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REVIEW

An overview of late-stage functionalization in today's drug discovery

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ABSTRACT

Introduction: Late-stage functionalization (LSF) can introduce important chemical groups in the very last steps of the synthesis. LSF has the potential to speed up the preparation of novel chemical entities and diverse chemical libraries and have a major impact on drug discovery. Functional group tolerance and mild conditions allows access to new molecules not easily accessible by conventional approaches without the need for laborious *de novo* chemical synthesis.

Areas Covered: A historical overview of late-stage functionalization and its applicability to drug discovery is provided. Pioneering methodologies that laid the foundations for the field are briefly covered and archetypal examples of their application to drug discovery are discussed. Novel methodologies reported in the past few years mainly stemming from the recent renaissances of photoredox catalysis and radical chemistry are reviewed and their application to drug discovery considered.

Expert opinion: It is envisioned that late-stage functionalization will improve the efficiency and efficacy of drug discovery. There is evidence of the widespread uptake of LSF by the medicinal chemistry community and it is expected that the recent and continuing endeavors of many academic laboratories and pharmaceutical companies will soon have an impact on drug development.

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1. Introduction

Chemical synthesis is a key enabler in drug discovery. Whether it is the generation of vast libraries of compounds, manipulation of natural products or developing structure-activity relationships from a lead compound, synthesis is an essential step in the drug discovery process. Late-stage diversification has long been the established approach for generating vast libraries of compounds from a common intermediate. Historically, cross coupling of pre-functionalized fragments with various handles has been the major method for diversification. In turn, problems arising from truncated libraries that have generated flat, uninspired compounds have limited the chemical landscape [1]. Late-stage functionalization of C–H bonds offers a tantalizing prospect of diversification, particularly as it includes sp^3-carbon atoms, opening up further chemical space. In order for late-stage diversification to be a useful tool for drug discovery, advances in high-throughput technologies and predictive techniques to accelerate biological testing of generated leads are required [2].

In addition to diversification, is the concept of late-stage functionalization (LSF), where chemists are not only functionalizing C–H bonds, but they are doing it selectively in the presence of many other functional groups [3,4]. This allows for the generation of chemical libraries and natural products alike, modulating key pharmacological properties such as metabolism or efficacy among many others, without the need for developing or redesigning synthetic methods and restarting synthesis.

LSF has the potential to revolutionize chemical synthesis across the spectrum, however this review will be focusing on its role in drug discovery. In particular we have focused on examples that functionalize complex drug-like molecules at C–H bonds rather than C–H functionalization that could be used to construct simpler intermediates. We will first highlight some established methods from LSF before examining some more recent methodologies.

2. Background

2.1. C–H functionalization

A typical understanding of the reactivity of organic molecules requires the presence of a heteroatom or unsaturation to install a new bond [5]. Installation of functional groups therefore is generally achieved via multiple transformations and functional group interconversions and hence the product bears little resemblance to the starting materials (Illustrated in Figure 1(a)). As the functional groups present in a drug are often imperative for biological activity, the development of reactions that transform the ubiquitous C–H bonds that make up the framework of drug molecules would offer a powerful tool for drug optimization and development (Figure 1(a)). Unfortunately such reactions are not trivial. On the topic of C–H bond activation, Goldman and Goldberg highlight that the C–H bond is often thought of as the 'un-functional group' and the common representation of organic molecules with 'invisible' hydrogens reflects both their ubiquitous

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Article Highlights

- Late-stage functionalization (LSF) allows for the rapid exploration of structure-activity relationships (SAR) and directed improvement of on-target potency.
- LSF has the potential to modulate the pharmacokinetic and pharmacodynamic properties of a drug without modifying functionality necessary for biological activity and also without the need for *de novo* synthesis.
- New methodologies in the fields of photoredox catalysis, metallophotoredox catalysis, transition metal catalysis, radical chemistry and redox chemistry have found recent application in the late-stage functionalization of drugs and drug-like molecules.
- There is some evidence of the uptake of LSF by the pharmaceutical industry and it is predicted that as more powerful and reliable methods are developed the impact of LSF on drug discovery will become more obvious.
- Before the potential of LSF can be realized, advances in analytical and biological technologies are necessary to facilitate the identification of analogues and evaluation of their biological activity.

This box summarizes key points contained in the article.

nature and lack of reactivity [6]. Despite this, it has long been a goal of chemists to selectively transform C–H bonds to new bonds (such as C–C, C–O, C–N and C–X). In a recent perspective article Hartwig presents a comprehensive review of C–H functionalization chemistry, from a chemistry curiosity to a useful methodology for synthetic chemists [7]. Pioneering C–H functionalization methods originally used for the conversion of light alkanes to liquid products, have been refined over time to find application in the synthesis of complex natural products and medicinally active compounds. The reliable regioselective functionalization of unprotected structurally complex molecules is a major challenge for synthetic chemistry. Over the past two decades there have been significant developments in the field of C–H functionalization chemistry. Improved methods with diverse substrate scopes and impressive functional group tolerance has meant that this chemistry is now applicable to the synthesis of complex molecules, including pharmaceuticals, in a reliable fashion [8]. Analytical technologies have also improved, allowing for the rapid identification of the site of functionalization without slow and laborious product isolation and structure determination [3,9].

2.2. Application to drug discovery

The development of a drug is a lengthy and expensive process. The rising cost of development and low approval rates has meant that pharmaceutical companies are looking to implement changes that streamline development processes and increase output [10]. A significant stage in the drug discovery process is hit-to-lead and lead compound optimization. Optimization of a hit to a lead candidate can take pharmaceutical companies several years and cost over half a billion dollars (around a third of the total cost) [11]. Novel synthetic methodologies that expedite the synthesis of analogue libraries have the potential to alleviate this bottleneck. In their recent review, Boström and coworkers highlight the synthetic chemistry used for hit and lead optimization efforts is generally dominated by a few known, robust reactions [2]. Reliable late-stage functionalization methodologies represent an opportunity to expand the medicinal chemists' toolbox and in turn increase the chemical space explored in drug discovery efforts.

Drug development involves a balance between improving the potency or affinity of a drug for a particular target and optimizing properties such as solubility and permeability to ensure the drug reaches the target of interest. Within the drug discovery process, late-stage functionalization offers a valuable tool for the optimization of a lead compound by the synthesis of a library of analogues. Additionally, directed functionalization can be used to block metabolically liable C–H bonds. It is frequently found that small changes in structure can have a profound impact on the biological profile of a molecule. An archetypal example of this is the so-called 'magic methyl' effect, whereby addition of a single methyl group can have a large effect on potency or affinity. A recent example of this comes from the development of MERTK (MER proto-oncogene, tyrosine kinase) inhibitors by Zhao and coworkers who observed a significant difference in potency and also selectivity over other kinases with the addition of a single methyl group (Figure 1(b)) [12]. This observation was made after an extensive SAR study involving the divergent synthesis of a library of analogues. An alternative and potentially more attractive approach would be to utilize LSF to selectively install such groups at the end of the synthesis.

Late-stage functionalization also has potential application in the growing field of fragment-based drug discovery, which involves optimizing low molecular weight fragments that bind to a target of interest [8]. Spectroscopic methods can be used to identify specific C–H bonds where introduction of additional substituents by LSF methodologies would be expected to give improved biological activity.

