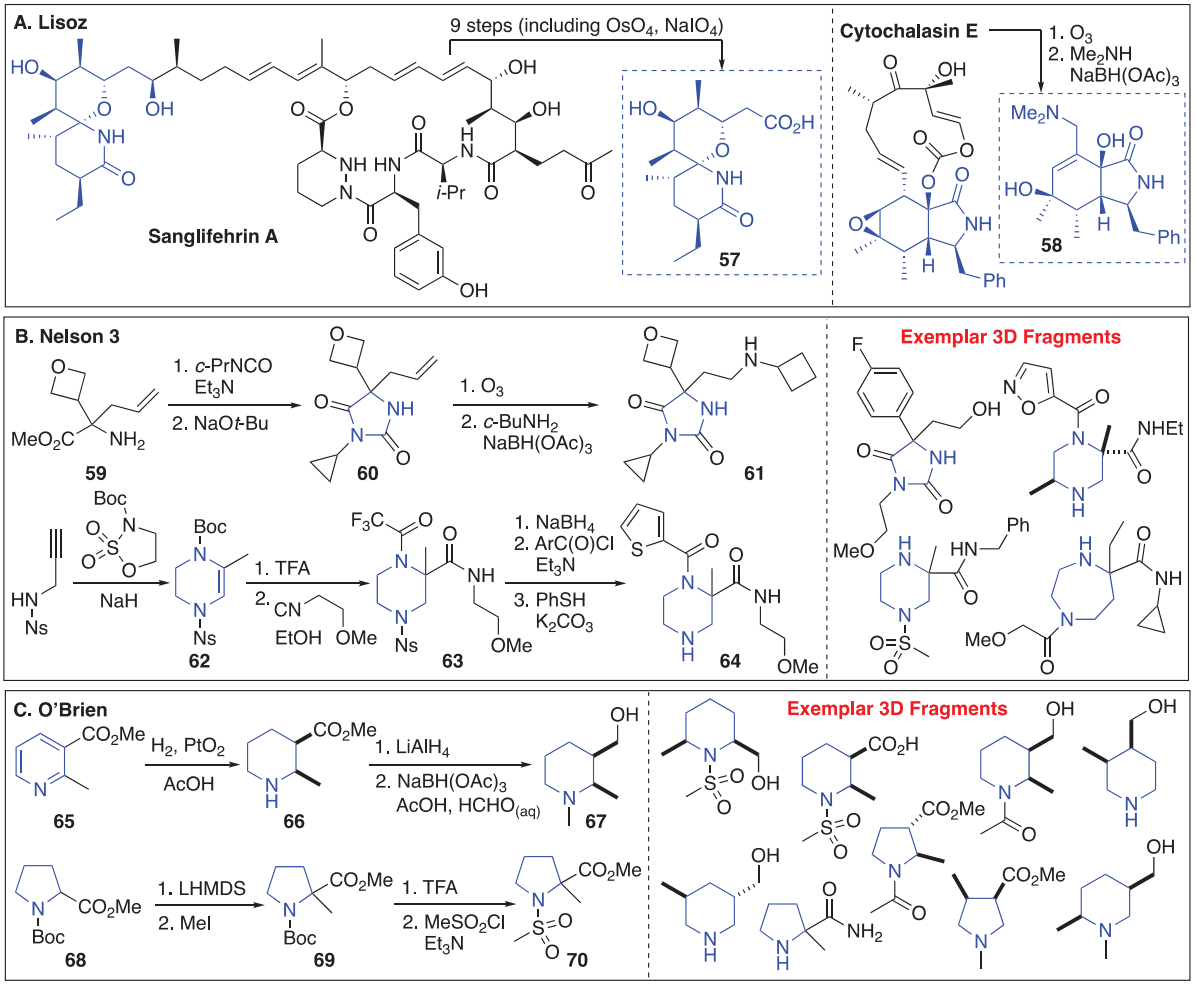


FIGURE 4
Synthesis of 3D fragments using computational design.

coupling with aryl bromides (to give **37** for example). Alternatively, ester hydrolysis of *trans*-**35** followed by amide and sulfone formation gave **38**. Different combinations of these reactions, together with ester reduction, delivered a library of 50 3D fragments (Fig. 2E, exemplar fragments).

