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Redefining the Synthetic Logic of Medicinal Chemistry. Photoredox-Catalyzed Reactions as a General Tool for Aliphatic Core Functionalization

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Accession Codes

CCDC 2125956 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

The authors declare the following competing financial interest(s): D.W.C.M. declares a competing financial interest with respect to the integrated photoreactor.

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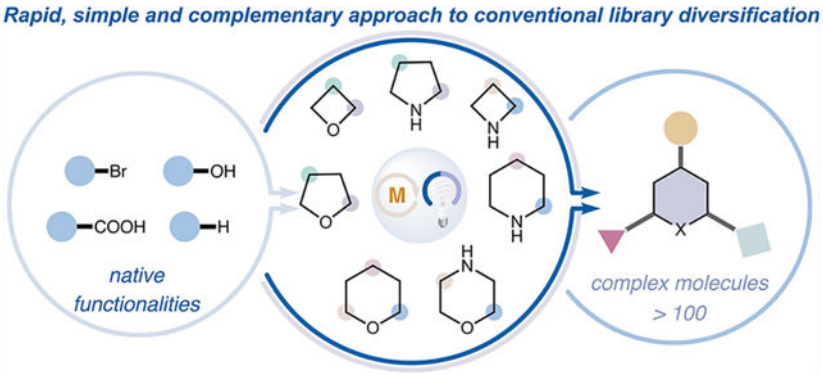
Abstract

C(sp^3)-rich aliphatic motifs in drug molecules are strongly associated with clinical success. Historically, the availability of compound libraries based on C(sp^3)-rich cores has been limited due to the challenging direct functionalization of aliphatic rings. Instead, most small molecule drug-like libraries are diversified around central aromatic rings. Herein, we present a general approach to the synthesis of diversified libraries featuring aliphatic core rings via photoredox catalysis under mild conditions.

Graphical Abstract



Therapeutically active small molecules represent an important class of medicinal agents. Most small molecule drugs are constructed around aromatic core architectures. These unsaturated scaffolds offer several pharmacological advantages, including resistance to metabolism, target affinity, and target specificity. Robust cross-coupling technologies, such as the Suzuki–Miyaura reaction,[1] S_NAr chemistry, and electrophilic aromatic substitution, offer powerful strategies for the functionalization of aromatic scaffolds en route to diverse small molecule libraries.[2]

To date, saturated ring systems have been relatively underexplored in MedChem. However, aliphatic motifs are strongly associated with improved pharmacological properties and an increased likelihood of clinical success.[3] Accordingly, there is a growing impetus within the industry to develop small molecule libraries built around high-value saturated core architectures. One approach is to append aliphatic motifs to an aromatic core ring structure. Multifunctionalization of aromatic scaffolds through electrophilic aromatic substitution, Suzuki coupling, and S_NAr reactions can provide collections of molecules for SAR studies. An orthogonal strategy is to start with a saturated core and append different functionalities, both aromatic and aliphatic, around the C(sp^3)-rich framework. This strategy is attractive as it can provide access to a complementary realm of chemical space. However, significant synthetic challenges exist. The multifunctionalization of saturated heterocycles has traditionally required multistep syntheses that cannot be readily conducted in parallel to generate structurally diverse libraries.[4]

Over the past 10 years, photoredox catalysis has emerged as a powerful, robust, and versatile tool for the synthesis of complex molecules from simple substrates bearing native functionalities.[5] Photoredox-based methods can achieve the direct functionalization of saturated heterocyclic core systems. As summarized in Figure 1c, heterocyclic substrates bearing a bromide, carboxylic acid, or C–H functionality can undergo direct arylation,[6] alkylation,[7] fluorination,[8] methylation,[9] trifluoromethylation,[10] or amination[11] through metallaphotoredox catalysis.

Herein, we demonstrate the functionalization of a range of saturated heterocycles en route to diverse collections of drug-like small molecules possessing saturated core motifs, exemplifying the power of photoredox catalysis to generate libraries of compounds bearing high-value aliphatic cores.