2.3. Established methodologies

There are a number of well established methodologies that utilize C–H groups as handles and points of diversification to functionalize complex molecules. In their recent review Cernak and coauthors provide a comprehensive review of the C–H functionalization chemistries available for the LSF of drug-like molecules [3]. Methodologies are broadly classed based on the their selectivity manifolds. Guided reactions achieve C–H selectivity by directing groups or steric interactions, while innate reactions achieve selectivity by the intrinsic reactivity of the C–H bond. An understanding of the selectivity manifolds encountered in C–H functionalization allows one to match the reactivity of a certain C–H bond with methodologies that could achieve functionalization at that particular bond. The diversification of sesquiterpene lactone sclareolide is a quintessential example of how different LSF methodologies (including oxygenation [13], chlorination [14], fluorination [15], bromination [16], amination [17], and azidation [18]) can install a range of diverse functional groups (Figure 1(c)). These reactions occur at the most reactive and accessible C–H bond (innate selectivity) allowing for a library of compounds to be synthesized from this reaction vector without the need for the *de novo* synthesis of each analogue.

A broad range of C–H functionalization reactions have been reported that have potential application in drug discovery. Some of the more established methods include borylation reactions for further diversification by cross-

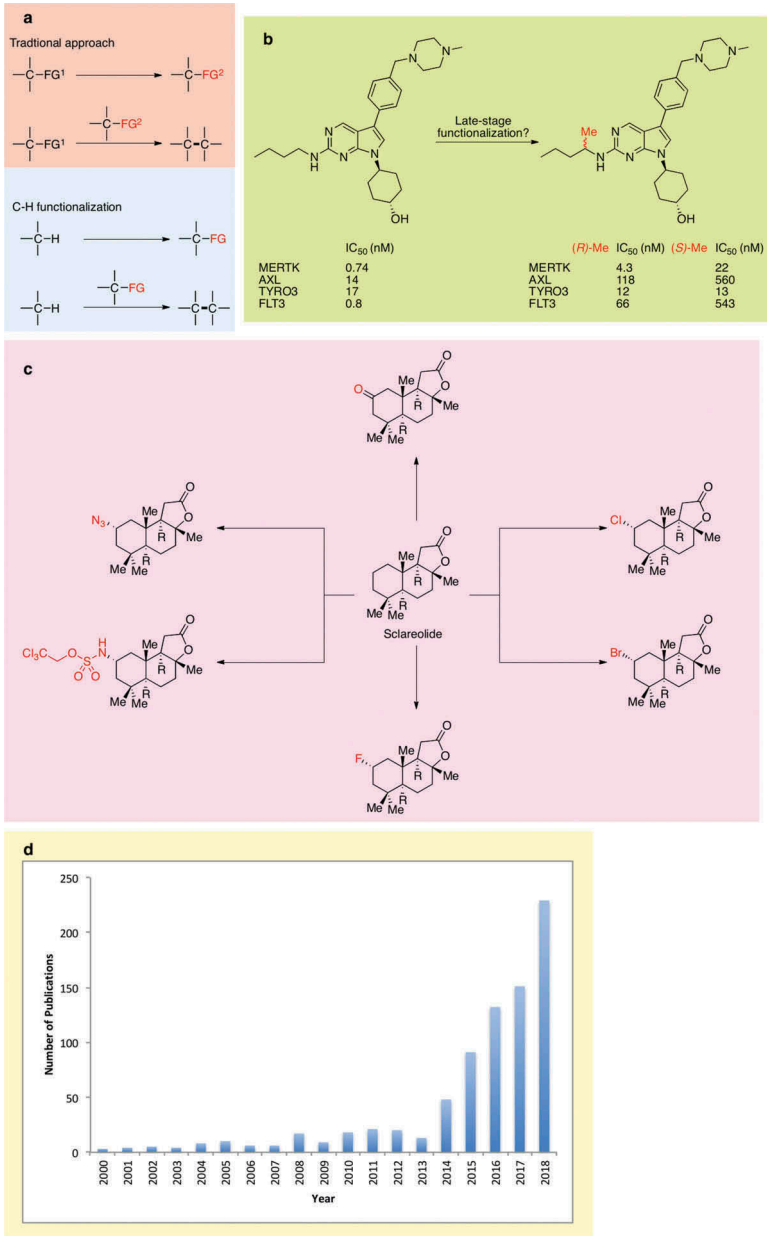

Figure 1. (a) A comparison of the traditional approach to organic synthesis by functional group transformations (red), and synthesis by means of C–H bond functionalization (blue). (b) The 'magic methyl' effect in action. Installation of a single methyl group drastically changes the affinity of the drug for a number of kinases. The installation of such small groups at the last stages of synthesis would accelerate the drug discovery process. (c) Various late-stage functionalization methodologies reported by a range of research groups to generate analogues of sclarolide. (d) The rapid rise in publications including the concept of late-stage functionalization, particularly in the past few years.

coupling [19], halogenation reactions [20], oxidation reactions for analogue and metabolite synthesis [21,22] and carbon-carbon bond formation reactions [23–25]. Literature reports containing the concept of LSF have increased markedly in the last few years as highlighted in Figure 1(d) [26]. In light of previous comprehensive reviews and the recent increase in interest, this review will focus on advances made in the past few years.

3. Recent advances

Since Cernak and coworkers' comprehensive LSF review in 2016 [3] there has been a discernible focus in the academic community to develop novel chemical reactions that facilitate LSF. It is a testament to the importance of the field that many of the preeminent minds in organic chemistry have included LSF strategies into their research programs. In the past few years there has been a large number of C–H functionalization methodology publications that include drug molecules in the substrate scope to demonstrate applicability to LSF.

3.1. Photoredox catalysis

The recent renaissance of photocatalysis has produced a series of new activation modes and a wide variety of bond forming reactions and synthetic methodologies [27]. Photoredox catalysis has

enabled the development of completely new reaction mechanisms that facilitate the construction of challenging carbon-carbon and carbon-heteroatom bonds. It is therefore not surprising that many synthetic methodologies for the LSF of unactivated C–H bonds employ photoredox catalysis.

Shaw and coworkers have developed a general method for site-selective C–H amination of arenes (Figure 2(a)) [28]. An organic photoredox-based catalyst system, consisting of an acridinium photooxidant and a nitroxyl radical, promotes site-selective amination of a variety of arenes with heteroaromatic azoles. Under the optimized reaction conditions *O*-acetylcapsaicin was coupled with pyrazole to give a single regioisomer in good yield (66%).

Heteroaromatic compounds are known to readily undergo C–H functionalization reactions with a variety of radicals via the Minisci reaction [29]. While such reactions are effective for simple heteroarenes, the acidic, oxidizing and overall harsh reaction conditions are not suitable for LSF of complex drug-like compounds. Photoredox catalysis however, allows for the efficient generation of radicals under mild conditions. There have been a number of recent publications that utilize photoredox catalysis to generate radicals from a range of sources. This review will include examples that have clearly demonstrated applicability to LSF.

Researchers from Merck have reported a photoredox-catalyzed method for the room temperature C–H hydroxymethylation of heteroarenes (Figure 2(b)) [30]. The authors demonstrate the selective generation of hydroxymethyl radicals from methanol using an iridium photoredox catalyst and benzoyl peroxide as a terminal oxidant. Under the developed reaction conditions, the isoquinoline-containing drug fasudil provided the hydroxymethylated product in 60% yield. In comparison, under standard Minisci conditions using ammonium persulfate in aqueous acid only 8% of the desired product was obtained.

Jin and MacMillan reported the use of readily available primary alcohols as alkylating agents in heteroarene C–H functionalization via a Minisci-type reaction (Figure 2(c)) [31]. The method successfully merges photoredox and hydrogen atom transfer catalysis to mimic the key step in enzyme-catalyzed DNA biosynthesis via a spin-center shift elimination of H_2O to generate radical intermediates from simple alcohols. The utility of the method in LSF is demonstrated by the alkylation of pharmaceutical milrinone, which proceeds in 43% yield under the mild reaction conditions.