Synthesis of 3D fragments using miscellaneous bespoke methodologies

The Bull group has also utilised different approaches to synthesise 3D fragments based on different scaffolds. In 2013, the Cu-catalysed *N*-arylation of 2-imidazolines was reported.[33] This delivered a set of relatively simple imidazoline-based 3D fragments in a connective, direct manner (Fig. 3A, Bull 1, exemplar fragments). Bull and co-workers have explored the preparation of a 3D fragment library based on a 2-arylsulfonyl oxetane scaffold, employing elaboration strategies including a new cyclisation approach for substituted oxetanes (Fig. 3B, Bull 2/3).[34,35] Thus, lithium hexamethyldisilazide (LHMDS)-mediated deprotonation of arylsulfonyl tosylate **39** and subsequent intramolecular tosylate displacement gave oxetane **40**; variation of the aryl group delivered different 3D fragments. Further functionalisations, such as lithiation-trapping, gave 3D fragments such as **41**. The pH stabilities, solubilities, metabolic stabilities and conformational preferences of this set of oxetane fragments (Fig. 3B, exemplar fragments) were also assessed. The solubilities of selected compounds in aqueous phosphate buffer were shown to be disappointingly low,[35] illustrating that not all 3D fragments have improved physicochemical properties.

Rees and colleagues at Astex have applied a precedented Rh-catalysed CH activation approach for dihydroisoquionolone synthesis[63] to the generation of dihydroisoquionolone-based 3D fragments (Fig. 3C, Rees).[38] Thus, the combination of *N*-pivaloyl hydroxamic acid derivatives such as **42** with *N*,*N*-dimethyl allylamine in the presence of a Rh(III) catalyst gave dihydroisoquionolone **43**. The study included a few different aryl/heteroaryl groups and allylated derivatives to give a range of typical 3D fragments (Fig. 3C).

In 2016, Spring and co-workers reported a modular and divergent synthetic approach for the generation of 3D fragments that

were based on 'partially saturated bicyclic heteroaromatic' scaffolds (Fig. 3D, Spring 1).[41] The 3D fragments were built from either a pyrazole or pyridine framework and involved the incorporation of two alkene handles for ring closure via ring-closing metathesis. For example, starting from nitro-pyrazole **44**, removal of the 2-(trimethylsilyl)ethoxymethyl (SEM) group, *N*-alkylation and ring-closing metathesis generated bicyclic pyrazole **45**. Similarly, pyridine **46** was converted into bicyclic pyridine **47** via alkylation of the methyl group, Stille cross-coupling and ring-closing metathesis. Both **45** and **47**, as well as analogues with different ring sizes and ring substituents, were then further functionalised by nitro group reduction, Boc group removal and alkene functionalisation to deliver a range of 3D fragments (Fig. 3D, exemplar fragments).

In an attempt to access new 3D chemical space, Nelson, Marsden and colleagues were attracted to the potential offered by bicyclic amides that contained a twisted amide functionality due to the presence of a bridgehead nitrogen (Fig. 3E, Nelson 2).[45] Thus, after ester hydrolysis and amine deprotection, amino ester **48** was cyclised in a dehydrative fashion using Bu_2SnO to give lactam **49**; similarly, **50** was transformed into **51**. The ring size and *N*-substituents were also varied. Furthermore, other downstream transformations led to the generation of 22 3D fragments (Fig. 3E, exemplar fragments). With the specific aim of targeting fragments with inherent 3D character, Cox, Cox and co-workers designed a library of 3D fragments based around the 2,4-methanoproline scaffold (Fig. 3F, Cox).[53] Using established methods, key 2,4-methanoproline building blocks **52** and **53** were prepared and then converted into a wide range of 3D fragments using standard transformations of the carboxylate functionality and *N*-amidation with different aryl/heteroaryl groups (Fig. 3F, exemplar fragments). This approach delivered a 54-member library of 3D fragments that had improved 3D characters (principal moments of inertia (PMI)[64] and plane of best fit (PBF)[65] scores) when compared to those in the AbbVie RO3 fragment library.

In 2020, Pomerantz and co-workers reported a one-step connective cyclisation methodology for the synthesis of 1,4-thiazepanones and their subsequent functionalisation to 1,4-thiazepanes (Fig. 3G, Pomerantz).[55] Reaction of αβ-unsaturated trifluoroethyl esters such as **54** with cysteamine gave 1,4-thiazepanone **55** via thiol conjugate addition and lactamisation. The corresponding 1,4-thiazepane **56** could be readily accessed upon reduction of the lactam functionality. Using different aryl groups, different amino thiols and some *N*-functionalisations, 54 3D fragments with 1,4-thiazepanone and 1,4-thiazepane scaffolds were prepared (Fig. 3G, exemplar fragments). Three of these 3D fragments were hits when screened against BRD4-D1.