The tetrahydropyran (THP) motif is widely present in natural products and drug-like compounds and is of great interest in MedChem. Traditional cyclization-based approaches to the assembly of THP analogue libraries typically require long, linear syntheses and are beset by a poor substrate scope and limited starting material availability. A simple iterative route to libraries of functionalized THPs would offer significant savings in terms of time, money, and waste. With this goal in mind, we sought to develop a strategy for the multifunctionalization of 4-bromo-tetrahydropyran, an inexpensive feedstock chemical that offers distinct sites of functionalization at the C_4–X and C_2–H positions. We envisioned a two-step iterative strategy, commencing with selective functionalization of the strong C_2–H bond via a metallaphotoredox decatungstate-mediated arylation.[6d] Subsequent metallaphotoredox-mediated coupling at the 4-bromo position would give access to dual-functionalized scaffolds. As shown in Figure 2a, this general strategy was successfully applied to the synthesis of a wide range of high-value saturated core structures. Thus, C–H functionalization followed by cross-electrophile coupling[6c] furnished 2,4-diarylated adducts (Figure 2a, **1**–**3**) in useful yields over two steps. Moreover, 4-alkyl analogues were readily accessed through sp^3–sp^3 coupling reactions recently developed by MacMillan's group[7] (4–6). Over the past several years, powerful methods have been developed for the direct conversion of the aliphatic C–Br bond to a C–CF_3, C–F,[8] C–Me, or C–alkyl bond.[7] Using this reaction strategy, we successfully applied the iterative coupling strategy to the synthesis of more than 30 difunctionalized THPs in two steps from 4-bromo-tetrahydropyran (see the Supporting Information).

We next sought to develop a two-step iterative functionalization protocol based on the 4-carboxymethyl-tetrahydropyran aliphatic core. Protocols by which to transform both α-amino acids and unactivated aliphatic carboxylic acids into transient alkyl radical species that productively engage aryl or alkyl coupling partners to furnish C–C coupled adducts have been developed.[12] Incorporation of this general C–C bond formation strategy into our iterative protocol would provide access to a menu of valuable aliphatic core structures bearing C–N, C–F, C–Ar, and C(sp^2)–C(sp^3) motifs. A three-step iterative strategy for the functionalization of the 4-carboxymethyl-tetrahydropyran core is outlined in Figure 2b. First, the 2-aryl group is installed through nickel decatungstate-mediated arylation.

Next, hydrolysis produces the carboxylic acid, which can undergo photoredox-mediated coupling to generate a range of difunctionalized THP-derived products bearing heteroaryl (**7** and **8**), trifluoromethyl (**9**), and fluoro (**10**) motifs at position 4. Construction of the medicinally relevant C–N bond is of particular interest, as this class of compound is not readily synthesized through classical approaches.[11] Under our protocol, activation of the carboxylic acid with iodonium-mesitylene produces the corresponding N-substituted adduct in <1 h. A series of 2,6-difunctionalized tetrahydropyran derivatives were readily accessed from commercially available 2-carboxymethyl-THP through an analogous three-step sequence. As shown in Figure 2c, 2,6-diarylated compounds incorporating medicinally relevant nitrogen-containing heterocycles such as pyridines, pyrazoles, or pyrimidine-like motifs were obtained in good overall yields [**11**–**13**, 32–48% (see the Supporting Information for additional examples)].

A priority of medicinal chemistry is the design of drug molecules with a lower molecular weight and a lower complexity. Tetrahydrofuran-based small molecules have found application as polymerase, kinase, and protease inhibitors, as they are able to interact with proteins through hydrogen bonding.[13] As shown in Figure 3a, the general three-step protocol outlined above (Figure 2) could be directly adapted to the functionalization of the five-membered commercially available methyltetrahydrofuran-2-carboxylate. Decatungstate-catalyzed arylation, followed by hydrolysis and decarboxylative coupling, delivered 2,5-disubstituted THF cores in good overall yields [**14**–**16** (see the Supporting Information for more examples)].

