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Emergent synthetic methods for the modular advancement of sp^3-rich fragments

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Fragment-based drug discovery is an important and increasingly reliable technology for the delivery of clinical candidates. Notably, however, sp^3-rich fragments are a largely untapped resource in molecular discovery, in part due to the lack of general and suitably robust chemical methods available to aid their development into higher affinity lead and drug compounds. This Perspective describes the challenges associated with developing sp^3-rich fragments, and succinctly highlights recent advances in C(sp^3)–H functionalisations of high potential value towards advancing fragment hits by 'growing' functionalised rings and chains from unconventional, carbon-centred vectors.

Introduction

Fragment-based drug discovery (FBDD) is an established approach for the development of small molecule tools and drugs.[1–3] More than forty compounds derived from FBDD approaches have entered clinical trials, and four drugs have been approved.[4] In contrast to traditional high-throughput screening, which relies upon the availability of vast numbers ($\sim10^6$ to 10^9) of lead or drug sized compounds, FBDD enables the efficient[5,6] exploration of chemical space[7–11] by screening smaller collections ($\sim10^3$) of smaller compounds (typically <20 heavy atoms).

Fragments are usually screened against pre-defined molecular targets using biophysical techniques, and generally exhibit high hit rates.[1] Fragment hits tend to be weak binders (typically μmol to mmol affinity), yet ligand-to-target interactions can often be maintained from hit-to-lead.[12] For instance, the initial hit that was developed into vemurafenib had ~200 μM affinity.[13] The essential role of synthetic chemistry in FBDD is ascertained by the range of strategies required for hit advancement,[14,15]

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Dan Foley earned his Master's in Chemistry at Univ. Manchester (2011), including industrial experience at Syngenta. He carried out his PhD (2015) with Profs S. Marsden and A. Nelson at Univ. Leeds, and was subsequently awarded an EPRSC Doctoral Prize Fellowship (2015–2017), which he carried out at Leeds and the Diamond Light Source. Further post-doctoral studies (2017–2018) were completed with with Prof. H. Waldmann at the Max Planck Institute of Molecular Physiology, Dortmund, where he held a Marie Skłodowska–Curie European Fellowship. Dan recently joined the faculty at the University of Canterbury, New Zealand, where his research is focused on the development of new synthetic methods of value to molecular discovery and medicinal chemistry.

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commonly including 'growing' hits, but also linking and merging fragments.[16]

The molecular properties of modern fragment libraries are often carefully controlled, *e.g.* by adhering to Astex's 'rule of three',[17] or even tighter constraints.[15] However, with respect to their molecular shapes, commercially available libraries have historically been dominated by flat (het)aryl compounds,[1,7,18,19] and sp^3-rich fragments have tended to be underrepresented in screening collections.[1,18]

It has been suggested that the introduction of shape-diverse fragments into screening collections may enable modulation of intractable molecular targets,[1,15,18,20] and allow the construction of unique chemotypes that may constitute valuable intellectual property. Drug candidates featuring fractions of sp^3-hybridised carbons in the range 0.4–0.5 have been associated with increased likelihood of clinical progression.[21] The proposed introduction of sp^3 enriched fragments into screening libraries has raised concerns regarding their potential hit rates,[7,22,23] however, reports detailing appreciable hit rates for sp^3-enriched fragments are beginning to emerge.[24,25] Furthermore, the identification of distinctively shaped hits may provide increased certainty about the validity of their binding.[18]

In recent years sp^3-rich fragment libraries have been designed to include 'functional handles' to allow elaboration from specific, often heteroatom-centred (*e.g.* amine) vectors using robust, well-established transformations (*e.g.* amide bond formations; reductive aminations).[26–29] However, in the absence of functionalisable synthetic handles, concerns may arise about the direct synthetic developability of sp^3-rich fragments due to a lack of predictable synthetic methods to aid their advancement.[30] Indeed, pre-emptive development and exemplification of synthetic chemistries for direct fragment elaboration has recently been framed as a pressing challenge for the synthetic chemistry community.[15,30] While sp^3-rich fragments pose challenges with regards to their synthetic (and biological) advancement, they also offer exciting opportunities for the development of new synthetic methods.[14,15,24,30–33] This review highlights recent enabling synthetic methods that are likely to be useful towards the advancement of sp^3-rich fragment hits into higher affinity lead and drug compounds.

Defining 'valuable' methods for fragment advancement

In a typical fragment screening campaign, a hit with suitable binding affinity against a given biomolecular target is selected for development. Structural analogues of the fragment hit are prepared (or sourced) and screened against the target, with a view towards rationalising the exploitable chemical space around the hit for structural advancement of the ligand. In particular, enhancements to the hit's binding affinity and ligand-to-target binding interaction networks are sought after, ideally leading to improvements in ligand efficiency.[1]

For typical commercial fragments, structural analogues of hit compounds may be readily prepared by 'growing' the molecule from heteroatom-centred vectors, allowing variation

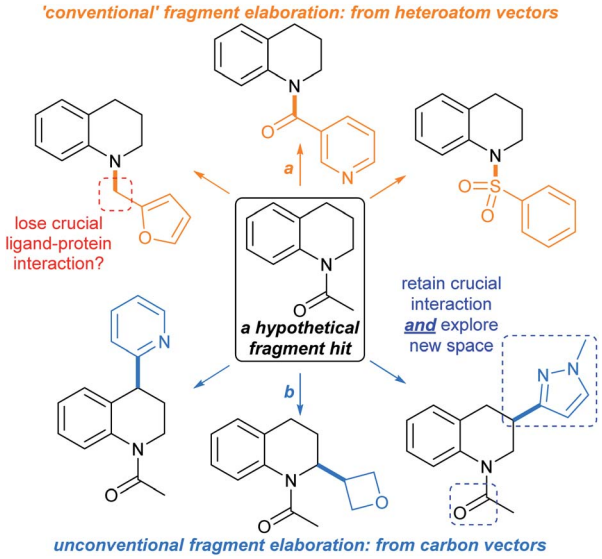

Fig. 1 Methods for fragment elaboration. (a) Conventional elaboration exploiting heteroatom-centred vectors; (b) unconventional elaboration by C(sp^3)–H functionalisations (focus of this Perspective).

of the peripheral functionalities and ring-systems (Fig. 1, orange arrows). Well-established synthetic methods such as amide bond formations, alkylations *etc.* are typically used.[34] However, elaboration of fragments from heteroatom vectors may disturb crucial fragment-to-target binding interactions, hampering development.[15]

Due to their weak affinities, and general lack of cellular activity, fragment hits are situated towards the lower end of the synthesis-value trajectory in drug discovery,[14] and therefore synthetic chemists typically want to avoid esoteric and/or tedious synthetic routes to deliver follow-up compounds, as these may only have limited value towards progressing a hit compound.

One approach to fragment elaboration has been to pre-emptively develop reactions that enable the exploration of chemical space around *specific* scaffolds.[35] In addition, we propose that *general* synthetic toolkits should be developed for the advancement of sp^3-rich fragment hits, and indeed herein show that many relevant methods are already in existence. Ideally these toolkits should tolerate functionalities that are likely to maintain ligand-to-target binding interactions,[15] without the need for protecting groups, with the aim of either (1) generating new binding interactions between the fragment and the target or (2) reinforcing existing binding interactions (Fig. 1, blue arrows). Such synthetic toolkits should ensure that fragments can be reliably advanced in predictable, modular, and additive ways.