In a similar fashion Matsui and coworkers have developed a novel method for the C–H alkylation of heteroarenes (Figure 2(d)) [32]. Primary, secondary and tertiary alkylfluoroborates are used to functionalize complex heteroaromatics using Fukuzumi's organocatalyst and potassium persulfate as a mild oxidant. A wide substrate scope is investigated including the alkylation of topoisomerase I inhibitor camptothecin. The isopropyl analogue is obtained in 57% yield using one equivalent of readily available potassium isopropyltrifluoroborate.

An alternate Minisci alkylation protocol reported by Nuhant and coworkers employs an inexpensive earth-abundant catalyst, decacarbonyldimanganese to generate alkyl radicals from alkyl iodides (Figure 2(e)) [33]. The high-throughput LSF of four drugs including hydroquinine is demonstrated for a range of alkyl iodides. Good to excellent yields are obtained in most cases (100% for the cyclohexyl derivative).

Wang and coworkers have utilized photoredox catalysis to generate carbyne equivalents to enable an assembly-point functionalization strategy for chiral carbon center construction (Figure 2(f)) [34]. Photoredox catalysis is used to generate diazomethyl radicals as direct equivalents of carbyne species, which undergo site-selective aryl C–H bond cleavage to enable diazomethylation. The carbyne source then allows for the successive installation of a chiral carbon center using orthogonal catalytic activation modes. The diazomethylation of complex drug molecules is demonstrated for a range of compounds including a protected duloxetine species. A host of diversification reactions are performed including N-H, O-H and C–H insertions, trifluoromethylation and cyclopropanation reactions to form a library of chiral compounds all in good to excellent yields as mixtures of diastereomers.

3.2. Metallophotoredox catalysis

New catalysis platforms that combine multiple catalytic manifolds have proven to be powerful methods to enable novel chemical transformations. The recent emergence of metallophotoredox catalysis, which combines photoredox catalysis and transition metal catalysis, harnesses the unique reactivity of different activation modes to overcome disfavored reaction pathways. The ability of photoredox catalysts to modulate the oxidation state of transition metal catalysts allows for the formation of reactive, high-valent catalyst species to enhance the rate of reaction [27]. The ability to selectively achieve challenging C–C and C–X disconnections means that metallophotoredox catalysis has found use in the LSF of small molecules.

The formation of sp^3 C–N bonds has been one of the major challenges in the field of cross-coupling chemistry. The MacMillan group has utilized metallophotoredox catalysis to develop a number of carbon–heteroatom bond forming reactions, including a fast and mild decarboxylative C–N bond forming reaction (Figure 3(a)) [35]. The reaction couples primary, secondary and tertiary alkyl carboxylic acids (through iodonium activation) and a range of nitrogen nucleophiles by the merging of iridium photocatalytic and copper catalytic cycles. Drug molecules containing alkyl carboxylic acids or nitrogen nucleophiles (such as the B-Raf enzyme inhibitor zelboraf) were shown to be viable coupling partners, with good to excellent yields obtained.

The MacMillan group has also utilized metallophotoredox catalysis to achieve important C–C bond forming reactions. Recently they disclosed a method for selective sp^3 C–H alkylation via a polarity-match-based cross-coupling (Figure 3(b)) [36]. The methodology employs photoredox, nickel and hydrogen atom transfer catalysis to achieve hydridic C–H bond abstraction (enabled by polarity matching), alkyl halide oxidative addition and reductive elimination to allow alkyl-alkyl coupling. The coupling is selective for the α-carbon of amines, ethers and sulfides, common functionalities found in drug-like molecules. Application to LSF was demonstrated with *N*-Boc

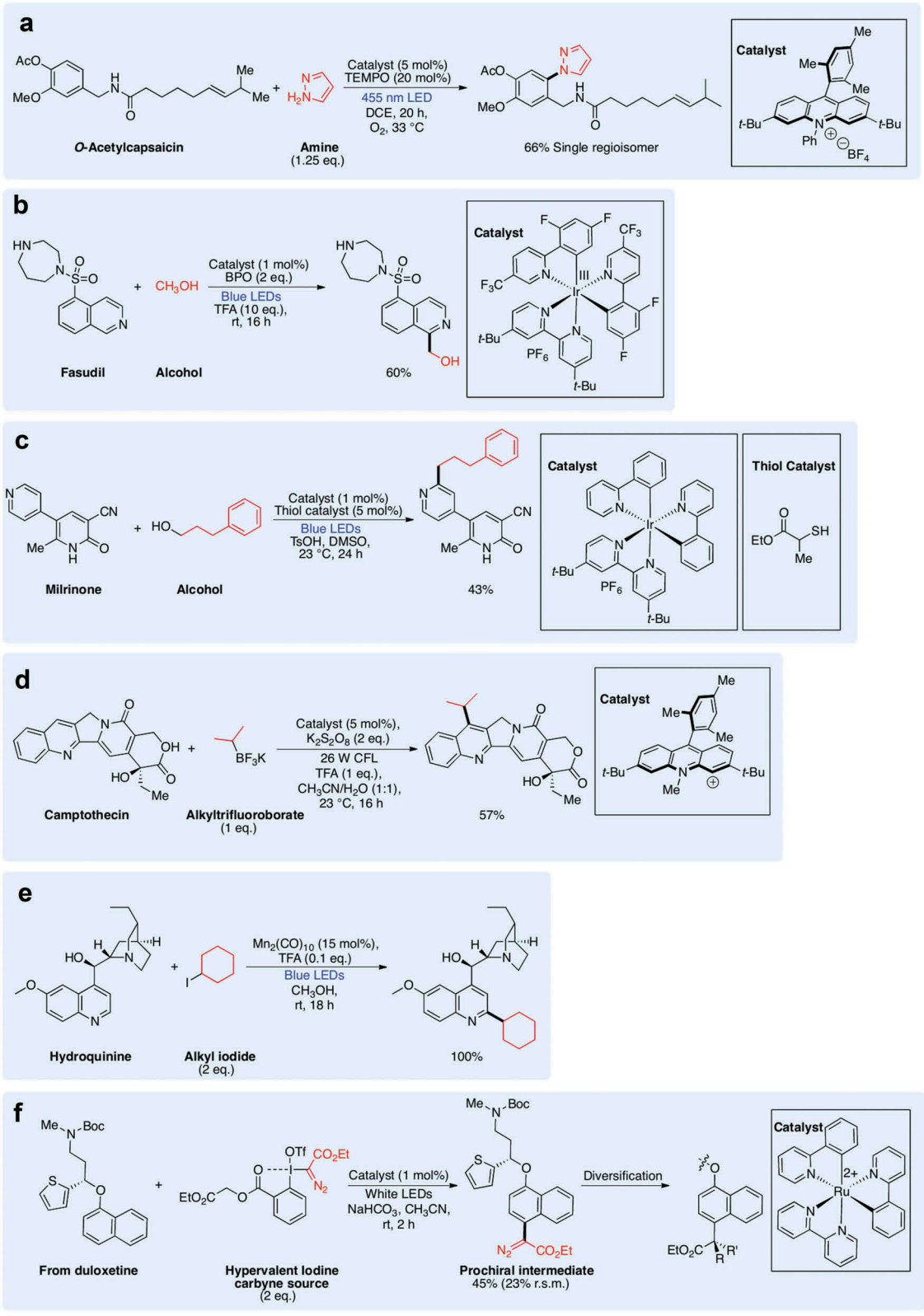

Figure 2. Late-stage functionalization of drug-like molecules using photoredox catalysis.

protected fluoxetine, which was alkylated in moderate yields (45–52%) at the methyl position with a range of alkyl bromides. The method offers an alternative to other reported strategies for the selective α-C–H functionalization of amines [37–39].