Four-membered ring systems are valuable scaffolds in modern medicinal chemistry, providing structural rigidity and enhanced oxidative stability.[14] Frequently, these nonplanar motifs exhibit improved properties, such as increased solubility, through pK_a and LogD modulation. Oxetane and cyclobutene rings are commonly employed as isosteres of gem-dimethyl motifs, amides, acids, esters, and ketones.[15] The iterative strategy was amenable to four-membered ring systems. As shown in Figure 3b, commercially available 3-bromooxetane underwent a two-step sequence to furnish 2,3-diarylated oxetanes. First, blue light-mediated cross-electrophile coupling, between the oxetane C(sp^3)–Br bond and the C(sp^2)–Br bond of a heteroaryl fragment, furnished 3-aryloxetane adducts in good yields (40–61%). Subsequent C–H arylation, mediated by the designated polyoxometalate under near-ultraviolet light, furnished the 2,3-functionalized oxetane rings with good yields [**17** and **18** (see the Supporting Information for more examples)].

Following a complementary strategy, we accessed 1,3-difunctionalized cyclobutanes from commercially available methyl 3-bromocyclobutane-1-carboxylate through a three-step sequence involving (1) near-ultraviolet light-driven arylation, (2) hydrolysis of the methyl ester, and (3) metallaphotoredox-based coupling involving either nickel catalysis to access 1,3-diarylated scaffolds (**19**) or copper catalysis to install a C–N bond (**20**) [Figure 3c (see the Supporting Information for further examples)].

Nitrogen-containing aliphatic heterocycles are abundant in drug-like molecules, and we anticipated that the development of a robust strategy for the orthogonal functionalization of these frameworks would be of significant interest to the pharmaceutical community.[16] We

set out to develop strategies for the synthesis of structures bearing azetidine, pyrrolidine, piperidine, and morpholine core structures. By selecting *tert*-butyl 3-bromoazetidine-1-carboxylate as the precursor, we were able to gain access to 2,3-diaryl azetidine derivatives. In analogy to the 3-bromooxetane functionalization protocol (Figure 3b), the 3-bromoazetidine derivative was subjected to blue light metallaphotoredox cross-electrophile coupling to yield 3-aryl-substituted azetidines; subsequent C–H coupling at C_2 of the saturated core yields the desired 2,3-diaryl azetidine derivatives [**21** and **22** (see the Supporting Information for further examples)].

The pyrrolidine ring is one of the most widely used heterocycles in MedChem programs.[17] Pyrrolidine systems possess up to four stereogenic carbons and exhibit pseudorotation, a phenomenon that provides advantageous conformers and increased three-dimensional coverage.[18] As seen for THF rings, pyrrolidines are viewed as useful vectors allowing exploration of binding to a target biomolecule. Tetrahydro-pyrroles were readily functionalized to generate 2,4- and 2,5-diaryl pyrrolidine derivatives with good efficiencies. As outlined in Figure 4a, starting from the 4-bromo, 2-methyl carboxylate Boc-protected pyrrolidine, we achieved the first arylation using a dual nickel–iridium photocatalytic cross-electrophile coupling. Subsequently, a simple hydrolysis yields the carboxylic acid that we subjected to the next visible light decarboxylative coupling to obtain the 2,4-diaryl pyrrolidines in good overall yield [**25** and **26** in 50% and 28% yields, respectively (see the Supporting Information for additional examples)]. In a further demonstration of the versatility of this methodology, we synthesized a series of 2,5-diaryl pyrrolidine regioisomers from inexpensive, commercially available Boc-L-proline-methyl ester. Installation of the 5-aryl moiety was achieved via a photoredox-mediated hydrogen atom transfer (HAT) and nickel catalysis. Subsequent hydrolysis gave the corresponding Boc-protected proline, which was submitted to nickel-decarboxylative coupling to yield 2,5-diaryl pyrrolidine adducts [**23** and **24** (see the Supporting Information for more examples)].

Piperidine heterocycles are common motifs in natural and biologically active molecules and are some of the most abundant heterocyclic scaffolds in commercial drug molecules.[17]

As outlined in Figure 4b, 2,4-diarylated piperidines (**27** and **28**) were obtained from the readily available *tert*-butyl 4-bromopiperidine-1-carboxylate precursor according to a three-step procedure, commencing with the selective installation of an aryl ring at the more hydridic, electron-rich C_2 position via dual polyoxometalate HAT and nickel catalysis. Subsequent metallaphotoredox-mediated electrophile cross-coupling of the C–Br delivered the 2,4-diaryl piperidine frameworks in good yields [Figure 4b, 27 and 28, 30–39% yields (see the Supporting Information for further examples)].