Suitable synthetic toolkits to achieve these aims differ slightly from late-stage optimisation toolkits where, in general, specific 'point mutations' to a lead compound are often sought for, such as the introduction of small functional groups (*e.g.* alcohols, amines), and only occasionally entire ring systems.[36]

In order to grow fragments into higher affinity ligands, new ring systems generally need to be added to drive improvements

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in affinity and develop high quality polar ligand-to-target binding interactions. Furthermore, the augmentation of fragment hits with functionalised aliphatic chains may offer opportunities to link hits together and generate lead compounds.[1]

This review serves to provide a snapshot of the current state-of-the-art for elaborating sp^3-rich heterocycles by forming new C–C bonds *via* C(sp^3)–H functionalisations, specifically with regard to methods that are likely to have value towards introducing new heteroatom-containing ring systems and linkers into sp^3-rich fragments. Due to the emphasis of FBDD on ligand structure, this Perspective is focused on overall synthetic transformations, rather than in-depth discussion of the mechanistic aspects of the reactions highlighted. The methods summarised herein may be considered an 'early-stage optimisation toolkit' for fragment development.

Nascent methods for fragment development

Heteroatoms either imbedded in, or exocyclic to, a fragment framework tend to enable crucial intermolecular binding interactions between a fragment and its biomolecular target. Synthetic methodologies that can exploit fragment functionalities whilst maintaining pre-existing fragment-to-target binding interactions are therefore likely to have high utility in hit advancement.[15] The following sections focus on new C–C bond forming methodologies that exploit C(sp^3)–H functionalisations to enable the incorporation of functionalised ring-systems and chains to sp^3-rich frameworks, with a view to increasing the potential for hits to interact with their intended molecular targets and increase their affinity (Fig. 2). Attention is given to recent methodologies that can introduce new vectors into sp^3-rich frameworks using *innate* selectivity (*i.e.* reactions exploiting the intrinsic reactivity of C–H bonds), and *guided* selectivity (*i.e.* harnessing pre-existing functionalities adorning a framework to either proximally or distally connect new C–C bonds).[36,37]

In choosing the methodologies that are discussed herein, key considerations were (1) the potential ability of the methodology to rapidly grow fragment hits and increase their potential for interactions with a biomolecule in a previously unprecedented manner; (2) robustness with respect to functional group-tolerance (where possible we have included examples demonstrating compatibility with unprotected amines and nitrogenous hetaryls); and (3) the atom efficiency of the transformation, where possible avoiding discussion of reactions where a large excess of a bespoke fragment hit would be required. With regards to their downstream synthetic development, chromatographically inseparable mixtures of diastereomers (and/or regioisomers) have the potential to frustrate the fragment-to-lead optimisation process. Therefore, where similar overall transformations are described, we offer guidance towards selecting methods that generally provide higher regio- and diastereocontrol. We wish to emphasise that the methodologies that we have chosen to discuss were not necessarily developed with the underlying intention of advancing fragments, and may have some limitations in this regard, however, we hope that the general framework provided herein can provide guidance to those developing new methodologies with this purpose in mind.

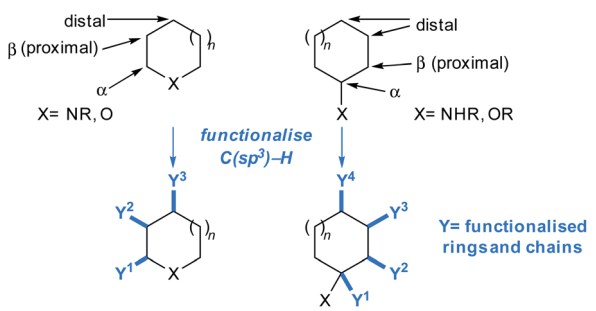

Fig. 2 Functionalisation types highlighted in this Perspective.

C(sp^3)–H functionalisations with (het) aryls

By introducing rigid rings with specifically placed heteroatoms, incorporation of (het)aryl ring systems to Fsp^3-rich fragments offers the potential for opportunities to strengthen the network of intermolecular interactions between a fragment hit and biological target. For instance, this may be achieved by introducing π–π stacking interactions with aromatic amino acid residues in a protein backbone; and, where heteroatoms feature in or on the aromatic ring, through introducing new hydrogen-bonding interactions. Inversely, functionalisation of aromatic fragments with sp^3-rich systems might be used as a means to enhance their aqueous solubility.[38]

Arylation strategies exploiting *innate* selectivity

Arylations proximal to alicyclic heteroatoms. Drawing inspiration from earlier protocols,[39–41] as part of a specific effort to functionalise sp^3-rich fragments, Grainger and Johnson described cross-dehydrogenative coupling of α-amino radicals with electron-deficient hetaryl rings under blue light irradiation (Scheme 1).[42] Notably, the substrate scope for the cyclic carbonyl-protected amine included privileged ring-systems, such as piperazine, (thio)morpholine, azetidine, pyrrolidine, and bridged bicyclic ring-systems. Interestingly, complete selectivity for arylation α- to protected amines was observed over (thio)ethers. The hetaryl component included pyridines, pyrazines, pyridazine, pyrimidine, and quinolines. A range of functional groups were tolerated on the alicyclic amines, including additional (unprotected) secondary amines, ketones, esters, and sulfonamides, whilst functional groups on the aromatic component included synthetic handles likely to be useful for further functionalisation, such as halides (F, Br) and esters. The carbonyl protected amine could be a carbamate (Boc), amide (Piv), or formamide, but α-amino radical generation was not possible next to strongly deactivating groups such

† Acyclic aliphatic scope not (fully) shown.

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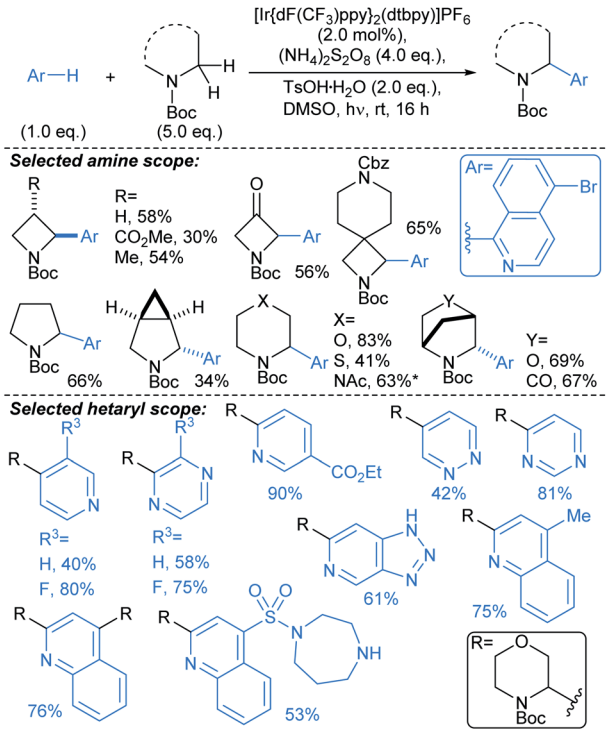
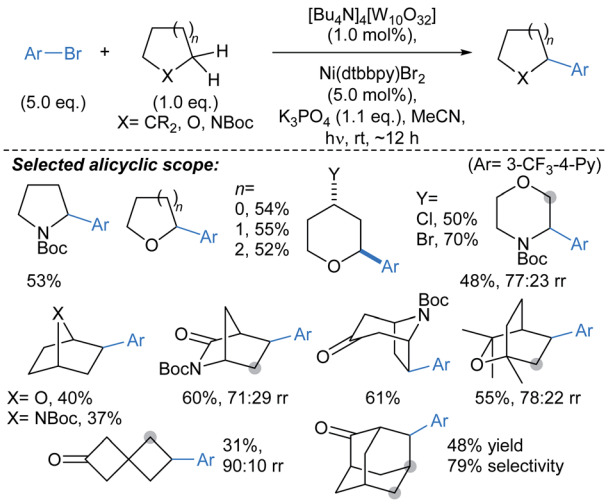


Scheme 1 Photoredox-mediated Minisci-type coupling of α-amino radicals with electron-deficient hetaryl rings.[42]† *55 : 45 rr (regiomeric ratio).

as trifluoracetyl and tosyl amines, which excitingly might provide a strategy for differentiating amine reactivity. It is notable that a related overall transformation was developed by MacMillan, enabling coupling of α-amino radicals with (het)aryl bromides.[43] An appealing feature of Grainger and Johnson's methodology is the demonstrated compatibility in 1536 well plates under air, which may prove beneficial in initial scoping investigations to elaborate specific fragments.