Strategy 3: Computational design and synthesis

There have been isolated examples in which a significant amount of computational design has been carried out before any synthesis of 3D fragments. Such an approach typically incorporates synthetic design aspects from the DOS and diversification of scaffolds strategies, but it can also be a standalone strategy. Three examples of this computational design and synthetic strategy are summarised in this section (Table 1, entries 10, 16 and 22; Fig. 4).

In 2017, Lisoz and co-workers from Novartis reported the construction of a 150-member 3D fragment library based around a set of natural product-like compounds (Fig. 4A, Lisoz).[42] This work was probably inspired by Waldmann and co-workers' seminal study on 2D and 3D fragments derived from natural products.[66] Three distinct strategies were combined in a computational approach. In the first strategy, 3D fragments were derived using *in-silico*-guided degradation of large natural products such as FK506, Sanglifehrin A and Cytochalisin E. Thus, 17,000 in-house compounds were computationally subjected to different cleavage reactions (ozonolysis, ester hydrolysis, Baeyer-Villiger oxidation) to give 66,000 products. Filtering based on favourable RO3-related physicochemical properties (150 < molecular weight < 300; and ClogP < 3) led to 9000 virtual compounds. Finally, compounds were selected for synthesis on the basis of their novelty and 3D shape, which was assessed using principal moments of inertia (PMI) analysis.[64] In this way, 3D fragment **57** was identified and synthesised from Sanglifehrin A via oxidative cleavage and further transformations (nine steps in total). Similarly, ozonolysis and reductive amination of cytochalisin E delivered 3D fragment **58** (Fig. 4A). The second strategy, which involved little computational input, relied on the visual assessment of known and available small natural products with regards to removing reactive functionality, introducing new stereocentres and identifying oxidative cleavage sites. On average, 2–4 3D fragments were synthesised from each natural product. In the third strategy, commercially available and in-house Novartis fragments were selected by applying 3D shape filters, natural product likeness' algorithms and RO3 fragment filters. A 150-member RO3-compliant 3D fragment library was produced using these three approaches. Nevertheless, only 15 3D fragments were disclosed in the paper, and several of these are structurally complex, which is not necessarily a desirable property in fragments.[14] The 3D selection criteria were not disclosed, but this is the first example in which 3D shape analysis of computationally generated fragment conformations was utilised to select 3D fragments for synthesis.

A related computational approach was used by Bayliss, Warriner, Nelson and colleagues to create a library comprising 80 shape-diverse, sp^3-rich 3D fragments, of which 60 were commercially sourced compounds available from the ZINC database (Fig. 4B, Nelson 3).[48] For the 20 synthetic 3D fragments, computational enumeration of 63 tangible scaffolds with one or two rounds of virtual decoration, based on four pieces of methodology previously developed by the group, initially generated 66,814 virtual 3D fragments. These fragments were then filtered according to molecular size ($18 \leq$ heavy atom count ≤ 22), lipophilicity ($-1 <$ AlogP < 3), shape coverage and diversity. The computational approach was multi-faceted and involved rounds of re-evaluation based on, for example, synthetic failures. Ultimately, only two of the four pieces of methodology (summarised in Scheme 4B) were utilised to produce the 20 synthetic 3D fragments. Thus, the reaction of α-allyl α-amino ester **59** with an isocyanate and subsequent cyclisation produced hydantoin **60**, which was then converted into 3D fragment **61**. Alternatively, the reaction of a propargyl sulphonamide and a cyclic sulfamidate gave tetrahydropiperazine **62**; and the reaction of trifluoroacetic acid (TFA) and an isocyanide delivered piperazine amide **63**, which was *N*-acylated and deprotected to give 3D frag-

ment **64**. Similar types of reactions with different scaffold decoration strategies ultimately generated the 20-member 3D fragment library, which had good 3D-shape coverage (Fig. 4B, exemplar fragments). One of these fragments was a hit from X-ray crystallographic screening against Aurora-A kinase.