Morpholine possesses unique features that render it attractive to medicinal chemists. The oxygen can act as a weak hydrogen bond acceptor, while the relatively electron-deficient cyclic system may participate in hydrophobic interactions. Morpholine's unique lipophilic–hydrophilic profile, along with its relatively low basicity compared with those of other N-heterocycles, serves to confer desirable drug-like properties. Substituted morpholines show promise as analgesic, antiobesity, antineurodegenerative, or anticancer drugs.[19] Despite great interest in this scaffold, the functionalization of morpholine rings remains quite challenging.

Starting with the readily available 4-(*tert*-butyl) 2-methyl morpholine-2,4-dicarboxylate, we selectively generated monoarylation products at the less hindered α-C–H bond, adjacent to the nitrogen (Figure 4c). We next submitted the methyl ester derivative to basic hydrolysis conditions to generate the carboxylic acid functional handle; subsequent nickel decarboxylative coupling with heteroaryl bromides yielded a variety of 2,5-morpholines in synthetically useful yields [**29** (see the Supporting Information for more examples)].

The piperazine skeleton is found in many biologically active compounds, and derivatives exhibit a wide range of pharmacological properties.[16] The commercially available 1,4-bis(*tert*-butoxycarbonyl) piperazine-2-carboxylic acid was first used as the coupling partner in a photoredox nickel-mediated decarboxylative coupling with 3-bromo-5-fluoropyridine to afford the 2-aryl piperidine analogue in 74% yield. Next, using the photochemical C–H functionalization mediated by decatungstate and nickel, we would be able to access different diastereomers because the starting material has four distinctive non-sterically encumbered strong C–H bonds (**30**). Indeed, the reaction proceeds smoothly for a variety of heteroaryl bromides, yielding the desired diastereomers in useful yields for MedChem targets (see the Supporting Information for more examples).

Finally, we have demonstrated the use of a simple aliphatic core as a central starting point to sequentially incorporate up to three different substituents. As shown in Figure 5, readily available oxetane, pyrrolidine, or THP derivatives were subjected to a three-step photoredox sequence to afford **31**, **32**, or **33**, respectively, in useful yields.

In conclusion, we have developed a robust photoredox iterative strategy for the selective rapid bifunctionalization of heterocyclic saturated ring cores. This methodology provides direct access to medicinally relevant polyfunctionalized core structures based on the azetidine, oxetane, cyclobutene, pyrrolidine, tetrahydrofuran, tetrahydropyran, piperidine, morpholine, and piperazine ring systems. This technology represents an unprecedented, versatile approach to the synthesis of libraries of drug-like derivatives containing aliphatic core structures. We foresee its wide implementation in both academic and industrial settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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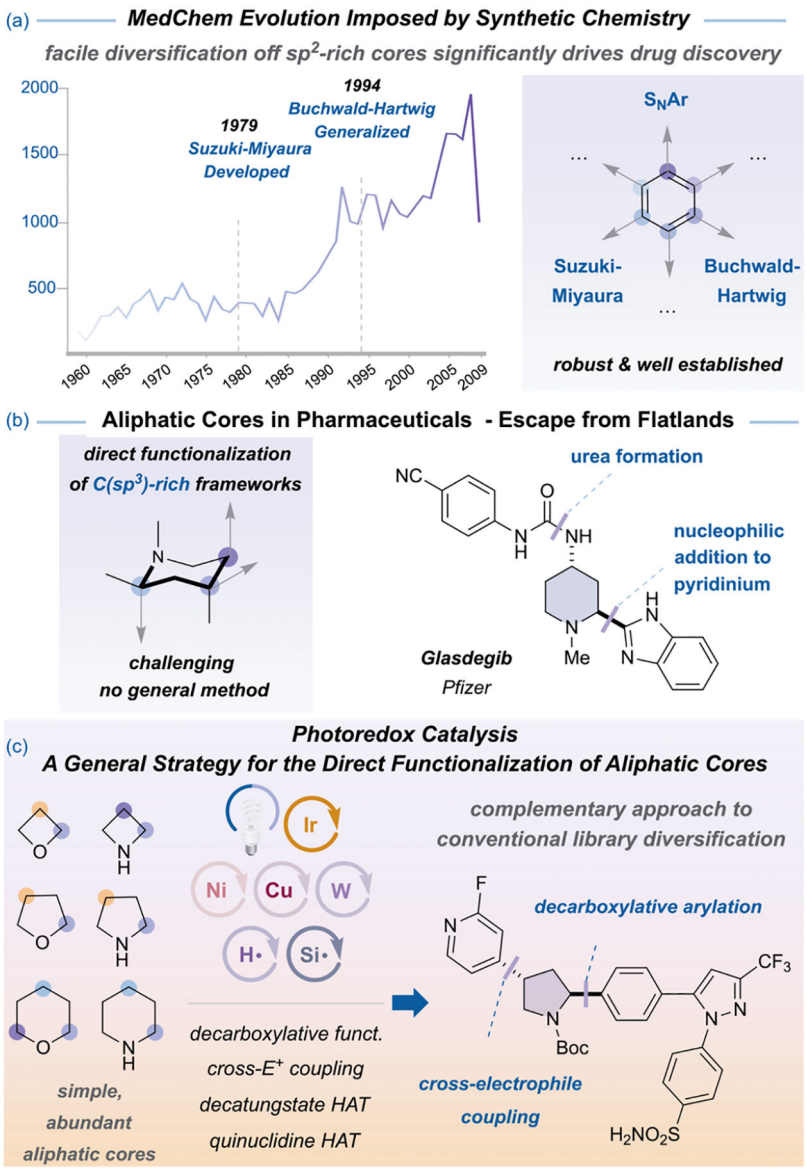