In 2018 the MacMillan group reported a metallophotoredox mediated decarboxylative trifluoromethylation reaction using an iridium photocatalyst, copper catalyst and Togni's reagent I as a trifluoromethyl source (Figure 3(c)) [40]. The incorporation of trifluoromethyl groups in drug

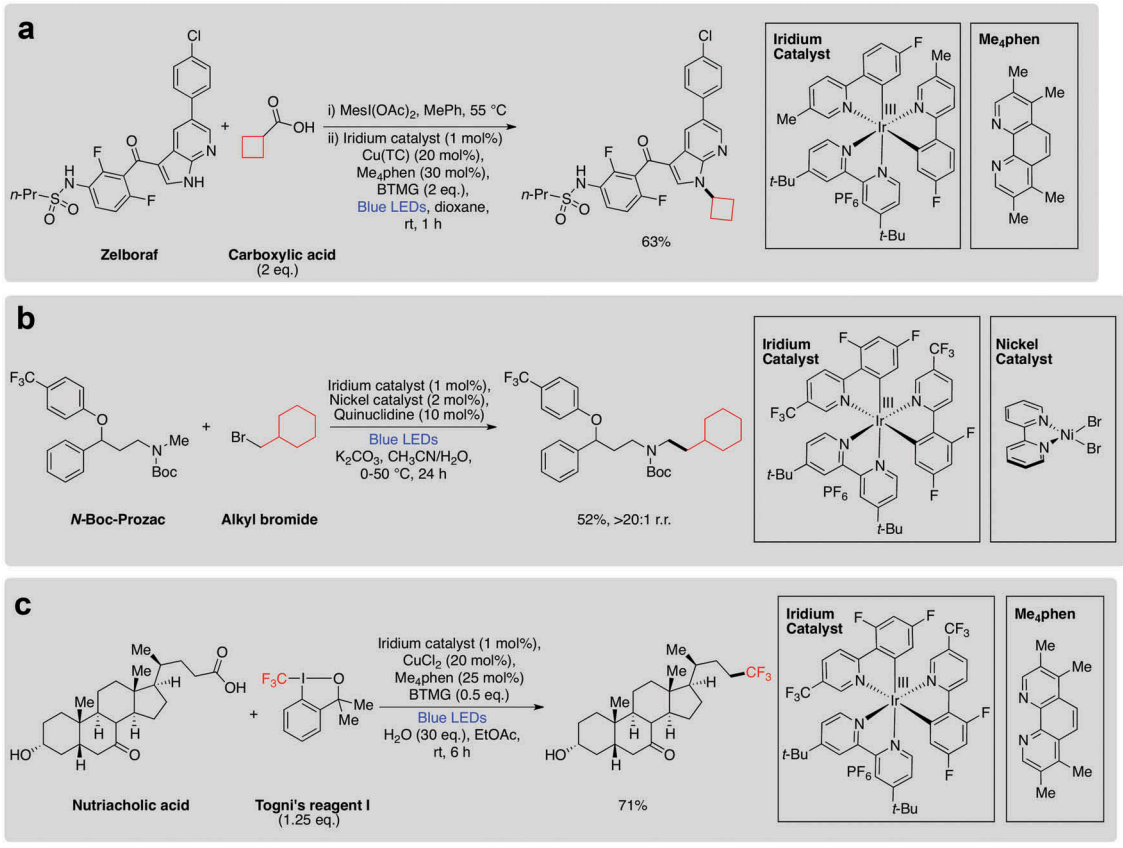

Figure 3. Late-stage functionalization using metallophotoredox catalysis.

candidates has proven to be a viable strategy to preclude *in vivo* metabolism and, in some cases, improve efficacy [41]. The reaction is shown to tolerate primary, secondary and tertiary carboxylic acids, the presence of an array of functional groups, and strained systems. The late-stage trifluoromethylation of a range of carboxylic acid containing drugs is demonstrated including the steroid nutriacholic acid, which provided the desired product in 71% yield.

3.3. Transition metal catalysis

Metal-mediated cross-coupling reactions for the construction of carbon-carbon and carbon-heteroatom bonds have revolutionized organic chemistry [42]. In general, transition metal-mediated cross coupling involves the coupling of two pre-activated species such as an organometallic species and an organohalide species. Recently though, transition metal-promoted functionalization of ubiquitous C–H bonds has emerged as a powerful tool for late-stage diversification and functionalization.

Many of the top-selling FDA approved drugs such as imatinib and meclizine contain a benzylic nitrogen group [43]. Standard methods to install nitrogen however rely on functional group transformations from pre-oxidized carbon-heteroatom precursors. This approach has obvious limitations for the functionalization of complex natural products and drug-like molecules. Clark and coworkers have developed a method for direct intermolecular manganese perchlorophthalocyanine-catalyzed benzylic C–H amination (Figure 4(a)) [44]. The reaction proceeds with impressive site-selectivity and functional group tolerance as demonstrated by the amination of a sulbactam derivative selectively at the more electron rich benzylic position and in the presence of the functional group rich β-lactam core.

Biaryl motifs are ubiquitous in pharmaceutically relevant compounds. Traditional cross-coupling methods have made the synthesis of biaryl units viable; however a more attractive approach would be C–H arylation. Generally however, such C–H functionalization methods do not tolerate the polar and reactive functionalities that tend to decorate pharmaceuticals. Simonetti and coworkers have developed a cyclometallated ruthenium catalyst which enables the arylation of densely functionalized molecules (Figure 4(b)) [45]. A mechanistic investigation revealed the Ru(II) catalyzed C–H arylation of directing-group containing arenes and aryl halides relied on the formation of bis-cycloruthenated species as the key intermediate required for oxidative addition. The authors demonstrate the utility of the reaction on a range of (hetero)aromatic compounds with an sp^2 nitrogen (such as sulfaphenazole) suitable for cyclometallation and for (hetero)aromatic (pseudo)halides with biological activity.

The functionalization of aryl C–H bonds with main group reagents such as silanes and boranes occurs with unique regioselectivity dictated by the catalyst used. The obtained compounds are useful intermediates for further functionalization and diversification. The silylation of aryl C–H bonds is less developed than the corresponding borylation reactions.