In 2020, the O'Brien group reported the design and synthesis of 56 pyrrolidine and piperidine 3D fragments that occupied under-represented fragment space, as established by PMI analysis[64] of the computationally generated conformations of virtual 3D fragments (Fig. 4C, O'Brien).[54] Using an unique approach, the conformations of enumerated virtual 3D fragments up to 1.5 kcal mol^{-1} above the energy of the global minimum energy conformer for each fragment were evaluated using PMI plots, and this evaluation was used to select the 3D fragments that were synthesised. The virtually enumerated libraries comprised disubstituted pyrrolidines and piperidines, and all regio- and diastereoisomers were considered. The 3D fragments were also designed to be broadly RO3-compliant and synthesis-enabled because they contain easily modifiable functional groups. A range of synthetic approaches was required to prepare 3D fragments that met the design criteria, although two key pieces of methodology, pyridine hydrogenation and enolate alkylation, were used several times. For example, hydrogenation of pyridine **65** gave piperidine **66** (which has high *cis* diastereoselectivity), which was subsequently reduced and *N*-methylated to give designed 3D fragment **67**. An enolate alkylation approach (**68** → **69**) was used to prepare 3D fragment **70**. Ultimately, a set of 56 shape-diverse 3D fragments (with appropriate solubility profiles) was prepared, and representative 3D fragments are shown in Fig. 4C. Most of these 3D fragments are available for screening at the Diamond XChem facility.

Conclusions and outlook for the future

In summary, there has been increasing interest in the design and synthesis of 3D fragment collections, and a variety of approaches and strategies have been implemented. Our analysis of the synthetic endeavours up to mid May 2020 has identified three distinct strategies, namely DOS, scaffold diversification (cycloadditions and miscellaneous methodologies) and computational design (in which 3D fragments were computationally enumerated and filtered on the basis of computationally generated 3D shape descriptors and other properties). As noted in some of the more recent contributions (e.g. Nelson 3,[48] Clausen,[51] Cox[53] and O'Brien[54]), a combination of two or all three of these strategies is perhaps the best way to design a 3D fragment library that addresses shape, functional group and scaffold diversity in addition to broadly meeting RO3 guidelines.

Critical inspection of the exemplar 3D fragments depicted in Figs. 1–4 showed that some of the 3D fragments are particularly complex, in terms of actual structure and functional groups, as well as the inherent 3D complexity; examples of the most complex fragments include some of those in Fig. 1E, 1H, 4A and 4B. The complexity of these types of 3D fragments could limit their hit rate, as noted by Hann *et al.*[14] Furthermore, some of the 3D fragments in Figs. 1–4 have high molecular weights. It is especially encouraging that a number of 3D fragment libraries have been utilised in screening studies, and validated hits have been obtained across a range of proteins.

From the synthetic routes presented in Figs. 1–3, it is clear that cycloaddition reactions of a wide range of types (but especially [3 + 2] cycloaddition utilising an azomethine ylide and Diels-Alder reactions) are extremely popular approaches (Fig. 1E, 1G, 2A, 2C and 2D). This is perhaps not surprising as these reactions deliver rigid, saturated scaffolds with sp^3 hybridisation and stereocentres. Such approaches are also able to generate spirocyclic scaffolds. Similarly, ring-closing metathesis and transition metal-mediated alkene and alkyne cyclisation reactions are widely used for similar reasons (Fig. 1A, 1D, 1F and 3D). One final methodology that has been used is enolate formation and alkylation (and, in one case, an analogous sulfone lithiation and trapping) (Fig. 1A, 1B, 3B and 4C). This approach is used to generate quaternary stereocentres and also to produce precursors to spirocyclic scaffolds.

Finally, as highlighted especially by the results from Young[40] and Spring,[56] fragment elaboration is relatively straightforward for DOS-derived 3D fragments. Limited fragment elaboration possibilities and an associated lack of 'fragment sociability'[29] can be the least favourable property of 3D fragments, and this in turn can mean that 3D fragment hits are not prioritised for follow-up. Nevertheless, strategies for 3D fragment synthesis that are based on scaffold diversification from a common piece of synthetic methodology or DOS approaches do provide significant opportunities for efficient fragment elaboration to form compounds that cover lead-like chemical space. Indeed, if a computational approach based on fragment properties, 3D shape and, potentially, 'fragment sociability' were then to be incorporated, this would create a workflow that could see 3D fragments employed more widely in both fragment libraries and fragment-to-lead optimisation campaigns. As a result, we believe that 3D fragments have an exciting future in the drug discovery process, and it is encouraging to see case studies emerging in which 3D fragment starting points have featured in hit-to-lead generation.[67] With an eye on the future use of 3D fragments, it is notable that many of the 3D fragments synthesised by the groups of Spring, Nelson/Marsden and O'Brien are available for high throughput X-ray crystallographic screening at the Diamond XChem facility.[68]

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