Figure 1.
Traditional vs state-of-the-art MedChem synthetic strategies in Pharma.

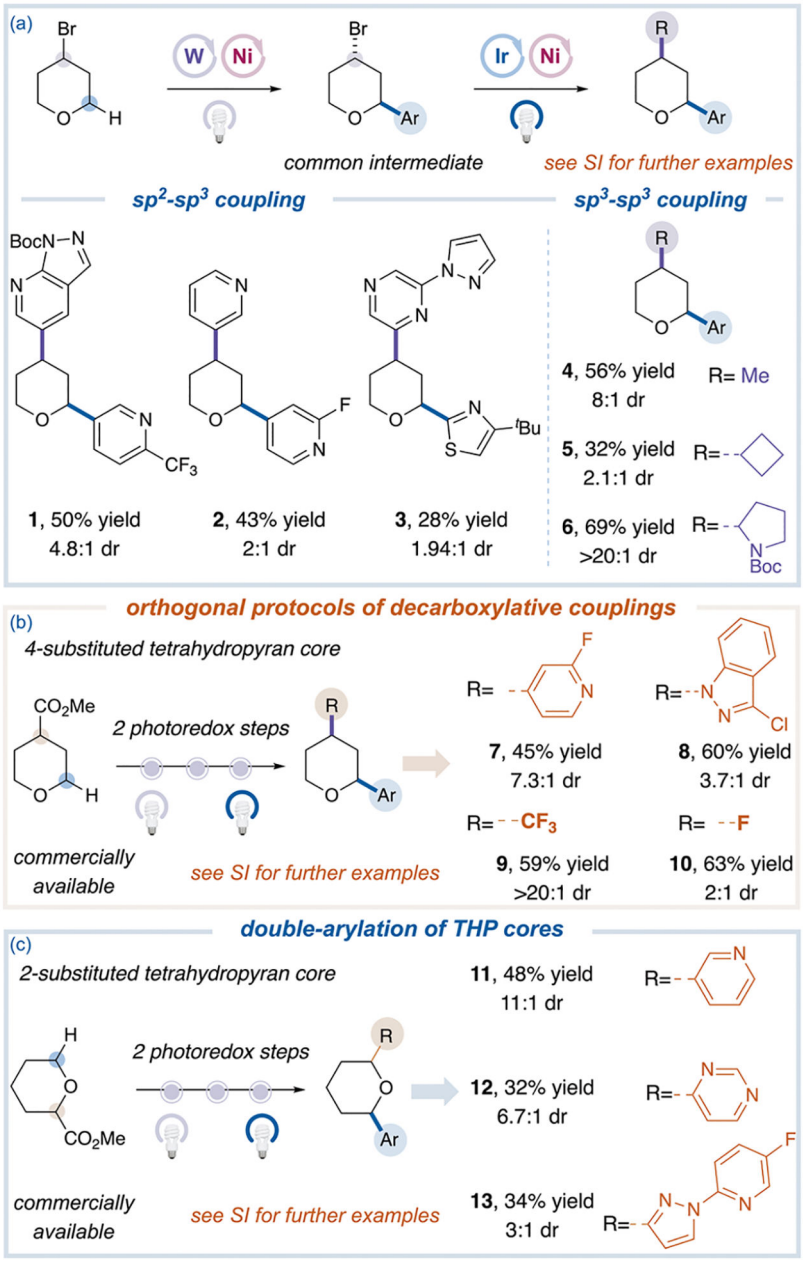

Figure 2.