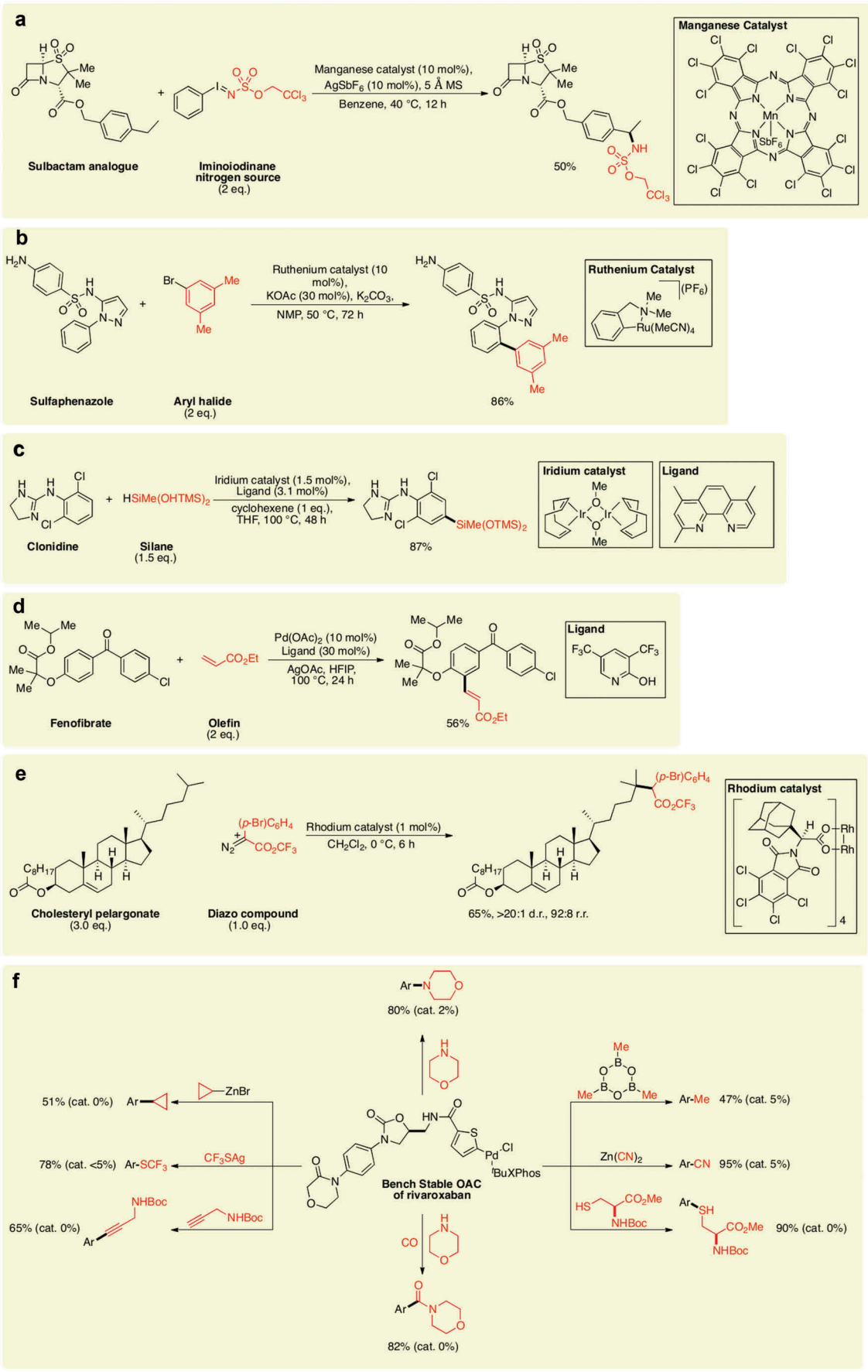

Figure 4. Late-stage functionalization using transition metal catalysis.

Despite their synthetic utility, reactions for the catalytic silylation of C–H bonds generally require harsh reaction conditions, excess of reagents and/or directing groups. Cheng and Hartwig have reported a method for the iridium catalyzed reaction of $HSiMe(OSiMe_3)_2$ and (hetero)arenes with high levels of sterically driven regioselectivity (Figure 4(c)) [46]. The silylation of a series of pharmaceutical compounds including clonidine (87% yield) demonstrates the applicability of this method for LSF.

The use of directing groups for the activation of C–H groups has been an important development in the LSF of complex molecules. Metal-catalyzed non-directed activation however would allow for the functionalization of more distant sites and could be applied to molecules that do not contain suitable directing groups. This challenging field has been hindered by the lack of suitably reactive catalysts to perform such transformations, especially on electron poor systems. Recently Wang and coworkers reported the use of a 2-pyridinone ligand that binds to palladium and accelerates non-directed C–H functionalization with the arene as the limiting reagent (Figure 4(d)) [47]. The site-selectivity of the transformation is governed by a combination of steric and electronic effects and hence provides a complementary method to directed C–H functionalization. A huge substrate scope is explored including a number of pharmaceutical compounds such as fenobrate, which underwent a site-selective olefination reaction in 56% yield.

One of the major challenges for the direct reaction of C–H bonds is site-selectivity, as most organic compounds possess many similar C–H bonds. Most procedures rely on substrate control where one particular C–H bond is more reactive than the others. However, a more general method would be to use catalyst control to afford selectivity akin to how nature uses enzymes to selectively functionalize certain C–H bonds. The Davies group has recently developed methods for the site-selective and stereoselective functionalization of unactivated C–H bonds [48,49]. In 2017 they disclosed a rhodium-carbene-induced C–H insertion at the most accessible tertiary C–H bond (Figure 4(e)) [49]. It is demonstrated that site-selectivity is catalyst dependent and judicious choice of catalyst, in this case Rh_2(*S*-TCPTAD)$_4$, affords C–H functionalization of cholesteryl pelargonate at the most accessible tertiary carbon as a single diastereomer in the presence of many C–H bonds.

A recent collaboration between Merck and Stephen Buchwald's laboratory has developed a novel approach to tackle the challenge of cross-coupling densely functionalized substrates (Figure 4(f)) [50]. They demonstrate that the use of stoichiometric quantities of preformed oxidative addition complexes (OACs) of drugs and drug-like aryl halides improves the rate and yield of cross-coupling reactions compared to the analogous catalytic reactions. The functional group tolerance of this method means it is well suited for the late-stage diversification of drug-like leads. The OAC derived from the drug rivaroxaban is shown to undergo a range of reactions including Buchwald-Hartwig, Suzuki, Negishi, Sonogashira and other cross coupling reactions, many of which do not yield the desired product under analogous catalytic conditions (yields from analogous reactions under standard catalytic conditions are in parentheses).

3.4. Radical reactions

The practicality (tolerant to air and moisture), high reactivity, and chemoselectivity of radical reactions allow for rapid access to biologically relevant molecules. Radicals are generally inert to a range of reactive functionalities present in most drug-like compounds such as alcohols and amines. This has motivated their application to the LSF of complex molecules.

The development of site-selective, intermolecular functionalization of isolated aliphatic C–H bonds is one of the most formidable challenges in organic chemistry. Rather than developing novel reaction manifolds to effect specific transformations, Czaplyski and coworkers have addressed the challenge of alkane functionalization by the site-selective installation of a highly versatile xanthate intermediate (Figure 5(a)) [51]. The C–H xanthylation proceeds in useful chemical yields with the substrate as the limiting reagent and an easily prepared *N*-xanthylamide under blue LED irradiation. The reaction tolerates a range of functional groups and is shown to be applicable to the LSF and diversification of complex molecules such as (+)-sclareolide where reaction occurs at a single site with 55% isolated yield on gram-scale. Further pharmaceutically relevant derivatization of the xanthate is demonstrated including azidation, deuteration, olefination and hydroxylation.

Nitrogen-rich heterocycles are amongst the most widely-used moieties in medicinal chemistry, yet are often the least compliant with two-electron functionalization methods [52]. The aforementioned affinity of radicals for nitrogen containing heterocycles has been exploited with great success by the Baran group via their development of sulfinates for early- and late-stage arene modification. In commercial partnership with MilliporeSigma, the Baran laboratory has developed 40 sulfinates (now marketed as Diversinates^{TM}) for alkyl, fluoroalkyl, aromatic, heteroaromatic and linker-type functionalization. A recent perspectives article highlights the use of sulfinates in over 50 examples in the patent literature for the functionalization of drug-like compounds [52]. A representative example is the difluoromethylation of an anti-cancer lead reported by Bayer Pharma Aktiengesellschaft (Figure 5(b)) [53]. In the presence of a simple oxidant such as *tert*-butyl hydroperoxide, the weak C-S bond of the sulfinate undergoes homolysis to generate a nucleophilic difluoromethyl radical, which under acidic conditions reacts exclusively adjacent to the N atom (C2) of the pyridine to give the difluoromethylated product in 42% yield. Another recent literature example from Boehringer Ingelheim demonstrates the use of the methodology with optimized reaction conditions for the generation of new drug-like analogues with improved *in vitro* metabolism and pharmacokinetic parameters [54].

3.5. Oxidation reactions

The selective oxidation of C–H bonds, analogous to what is found in nature, can have profound effects on the physical and biological properties of small molecules. The development of finely tuned catalysts allows for site selective oxidation on a range of functionally and topologically diverse compounds. These reactions have been applied to the field of LSF to rapidly change the properties of drugs.