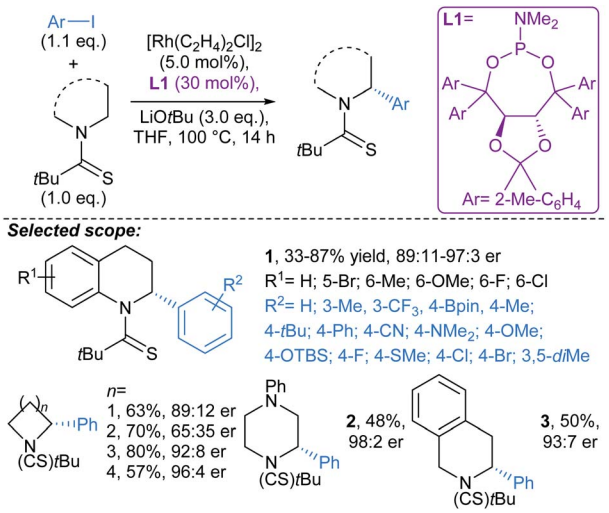
Arylations at sterically accessible hydridic C(sp^3)–H bonds. MacMillan developed site-specific arylation of complex aliphatic frameworks using a light-activated polyoxometalate hydrogen atom transfer catalyst (decatungstate) in combination with a Ni catalyst, under irradiation from near UV LEDs (Scheme 2).[44] For heteroalicyclic substrates, arylation of methylene groups α- to ring heteroatoms was observed. For more complex bridged and spirocyclic substrates, preference for H-abstraction at the most sterically accessible, electron-rich C–H was observed.

Arylation strategies exploiting *guided* selectivity. The methodologies discussed in this section generally proceed with high diastereoselectivity, and tend to proceed with higher regiocontrol than, for instance, the arylation at sterically accessible hydridic C(sp^3)–H bonds (Scheme 2, above). A disadvantage of guided arylations is that they necessarily require the careful design and synthesis of prefunctionalised starting materials, however, a major advantage is that in subsequent fragment optimisation the installed functionality can later serve as a specific, often stereodefined, vector for further derivatisation.



Scheme 2 Arylations α- to alicyclic heteroatoms, mediated by a decatungstate photocatalyst.[44] Unless otherwise stated, rr (regiomeric ratio) and dr are >95 : 5.

Arylations proximal to alicyclic heteroatoms. Glorius described enantioselective arylation of aliphatic nitrogenous rings bearing a thioamide directing group, using aryl iodides and a Rh catalyst, in the presence of chiral phosphoramidite ligand **L1** (Scheme 3).[45] The reaction scope was extensively explored for tetrahydroquinolines, providing arylated products **1** in 33–87% yield and 89 : 11–97 : 3 er. A range of aryl iodides were tolerated in the protocol, including substrates bearing boronate ester (Bpin), cyano, amine, (protected) alcohol, and halide functional groups. Without further optimisation, the method was immediately applicable to 4–7-membered saturated azacycles, including a piperazine (→**2**), and in general high enantioselectivities were achieved (up to 98 : 2 er). Remarkably, functionalisation of tetrahydroisoquinoline gave complete regioselectivity for arylation at the non-benzylic methylene (→**3**). The procedure was also carried out using



Scheme 3 Rh-catalysed arylation of nitrogenous heterocycles.[45]

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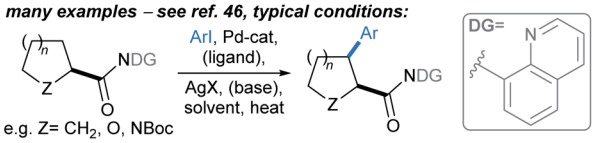
a non-chiral ligand (PCy_3) to give comparable yields of racemic tetrahydroquinolines. A marked advantage of this approach over previous[46] guided C(sp^3)–H activation approaches is that the directing group can be removed following the arylation by treatment NaOMe. Related protocols were developed by Yu[47] and Gong.[48]

Arylations distal to alicyclic amines. Sanford described Pd-catalysed transannular C(sp^3)–H arylations of azacycles bearing an amine-derived fluorinated directing group, using aryl iodides (Scheme 4a).[49–51] Although the aryl iodide was used in large excess, a number of bridged alicyclic amines were compatible in this process, including tropane, homotropane, and 7-azanorbornane. Li, Dechanstreiter, and Dandapandi developed a second generation protocol in which they demonstrated compatibility with a wide variety of hetaryl iodides (2–3 eq.), including pyrazines, thiazoles, pyridines, and (aza)indoles, along with expanded amine substrate scope, including spirocyclic amine **4** (Scheme 4b).[52] The key to the success of this reaction was a ligand screen which identified ligand **L2** as optimal for heteroarylation. In both protocols, the directing group was removed using SmI_2, and although we note that this deprotection protocol may have limited functional group tolerance, the overall transformation is a highly meritorious synthetic advance.

Arylations distal to exocyclic functional groups

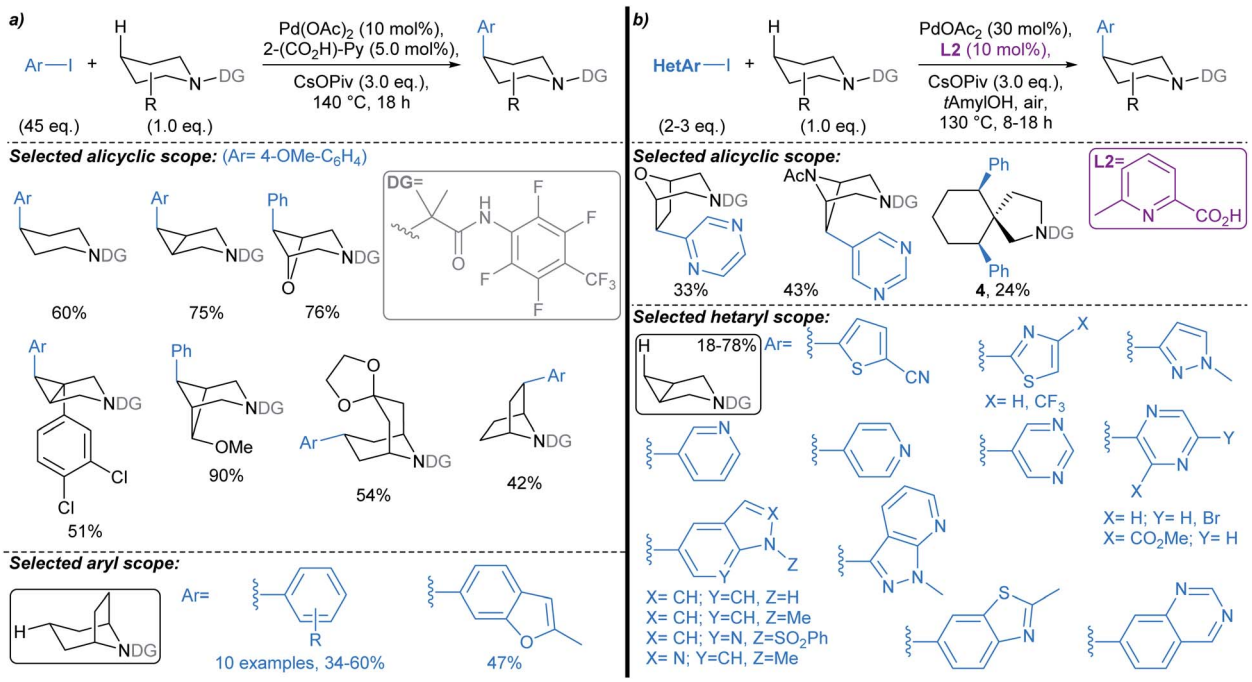
Arylations distal to alicyclic carboxylic acids. Arylation of alicyclic rings using removable carboxylic acid-derived directing groups has been an intensive and extensive area of recent development. For instance, it is possible to functionalise a variety of alicyclic rings β- to pendant 8-aminoquinoline amides (Scheme 5). Interested readers are directed to the recent comprehensive review of this area by Bull.[46]