Iterative functionalization of the THP core.[20]

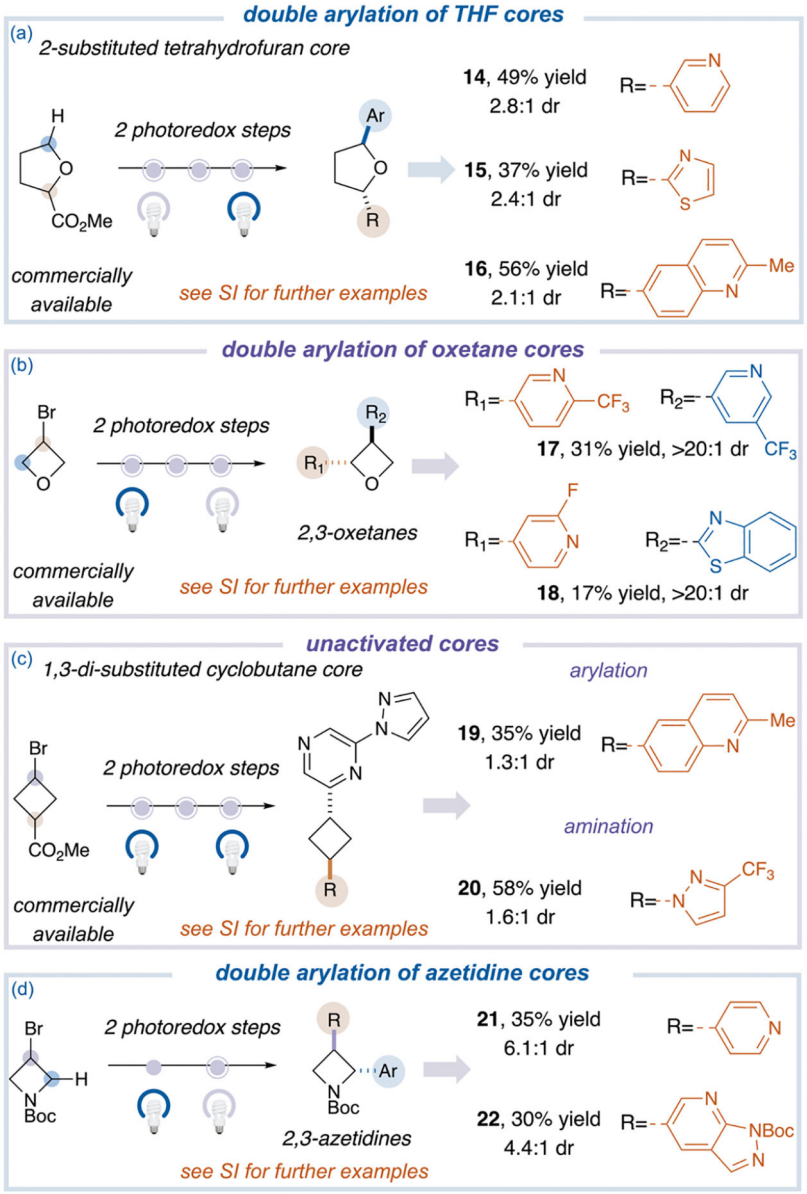

Figure 3.
Small oxygen-, carbon-, and nitrogen-containing aliphatic cores.[20]