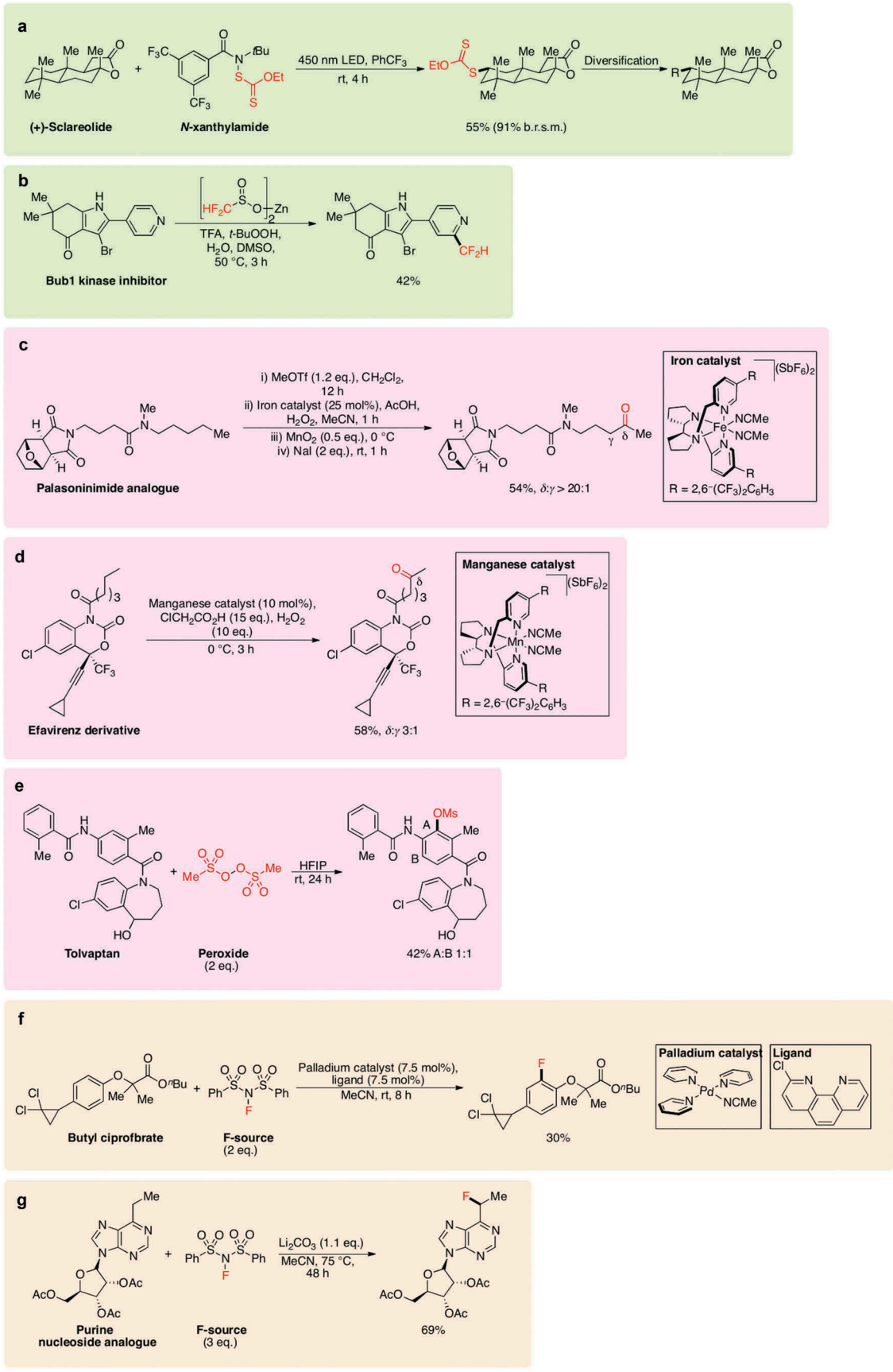

Figure 5. Late-stage functionalization using radical chemistry (green, (a,b)), oxidation reactions (pink, (c–e)) and the installation of halogens (light red, (f–g)).

Amides are considered privileged scaffolds in medicinal chemistry and hence C–H functionalization methodologies for LSF should tolerate this ubiquitous functional group. The Chen-White catalyst Fe(PDP) and related Fe(CF_3PDP) have been utilized for the site-selective oxidation of tertiary and secondary C–H bonds [13,55,56]. Selectivity is based on the electronic, steric and stereoelectronic properties of the substrate. A limitation of the method is that such oxidations in the presence of amides generally lead to direct oxidation of nitrogen [57] or proximal oxidation of hyperconjugatively activated *α*-C–H bonds [58]. To circumvent this problem, the White laboratory has developed an imidate salt strategy that promotes remote, nondirected, site-selective aliphatic C–H oxidation in amide-containing molecules (Figure 5(c)) [59]. Methyl trifluoromethanesulfonate is used as a reversible alkylating agent. The imidate salt enables C–H oxidation of a complex amide-containing palasoninimide B analogue with Fe(CF_3PDP) in good (54%) yield and excellent site-selectivity.

Despite significant advances in the field of aliphatic oxidation chemistry, the ability to oxidize strong methylene C–H bonds in the presence of more oxidatively labile aromatic functionalities remains a major challenge. The White laboratory has recently disclosed a manganese catalyst (Mn(CF_3PDP)) system that achieves this elusive chemoselectivity (Figure 5(d)) [60]. This development is particularly important for late-stage alkyl C–H oxidation of medicinally relevant aromatic compounds substituted with halogen, oxygen, nitrogen, heterocyclic and biaryl moieties. Similar to the previously reported Chen-White catalyst system the manganese catalyst oxidizes methylene sites selectively based on differences in electronic, steric and stereoelectronic environments. The applicability of this method for LSF is demonstrated for a series of complex substrates including an efavirenz derivative where site selective oxidation of the most distal methylene is achieved in 58% yield.

Aromatic C–O bond formation is an important transformation to facilitate metabolite synthesis for drug discovery and development [61]. Börgel and coworkers have developed a novel methodology for the late-stage C–O bond formation of arenes (Figure 5(e)) [62]. Readily accessible bis(methanesulfonyl) peroxide enables the mesylation of a range of functionally diverse arenes including pharmaceuticals such as tolvaptan under mild conditions. The high functional group tolerance is rationalized by the formation of a charge-transfer interaction between the peroxide and substrate arenes. The resulting aryl mesylates provide access to potential oxidation metabolites or may be used to directly install a C–F bond to block metabolism.

3.6. Halogenation reactions

Halogenated compounds are of particular interest for medicinal chemists as either functional handles for further reactions or as modulators of the physical and biological properties of drug molecules in order to improve efficacy and bioavaliability [63]. Furthermore halogenation also provides for structure-activity relationship studies and the exploration of medicinal chemistry concepts such as the Topliss scheme [64]. Traditional halogenation of arenes such as direct electrophilic substitution reactions and Sandmeyer reactions suffer from issues of regioselectivity, the use of toxic reagents and requisite prefunctionalization in certain cases. Methodologies to directly install C–X bonds selectively through C–H functionalization are therefore of great interest.

The importance of aryl fluorides in the pharmaceutical industry has seen the development of numerous methods for their synthesis through the conversion of various functional groups. However, there is a paucity of general methods for direct aromatic C–H fluorination. Yamaoto and coworkers have reported an undirected, palladium catalyzed method for C–H aromatic fluorination using a mild fluorine source (Selectfluor or NSFI) (Figure 5(f)) [65]. The reaction proceeds via a transition metal-fluoride electrophile that is reactive enough for the fluorination of otherwise inert arenes. The LSF of drug candidates is demonstrated (for example butyl ciprobrate) without the need for prefunctionalization or laborious *de novo* synthesis.