Scheme 5 Pd-catalysed directed C(sp^3)–H α-arylations distal to alicyclic carboxylic acids.[46]

Arylations distal to exocyclic amines. Removable amine-derived directing groups have proven useful tools for regio- and diastereoselective metal-catalysed C(sp^3)–H functionalisations,[46,53] but ultimately suffer from the requirement for steps for their addition and removal. In particular, removal can often require harsh reaction conditions, such as the use of strong oxidising or reducing reagents, or acids. The development of transient directing groups – which do not require additional synthetic transformations for installation/removal – has been very encouraging.[54]

Yu first described Pd-catalysed γ-arylation of secondary exocyclic amines using aryl iodides and 2-hydroxynicotinaldehyde as a transient directing group (TDG) in 2016.[55] Development of this reaction to enable compatibility with hetaryl iodides was achieved through the cooperative effect of a TDG in combination with a 2-pyridone ligand (*e.g.* **L3**, **L4**), which acted as an internal base to accelerate Pd insertion into C(sp^3)–H bonds, and mitigated unproductive side reactions.[56]



Scheme 4 Pd-catalysed directed C(sp^3)–H arylations of alicyclic amines.[50,52] (a) Original procedure developed by Sanford; (b) next generation protocol by Li, Dechanstreiter, and Dandapandi, incorporating ligand **L2**, and demonstrating substantial scope with respect to the aryl iodide coupling partner.

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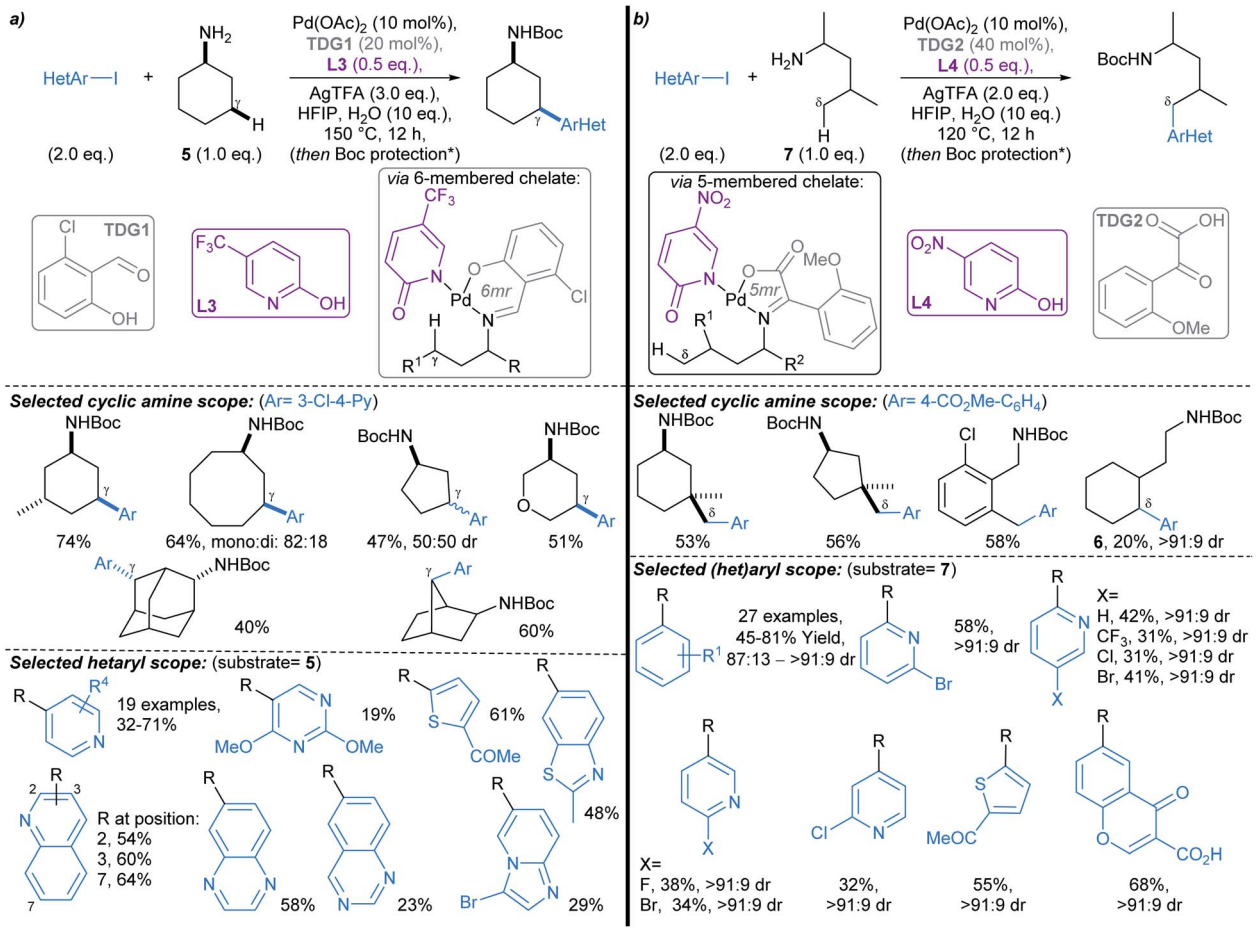

Scheme 6 Pd-catalysed directed γ- and δ-C(sp^3)–H arylations (panels a and b, respectively) using transient directing groups.[56]† *Boc protection sequence: (1) 2 M HCl, THF; (2) 10 M NaOH; Boc_2O.

Both γ- and δ-arylations were possible using the latter methodology (Scheme 6a and b, respectively), with the regioselectivity controlled through careful choice of TDG and ligand. TDGs that coordinate Pd(II) and form a six-membered chelate were selective for γ-C–H bond activation (*e.g.* **TDG1**), whereas TDGs that coordinate with Pd(II) *via* a five-membered chelate activated δ-C–H bonds (*e.g.* **TDG2**). γ-Arylation of cyclohexylamine **5** was demonstrated using hetaryl iodides, including functionalised pyridines, pyrimidines, quinolines, and quinoxalines (Scheme 6a). In general, complete diastereoselectivity for the γ-*cis* arylated products was achieved in monocyclic aliphatic ring systems, with the exception of cyclopentylamine, which gave the γ-arylated product in 50 : 50 dr. Similar scope coupling hetaryl bromides was achieved using an alternative TDG. The δ-arylation protocol proceeded in with high diastereoselectivity (up to >91 : 9 dr), showing preference for activation of methyl C–H bonds (Scheme 6b), but δ-methylene arylation was possible in the absence of δ-methyl groups (→**6**).

Arylations distal to exocyclic alcohols. Yu developed a previously unprecedented Pd-catalysed β-arylation of aliphatic alcohols, directed by an *O*-tethered salicylic aldehyde-derived directing group (Scheme 7).[57] The reaction was proposed to proceed through a 6,5-fused palladacycle intermediate, to which coordination of an electron deficient 2-pyridone ligand **L5** was crucial for accelerating C–H bond cleavage. The procedure was shown to be compatible with an impressive range of cyclic and acyclic alcohol derivatives, as well as a large range of functionalised (het)aryl iodide coupling partners. In general, high diastereoselectivity for the *cis* arylated products was achieved for 4- and 5-membered ring alcohols (>95 : 5 dr), but poorer stereocontrol was observed for 6- and 7-membered ring alcohols (60 : 40 to 67 : 33 dr). Due to the wide prevalence of alcohols in pharmaceuticals, this transformation is likely to have high value for fragment functionalisation. It is worth noting that while the directing group is not transient, it could be readily installed in a single operation, and was removed by $Pd(OH)_2/C$ catalysed hydrogenolysis.