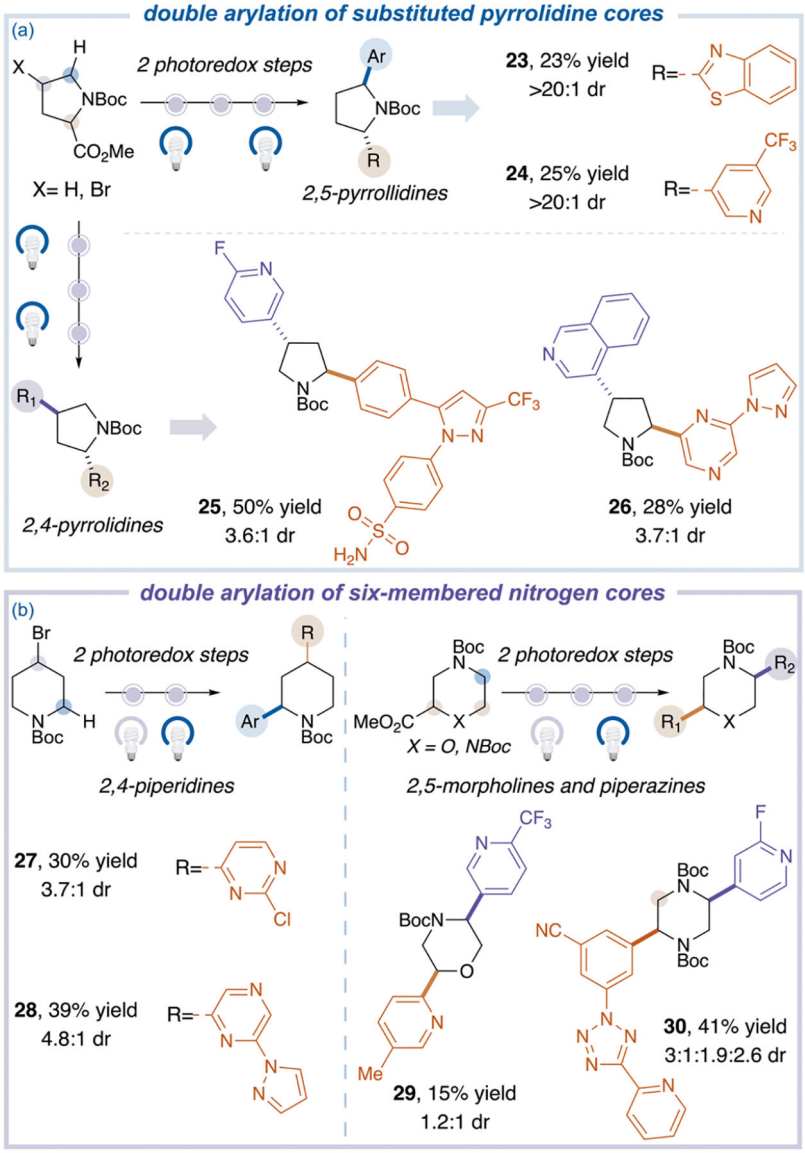

Figure 4.

Five- and six-membered nitrogen-containing aliphatic cores.[20]

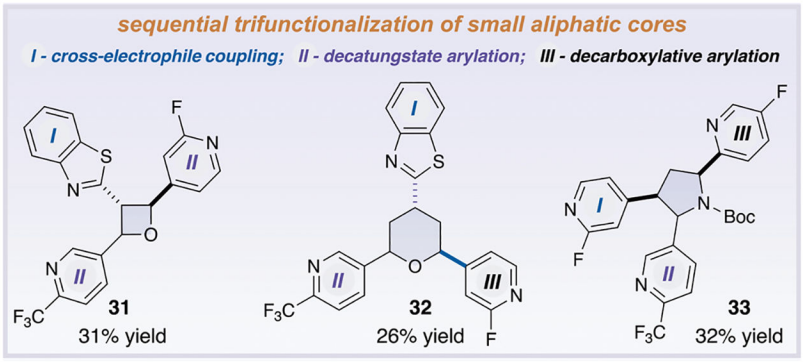

Figure 5.
Iterative arylation via photoredox catalysis to obtain trifunctionalized aliphatic cores.