The addition of mono- or difluoroalkyl groups to drug scaffolds is an established approach to modulate drug pK_a, influence potency and membrane permeability, and mitigate metabolism. Meanwell and coworkers have developed a method for direct benzylic sp^3 C–H fluorination, a complementary method to the addition of fluoroalkyl radicals to heterocycles (Figure 5(g)) [66]. Mono- and difluorination of a diverse range of alkyl heterocycles including relevant pharmaceuticals is achieved via a transient sulfonylation by the electrophilic fluorinating agent *N*-fluorobenzenesulfonimide (NSFI).

4. Conclusion

The LSF of drug-like molecules has the potential to advance the drug discovery process. The ability to selectively functionalize a drug-like compound at the last stages of the synthesis and at normally unreactive C–H bonds in the presence of more reactive functionalities will accelerate hit-to-lead optimization. Alternatively, reactions can be used to study the ADME (absorption, distribution, metabolism and excretion) properties of a drug lead or to develop tool compounds for chemical biology studies. While we have focused on the necessity of selectivity for LSF, non-selectivity could also be an asset in the realm of drug discovery. Provided that purification is possible, the ability to generate multiple analogues from a single lead, will greatly enhance the ability for broad structure-activity relationship studies.

5. Expert opinion

This review highlights the emergence of the field of LSF and its application to the modification of known drugs and drug-like molecules. With the development of new bond forming technologies the field has gathered significant momentum in recent years. Within the field of C–H functionalization there has been a significant paradigm shift, from developing activation methodologies for the synthesis of complex natural products, to establishing reactions that can modify drug-like molecules for the purpose of drug development. The shift is evident from the plethora of recent synthetic methodology papers that include drugs or drug-like molecules in the substrate scope to demonstrate not only functional group

tolerance, but also applicability to the development of medicinal agents. The collective efforts of many academic laboratories and partnerships between industry and academia has lead to a greater understanding of the factors that are critical to the success of C–H functionalization reactions. These efforts are now finding application in the development of pharmaceuticals. The wide variety of C–H functionalization methods now available, with impressive functional group tolerance and site selectivity, has provided medicinal chemists with, as Cernak and coworkers describe it, 'a toolbox' of reactions to modify drugs. The recent renaissances of photoredox catalysis and radical chemistry have facilitated difficult and previously inaccessible bond forming reactions under mild conditions and in the presence of various functional groups. LSF has numerous potential applications in drug discovery including the generation of a large number of analogues to explore structure-activity relationships, the synthesis of analogues with improved physicochemical properties, the synthesis of metabolites and conversely the blockage of potential metabolically labile sites. With a toolbox of C–H functionalization reactions, medicinal chemists can access relevant analogues that would otherwise require laborious *de novo* synthesis. Not only does this save time but also it significantly improves the 'greenness' of the drug discovery process.

With the limitation of publically available information it is difficult to gauge the uptake of LSF by pharmaceutical companies. There are numerous patents filed by pharmaceutical companies that utilize methodologies discussed in this review. For instance, Phil Baran's alkyl sulfinate chemistry (Diversinates) has been widely adopted by the medicinal chemistry community, with over 50 patents describing its use in the past 5 years [52]. In their recent review, Campos and coworkers highlight the continuing importance of synthetic chemistry in the pharmaceutical industry [67]. The advances made in recent years and the proposed future innovations all carry the themes of expanding chemical space and expediting the discovery of drugs to treat diseases faster and more efficiently. These themes are at the core of LSF. While LSF is still its infancy, the field is expanding at a rapid pace, with an increasing number of publications appearing every year. There is however still much room to further improve the reliability of these reactions on wider substrate scopes and to establish rigorous tools to predict the reactivity and selectivity of different C–H groups toward these reactions. New technologies that facilitate the purification and identification of the products of LSF reactions will also increase the impact of the field. Another aspect of drug discovery that is applicable to LSF is that of the synthesis of chemical tools for chemical biology studies. LSF offers an appealing method to modify bioactive molecules in order to probe biological activity via chemoproteomic pull-down experiments, fluorescence imaging studies, antibody attachment for targeted delivery studies and radiotracer synthesis for distribution studies or imaging agent development. As academic and pharmaceutical laboratories continue to develop more powerful and reliable methods for the LSF of complex molecules, the impact on the drug discovery process will undoubtedly become more obvious.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Lovering F, Bikker J, Humblet C. Escape from flatland: increasing saturation as an approach to improving clinical success. J Med Chem. 2009 November 12;52(21):6752–6756.
2. Boström J, Brown DG, Young RJ, et al. Expanding the medicinal chemistry synthetic toolbox. Nat Rev Drug Discovery. 2018 August 24;17:709. online.
• **Useful review discussing the need to expand the reactions used in medicinal chemistry.**
3. Cernak T, Dykstra KD, Tyagarajan S, et al. The medicinal chemist's toolbox for late stage functionalization of drug-like molecules. Chem Soc Rev. 2016;45(3):546–576.
•• **Comprehensive review of the principles of late-stage functionalization.**
4. Dominguez-Huerta A, Dai X-J, Zhou F, et al. Exploration of new reaction tools for late-stage functionalization of complex chemicals. Can J Chem. 2018 February 01;97(2):67–85.
5. Godula K, Sames D. C-H bond functionalization in complex organic synthesis. Science (New York, NY). 2006 Apr 7;312(5770):67–72.
6. Goldman AS, Goldberg KI. *Organometallic C—H bond activation: an introduction. Activation and functionalization of C—H bonds*. Washington (DC): American Chemical Society; 2004. p. 1–43.
7. Hartwig JF. Evolution of C–H bond functionalization from methane to methodology. J Am Chem Soc. 2016 January 13;138(1):2–24.
8. Blakemore DC, Castro L, Churcher I, et al. Organic synthesis provides opportunities to transform drug discovery. Nature Chem. 2018 April 01;10(4):383–394.
• **Perspective article discussing the impact devleopments in organic synthesis can have on future drug discovery.**
9. Yao H, Liu Y, Tyagarajan S, et al. Enabling efficient late-stage functionalization of drug-like molecules with LC-MS and reaction-driven data processing. Eur J Org Chem. 2017 December 22;2017(47):7122–7126.
10. Adams CP, Brantner VV. Spending on new drug development1. Health Econ. 2010 Feb;19(2):130–141.
11. Paul SM, Mytelka DS, Dunwiddie CT, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010 Mar;9(3):203–214.
12. Zhao J, Zhang D, Zhang W, et al. Highly selective MERTK inhibitors achieved by a single methyl group. J Med Chem. 2018 November 21;61(22):10242–10254.
13. Chen MS, White MC. Combined effects on selectivity in Fe-catalyzed methylene oxidation. Science (New York, NY). 2010 Jan 29;327(5965):566–571.
14. Liu W, Groves JT. Manganese porphyrins catalyze selective C–H bond halogenations. J Am Chem Soc. 2010 September 22;132(37):12847–12849.