Yu developed a conceptually related Pd-catalysed approach, mediated by an *O–N* tethered iminopyruvate-derived directing group, that enabled C(sp^3)–H arylation γ- to aliphatic alcohols (Scheme 8). This proceeds *via* the formation of a six-membered palladacycle.[58] Combination of **DG1** with 2-pyridone ligand **L6**, enabled arylation of substrates *without* active C–H bonds β- to the alcohol (*i.e.* substrates with no β-methyl or -methylene groups, Scheme 8a). For substrates *with* active C–H bonds β- to the alcohol, use of **DG2**, without a 2-pyridone ligand, allowed

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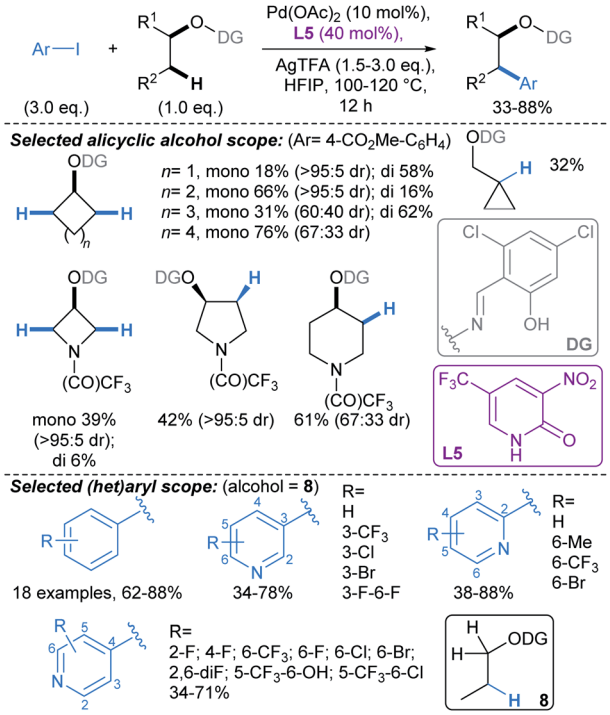


Scheme 7 Pd-catalysed directed β-C(sp^3)–H arylations of alcohols using an *O*–*N* tethered directing group.[57]

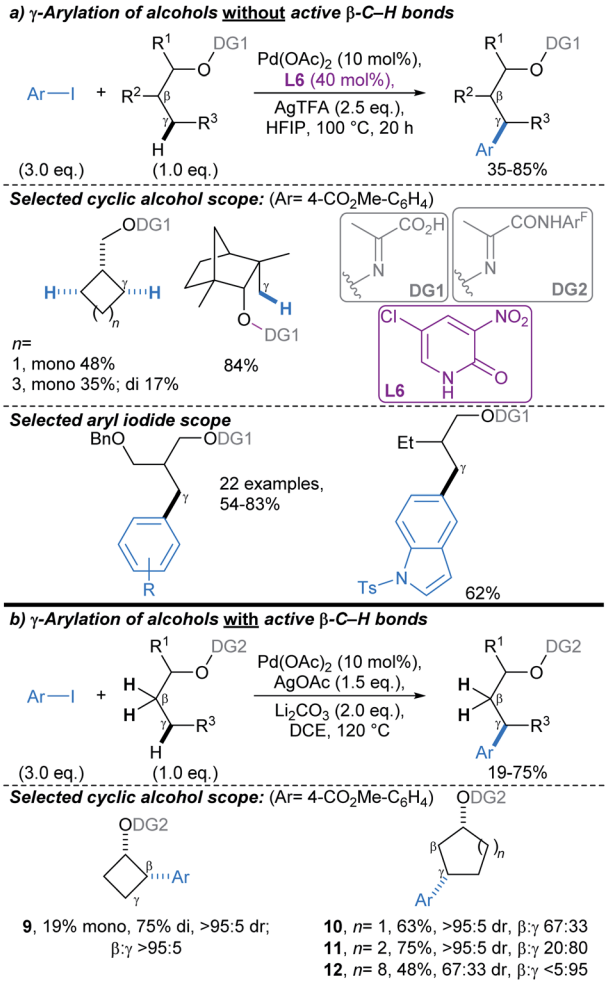
selective activation of γ-methylene C–H bonds (Scheme 8b). Interestingly, in the latter protocol, γ-C–H arylation was less favourable in smaller rings due to their rigid geometric strain: β : γ selectivity for small ring alcohols, **9** and **10**, were >95 : 5 and 67 : 33, respectively, *versus* β : γ selectivity of 20 : 80 and <5 : 95 for the medium (**11**) and large (**12**) ring substrates. The directing group could be installed in a two-step, one-pot procedure, and was removed by Pd/C catalysed hydrogenolysis.

C(sp^3)–H functionalisations with aliphatic ring-systems and chains

Incorporation of aliphatic rings and chains to Fsp^3-rich fragments offers the potential for opportunities to strengthen the network of intermolecular interactions between a fragment hit and biological target, for instance, by enabling new hydrogen-bonding interactions between specifically placed heteroatoms on or in the heteroaliphatic ring. In addition, incorporation of appropriately oriented functionalised aliphatic chains may enable fragment hits binding to adjacent protein sub-pockets to be linked[1] together to accelerate ligand development.

Alkylation strategies exploiting *innate* selectivity

Alkylations proximal to alicyclic heteroatoms. Photoredox catalysis enables intermolecular alkylations next to heteroatoms in alicyclic rings.[59] MacMillan described C(sp^3)–H alkylations α- to alicyclic heteroatoms using alkyl bromides, and a catalytic system comprising a Ni-catalyst **13**, Ir-centred photocatalyst, and a quinuclidine hydrogen-atom transfer (HAT)



Scheme 8 Pd-catalysed directed γ-C(sp^3)–H arylations of alcohols using an *O*-tethered directing group.[58] (a) γ-Arylation of alcohols *without* active β-C–H bonds; (b) γ-arylation of alcohols *with* active β-C–H bonds. Ar^F = 2,3,5,6-tetrafluoro-4-(trifluoromethyl) phenyl.

catalyst, under blue LED irradiation (Scheme 9).[60] With respect to the α-heteroatom radical, a range of simple alicyclic (protected) amines, ethers, and thioethers, were compatible with the process, including 4- to 7-membered rings. Alkyl bromides bearing a range of functionalities proved suitable substrates in the protocol, including protected alcohol, masked aldehyde (diacetal), ester, cyano, and chloro functional groups, along with a hetaryl substituent (2-Py).

Toullec and Vincent used an approach combining the photoreactivity of benzophenone with Cu catalysis to couple alkyl radicals and electron deficient alkenes under UV-A irradiation (Scheme 10).[61] A range of electron deficient alkenes were found to be productive coupling partners in the reaction, including alkyl acrylates, acrylonitriles and vinyl ketones. Interestingly in the absence of $Cu(OAc)_2$, the alkenes polymerised (>95%), suggesting that Cu plays a role in limiting alkene polymerisation. The reaction was regioselective for functionalisation α- to (*N*,*O*) heteroatoms, including next to unprotected tertiary amines, Boc-protected amines, ethers, and unprotected primary and secondary alcohols. Further selectivity studies showed that

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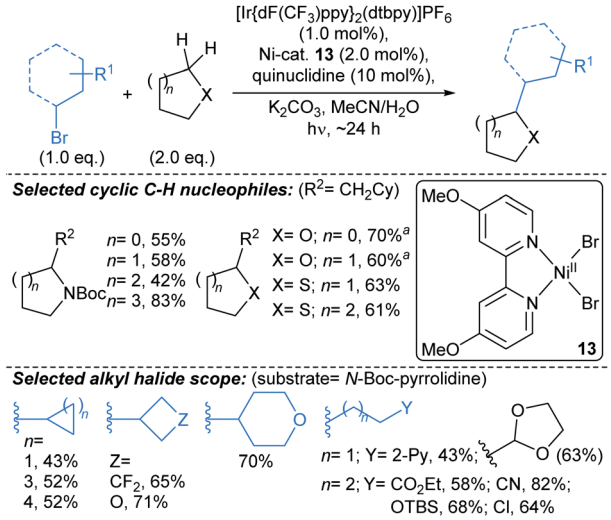
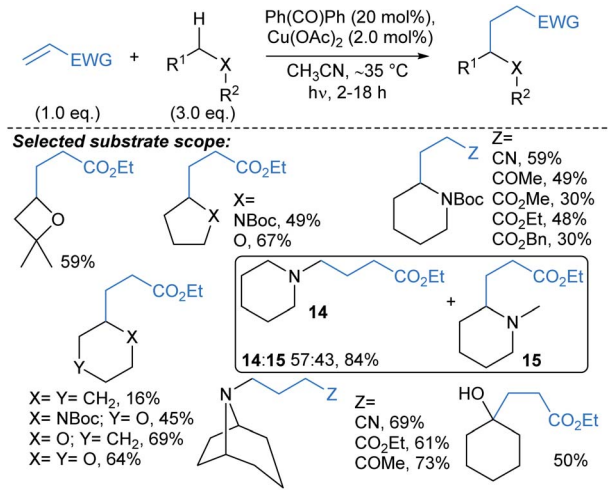


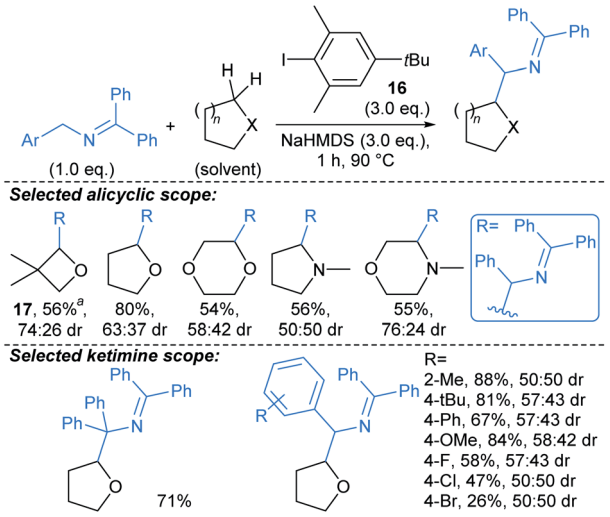
Scheme 9 Alkylations α- to alicyclic heteroatoms using a Ir/quinuclidine/Ni catalyst system.[60]† [a]50 eq. of cyclic ether used in the reaction.



Scheme 10 Benzophenone/Cu-catalysed coupling of alkyl radicals and electron deficient alkenes.[61]†

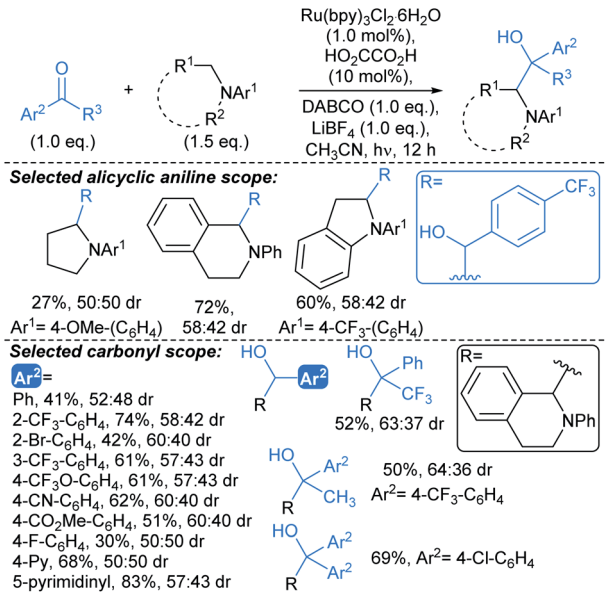
for *N*-Boc morpholine, functionalisation α- to Boc-protected amine was favoured over the ether. In addition, *N*-methylpiperidine showed a slight preference (57 : 43) for methyl (→**14**) *versus* α-methylene alkylation (→**15**). Noteworthy protocols that deliver similar overall transformations were developed by Barriault,[62] Knowles and Alexanian,[63] and Nicewicz.[64,65]

Zhang, Yang, and Walsh described cross-dehydrogenative coupling of saturated heterocycles with benzophenone imines (Scheme 11).[66] 2-Azaallyl anions are highly reducing, and by reducing aryl iodide **16** to the corresponding aryl radical they can generate a sterically hindered sacrificial hydrogen atom abstractor. This aryl radical subsequently enables H-abstraction from a suitable donor such as an ether, unprotected amine (or toluene derivative, not shown), followed by combination of the



Scheme 11 Cross-dehydrogenative couplings between saturated heterocycles and benzophenone imines.[66]† [a]5.0 eq. heteroaliphatic donor used.

resulting radical with the 2-azaallyl radical. Although the donor was generally used as solvent, five equivalents of more expensive substrates were effectively coupled using benzene as solvent (*e.g.* →**17**). Interestingly, for *N*-methyl cyclic amines, coupling was only observed adjacent to the amino group on the ring. No or poor (up to 74 : 26 dr) diastereoselectivity is generally observed in the products, so with regard to use of this method for fragment-to-lead optimisation, next generation protocols would benefit from inducing stereocontrol in the procedure. Related protocols have been developed using photoredox catalysis,[66] but the methodology highlighted offers the advantage of avoiding transition metal catalysts. The



Scheme 12 Photocatalysed coupling of α-amino radicals with benzaldehydes and aryl ketones.[67]†

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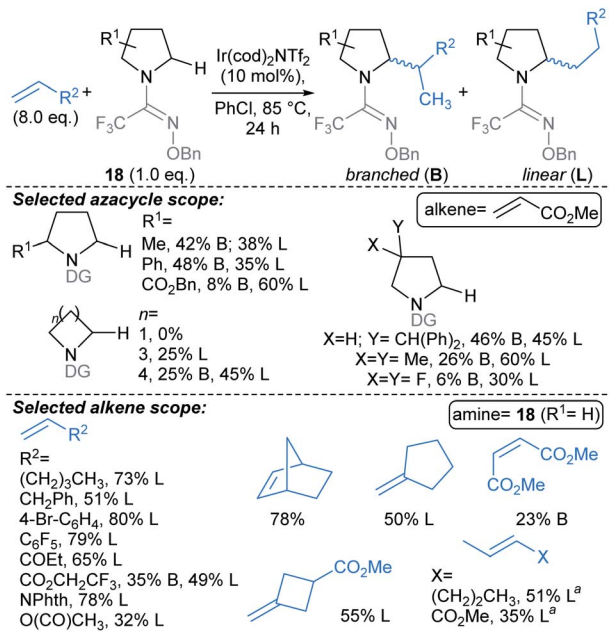
benzophenone imine products can be readily hydrolysed to provide the free primary amines.

A related protocol developed by Wang enabled coupling of α-amino radicals with benzaldehydes and aryl ketones to give 1,2-amino alcohols, under irradiation from white light LEDs (Scheme 12).[67] This was postulated to proceed by a Brønsted acid-activated proton-coupled electron transfer pathway. The optimised conditions exhibited tolerance of a range of functionalities on benzaldehyde coupling partners, including nitrile and ester functionalities, along with nitrogenous heteroaromatic benzaldehydes (4-pyridyl; 5-pyrimidinyl). The substrate scope with respect to ketones included substituted acetophenones and benzophenones. Aldimines were also suitable coupling partners, furnishing vicinal diamines (not shown). The demonstrated scope of this methodology was limited to coupling anilines with aldehydes and ketones, therefore for the development of next generation protocols, compatibility with amines bearing removable protecting groups would offer a marked advantage. As for the procedure above (Scheme 11), no or poor (up to 60 : 40 dr) diastereoselectivity is observed for this transformation, which, without further development might limit its utility in fragment-to-lead optimisation.

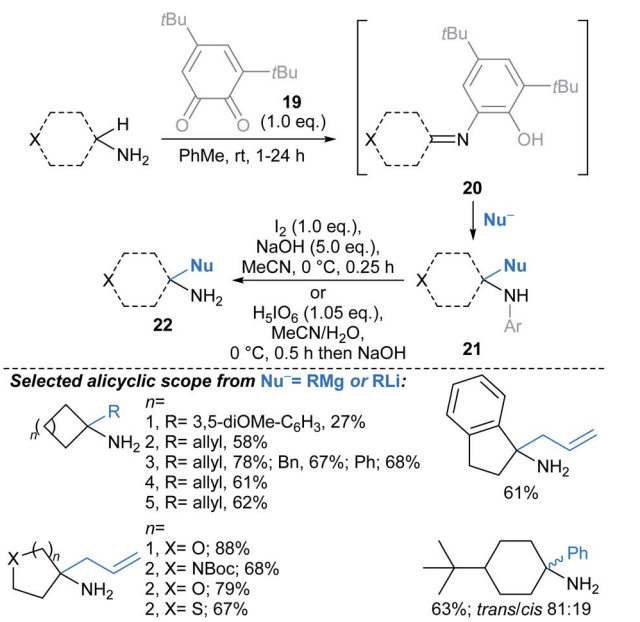
Alkylation strategies exploiting *guided* selectivity

Alkylations proximal to alicyclic heteroatoms. Yu described Ir(I)-catalysed α-C(sp^3)–H alkylation of saturated azacycles with alkenes,[68] directed by novel amidoxime directing groups (Scheme 13), building upon work from their earlier protocol.[69] Using a trifluoromethyl *O*-benzyl amidoxime directing group, alkylation of a variety of substituted pyrrolidine substrates was achieved. A range of alkenes were compatible in the process including disubstituted terminal alkenes and internal alkenes. The optimised conditions enabled successful alkylation of azepane, but were unsuccessful for azetidine, and low yielding for piperidine. However, alkylation of substituted piperidines and tetrahydroisoquinoline was achieved more efficiently using methyl *O*-benzyl amidoxime as the directing group (not shown), although *anti*-dialkylation products were also often yielded. Both directing groups could be readily installed and removed, each in one step, although relatively harsh conditions were used for removal (DIBAL-H), which may affect downstream functional group compatibility. Improving the regiocontrol of this reaction is likely to render it more amenable to fragment elaboration purposes, especially if, for instance, ligand control can be used to provide selective routes to the respective linear and branched regioisomers, along with introducing diastereoselectivity in forming the latter. While this reaction shows exciting promise for future development, at present the innately guided alkylation protocols shown in Schemes 9 and 10 are perhaps more attractive choices to functionalise fragments to prepare linear-type alkylation products.

Alkylations proximal to exocyclic amines. Dixon described a one-pot quinone-mediated protocol for the preparation of primary α-tertiary amines from α,α-disubstituted primary amines (Scheme 14).[70] Condensation of primary amines with quinone **19** triggered a 1,5-hydride shift to generate ketimines **20**. Subsequent addition of nucleophiles, including Grignard, organolithium reagents, and TMSCN, gave α-tertiary anilines **21**. Alternatively, a protocol harnessing Ir photoredox catalysis enabled polarity reversal at the imine **20**, generating an α-amino radical, which was intercepted by an allyl sulfone electrophile (not shown). The anilines **21** generated could be rapidly



Scheme 13 Ir-catalysed α-C(sp^3)–H alkylation of saturated azacycles with alkenes. [a]Isomerises to give the linear product.[68]†



Scheme 14 Quinone-mediated oxidation of primary amines followed by addition of nucleophiles, furnishing primary α-tertiary amines.[70]† Conditions for Grignard addition: RMgX or RLi (6.0 eq.), TMEDA (1.0 eq.), 0–25 °C, 1–24 h.

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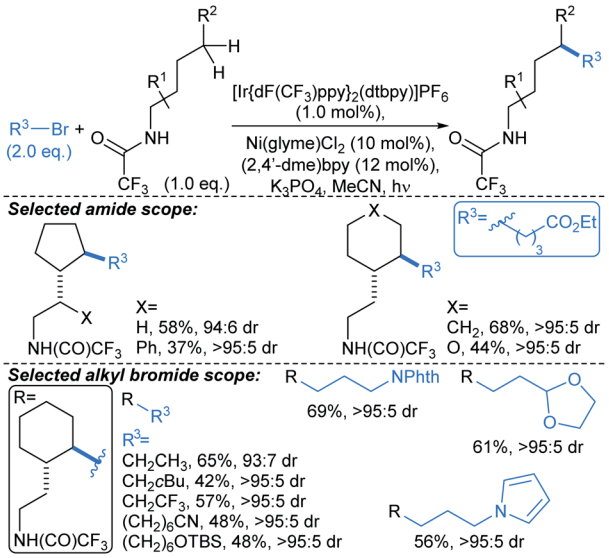
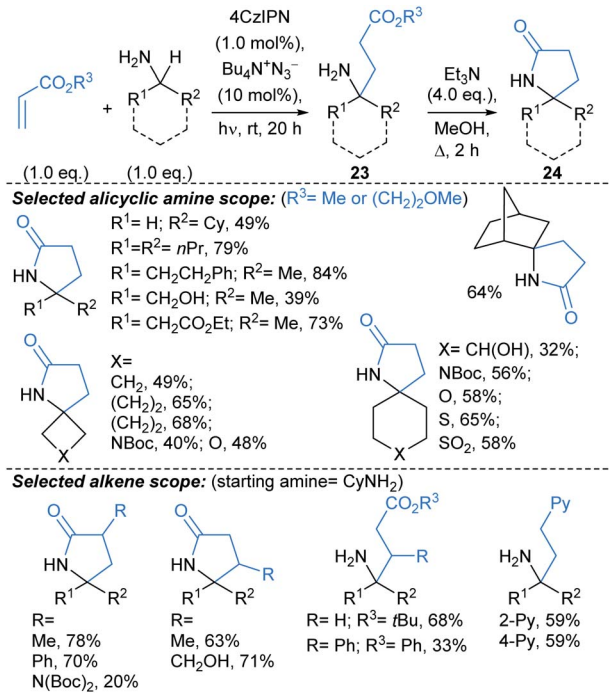
deprotected using I_2 or H_5IO_6 mediated oxidations to provide the free amines **22**.

Creswell developed a catalytic approach for C(sp^3)–H alkylation of unprotected primary amines (Scheme 15).[71] Under blue LED irradiation, alicyclic primary amines were alkylated at the α-position with alkyl acrylates, using a process combining an organophotocatalyst with $Bu_4N^+N_3^-$ as a HAT catalyst. Treatment of the alkylated products **23** with Et_3N delivered spirocyclic γ-lactams **24**, in a one-pot telescoped procedure. The approach was successfully applied to molecules containing polar functionalities such as unprotected alcohols, (thio)ethers, sulfonamides, sulfones, and nitrogenous hetaryl rings, along with protected amines and ketones. The reaction was compatible with functionalised acrylates and styrenes. Notably, the alkylation also worked using a continuous flow photoreactor (reaction times 10–20 min, *versus* 20 h for the batch set up).

Alkylations distal to exocyclic amines. Rovis developed a site specific C(sp^3)–H alkylation directed by distal trifluoroacetamides, using a catalytic system comprising an Ir photocatalyst and Ni catalyst (Scheme 16).[72] The trifluoroacetamide directing group directs alkylation at δ-methylenes, selectively overriding the innate tendancy for alkylation α- to the amide nitrogen. The proposed reaction mechanism proceeds by photocatalyst-mediated oxidation of the trifluoroacetamide to a nitrogen-centred amidyl radical, enabling subsequent intramolecular 1,5-hydrogen atom transfer from the δ-methylene. The resulting alkyl radical then undergoes Ni-catalysed cross coupling with the alkyl bromide. In cyclic systems, cross-coupling gave high diastereoselectivity for *trans* products. A range of alkyl bromide coupling partners were compatible, including substrates bearing trifluoromethyl, nitrile, silyl-protected alcohol, and phthalimide-protected amine functionalities. Importantly, the exemplified reaction scope demonstrates excellent diastereoselectivity, with products being formed in up to >95 : 5 dr. This methodology might be harnessed to introduce fragment linkers to an existing fragment before deprotection and derivatisation at the amide nitrogen. Related approaches by Rovis,[73] and Knowles,[74] use Michael acceptors to trap the δ-methylenyl alkyl radicals.



Scheme 16 Ir- and Ni-photocatalysed δ-C(sp^3)–H alkylation of trifluoroacetamides.[72]†



Scheme 15 Photocatalysed alkylation–lactamisation of primary amines.[71]†

Future outlook

In this Perspective we outlined the need for methods to elaborate sp^3-rich fragments, and have identified existing methodologies that are likely to be useful towards achieving this challenging goal. As an illustrative "thought experiment", we have considered how the methods discussed might be applied to develop known sp^3-rich fragment hits,[4,75–78] without an unreasonable level of prior manipulation to the hit's structure (Fig. 3). Since the fragments shown were already successfully developed[79–82] into lead compounds, we are not suggesting that it would necessarily be biologically relevant to develop these hits in the manners shown. However, we believe that Fig. 3 showcases potential instances where the methods discussed could prove to be useful as synthetic tools for fragment-to-lead development. A limitation of this exercise is that it is likely that there are sp^3-rich fragment hits that were not previously developed into leads due to the confines of the available methodologies for fragment elaboration at the time of hit discovery,[30] but such hits might now be developable using methodologies highlighted in this manuscript.

Almost all of the methods discussed in this review were not specifically developed for the purpose of advancing fragments, and in some instances, the presently available methods have deficiencies with respect to their regio- and diastereoselectivity,

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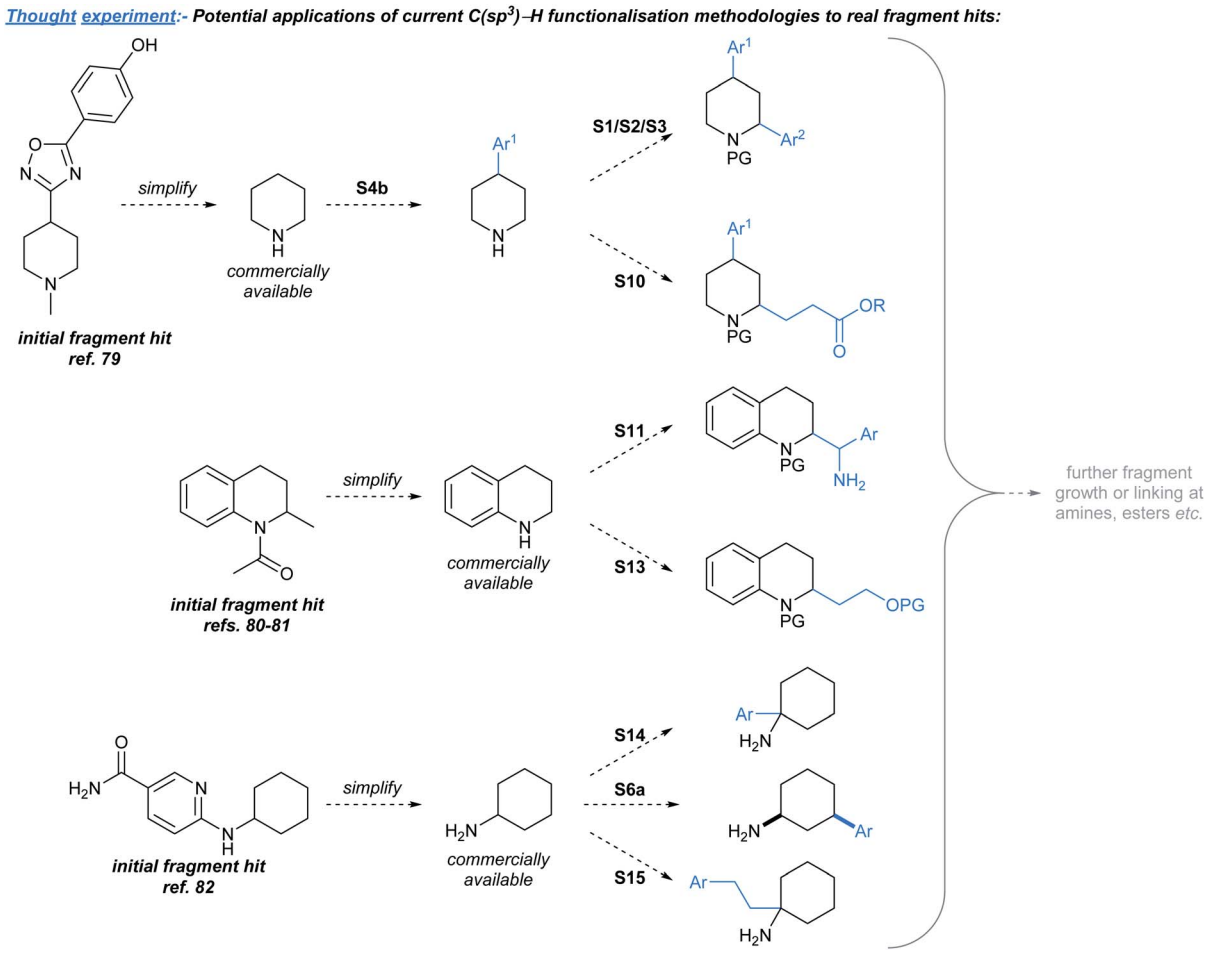

Fig. 3 A "thought experiment" showing how known sp^3-rich fragment hits might be structurally advanced using methodologies highlighted in this Perspective. "S#" refers to the specific scheme number in this manuscript for the transformation shown. For brevity, protecting group manipulation strategies are not shown. PG = protecting group.

atom efficiency, and compatibility with functional groups typically found in fragment hits (*e.g.* unprotected amines). Moving forwards, practitioners of fragment-based drug discovery will significantly benefit from the development of robust methods that resolve such challenges. Nonetheless the state-of-the-art hints at a bright future for both mission-driven[14,15,30] and 'blue skies' methodology development for sp^3-rich fragment-to-lead optimisation.

High yielding synthetic transformations that harness the bespoke fragment component as the limiting reagent, and that allow functionalisations of heteroalicyclic systems without the requirement for installation and removal of protecting groups and/or fixed directing groups, will revolutionise the efficiency of sp^3-rich fragment advancement. In some instances, ligand development may allow improvements to the regio- and diastereoselectivity of the methods discussed in this review. Reaction conditions that tolerate exposure to air and water will have high utility in array and automated reactions, enabling systematic growth and diversification at specific fragment vectors to explore biologically relevant chemical space, establish structure–activity relationships, and drive hit advancement. Biocatalysis is also likely to play an important future role in fragment elaboration, as recently highlighted by Cosgrove and Turner.[33]

Conclusions

We have summarised exciting recent synthetic developments that are likely to have high value towards elaborating sp^3-rich fragments. There remains huge scope for the establishment of efficient new classes of reactions that can enable fragment growth from specific vectors, incorporating structural motifs that can further their potential for interaction with their molecular targets. Future advances in this field will drive marked improvements in the development of fragment hits into higher affinity compounds, and ultimately new drugs.

Author contributions

D. J. F. conceived the idea for the Perspective. D. J. F. and M. J. C. conducted the literature investigation and wrote the draft manuscript. D. J. F. wrote the final manuscript.

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Conflicts of interest

There are no conflicts to declare.

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