15. Liu W, Huang X, Cheng MJ, et al. Oxidative aliphatic C-H fluorination with fluoride ion catalyzed by a manganese porphyrin. Science (New York, NY). 2012 Sep 14;337(6100):1322–1325.
16. Schmidt VA, Quinn RK, Brusoe AT, et al. Site-selective aliphatic C–H bromination using N-bromoamides and visible light. J Am Chem Soc. 2014 October 15;136(41):14389–14392.
17. Chen K, Eschenmoser A, Baran PS. Strain Release in C–H Bond Activation? Angew Chem. 2009 December 14;48(51):9705–9708.
18. Huang X, Bergsten TM, Groves JT. Manganese-catalyzed late-stage aliphatic C–H azidation. J Am Chem Soc. 2015 April 29;137(16):5300–5303.
19. Chadha N, Silakari O. Indoles as therapeutics of interest in medicinal chemistry: bird's eye view. Eur J Med Chem. 2017 July 07;134:159–184.
20. Petrone DA, Ye J, Lautens M. Modern transition-metal-catalyzed carbon–halogen bond formation. Chem Rev. 2016 July 27;116(14):8003–8104.
21. Newhouse T, Baran PS. If C-H bonds could talk: selective C-H bond oxidation. Angew Chem (int Ed in English). 2011 Apr 4;50(15):3362–3374.
22. Genovino J, Sames D, Hamann LG, et al. Accessing drug metabolites via transition-metal catalyzed C–H oxidation: the liver as synthetic inspiration. Angew Chem. 2016;55(46):14218–14238.
23. Yeung CS, Dong VM. Catalytic dehydrogenative cross-coupling: forming carbon−carbon bonds by oxidizing two carbon−hydrogen bonds. Chem Rev. 2011 March 09;111(3):1215–1292.
24. Engle KM, Mei T-S, Wasa M, et al. Weak coordination as a powerful means for developing broadly useful C–H functionalization reactions. Acc Chem Res. 2012 June 19;45(6):788–802.
25. Schnuerch M. Exploiting the C-H bond in metal-catalyzed C-C bond-forming reactions. ARKIVOC (Gainesville, FL, US). 2015;(1Spec.Issue):212–243.
26. Scifinder, version 2019. 2019. Chemical Abstracts Service: Columbus, OH.
27. Shaw MH, Twilton J, MacMillan DWC. Photoredox catalysis in organic chemistry. J Org Chem. 2016 August 19;81(16):6898–6926.
•• **Comprehensive review of photoredox catalysis.**
28. Romero NA, Margrey KA, Tay NE, et al. Site-selective arene C-H amination via photoredox catalysis. Science. 2015 Sep 18;349(6254):1326–1330.
29. Minisci F, Fontana F, Vismara E. Substitutions by nucleophilic free radicals: A new general reaction of heteroaromatic bases. J Heterocycl Chem. 1990 January 01;27(1):79–96.
30. Huff CA, Cohen RD, Dykstra KD, et al. Photoredox-catalyzed hydroxymethylation of heteroaromatic bases. J Org Chem. 2016 August 19;81(16):6980–6987.
31. Jin J, MacMillan DWC. Alcohols as alkylating agents in heteroarene C–H functionalization. Nature. 2015 August 26;525:87. online.
32. Matsui JK, Primer DN, Molander GA. Metal-free C–H alkylation of heteroarenes with alkyltrifluoroborates: a general protocol for 1°, 2° and 3° alkylation. Chem Sci. 2017;8(5):3512–3522.
33. Nuhant P, Oderinde MS, Genovino J, et al. Visible-light-initiated manganese catalysis for C–H alkylation of heteroarenes: applications and mechanistic studies. Angew Chem. 2017;56(48):15309–15313.
34. Wang Z, Herraiz AG, Del Hoyo AM, et al. Generating carbyne equivalents with photoredox catalysis. Nature. 2018 January 31;554:86. online.
35. Liang Y, Zhang X, MacMillan DWC. Decarboxylative sp3 C–N coupling via dual copper and photoredox catalysis. Nature. 2018 July 01;559(7712):83–88.
36. Le C, Liang Y, Evans RW, et al. Selective sp3 C–H alkylation via polarity-match-based cross-coupling. Nature. 2017 June 21;547:79. online.
37. Chen W, Ma L, Paul A, et al. Direct α-C–H bond functionalization of unprotected cyclic amines. Nature Chem. 2017 November 06;10:165. online.
38. Ahneman DT, Doyle AG. C–H functionalization of amines with aryl halides by nickel-photoredox catalysis. Chem Sci. 2016;7(12):7002–7006.
39. Vasu D, Fuentes de Arriba AL, Leitch JA, et al. Primary α-tertiary amine synthesis via α-C–H functionalization. Chem Sci. 2019;10(11):3401–3407.
40. Kautzky JA, Wang T, Evans RW, et al. Decarboxylative trifluoromethylation of aliphatic carboxylic acids. J Am Chem Soc. 2018 May 30;140(21):6522–6526.
41. Hagmann WK. The many roles for fluorine in medicinal chemistry. J Med Chem. 2008 August 01;51(15):4359–4369.
• **Review of the use of fluorine in medicinal chemistry.**
42. Johansson-Seechurn CCC, Kitching MO, Colacot TJ, et al. Palladium-catalyzed cross-coupling: a historical contextual perspective to the 2010 nobel prize. Angew Chem. 2012 May 21;51(21):5062–5085.
•• **Comprehensive historical review of palladium catalysed cross-coupling chemistry.**
43. McGrath NA, Brichacek M, Njardarson JT. A graphical journey of innovative organic architectures that have improved our lives. J Chem Educ. 2010 December 01;87(12):1348–1349.
44. Clark JR, Feng K, Sookezian A, et al. Manganese-catalysed benzylic C(sp3)–H amination for late-stage functionalization. Nature Chem. 2018 June 01;10(6):583–591.
45. Simonetti M, Cannas DM, Just-Baringo X, et al. Cyclometallated ruthenium catalyst enables late-stage directed arylation of pharmaceuticals. Nature Chem. 2018 July 01;10(7):724–731.
46. Cheng C, Hartwig JF. Iridium-catalyzed silylation of aryl C–H bonds. J Am Chem Soc. 2015 January 21;137(2):592–595.
47. Wang P, Verma P, Xia G, et al. Ligand-accelerated non-directed C–H functionalization of arenes. Nature. 2017 November 22;551:489. online.
48. Liao K, Negretti S, Musaev DG, et al. Site-selective and stereoselective functionalization of unactivated C–H bonds. Nature. 2016 May 11;533:230. online.
49. Liao K, Pickel TC, Boyarskikh V, et al. Site-selective and stereoselective functionalization of non-activated tertiary C–H bonds. Nature. 2017 November 20;551:609. online.
50. Uehling MR, King RP, Krska SW, et al. Pharmaceutical diversification via palladium oxidative addition complexes. Science. 2019;363(6425):405.
51. Czaplyski WL, Na CG, Alexanian EJ. C–H xanthylation: a synthetic platform for alkane functionalization. J Am Chem Soc. 2016 October 26;138(42):13854–13857.
52. Smith JM, Dixon JA, deGruyter JN, et al. Alkyl sulfinates: radical precursors enabling drug discovery. J Med Chem. 2019;62(5):2256–2264.
53. Graham K, Klar U, Briem H, et al., inventors; Bayer Pharma Aktiengesellschaft, Germany, assignee. Preparation of 3-amino-1,5,6,7-tetrahydro-4H-indol-4-ones as anti-cancer agents patent WO2016202755A1. 2016.
54. Kuttruff CA, Haile M, Kraml J, et al. Late-stage functionalization of drug-like molecules using diversinates. ChemMedChem. 2018 May 23;13(10):983–987.
55. Chen MS, White MC. A predictably selective aliphatic C–H oxidation reaction for complex molecule synthesis. Science. 2007;318(5851):783.
56. Gormisky PE, White MC. Catalyst-controlled aliphatic C–H oxidations with a predictive model for site-selectivity. J Am Chem Soc. 2013 September 25;135(38):14052–14055.
57. Rella MR, Williard PG. Oxidation of peptides by methyl(trifluoromethyl)dioxirane: the protecting group matters. J Org Chem. 2007 January 01;72(2):525–531.
58. Campos KR. Direct sp3 C–H bond activation adjacent to nitrogen in heterocycles. Chem Soc Rev. 2007;36(7):1069–1084.
59. Nanjo T, de Lucca EC, White MC. Remote, late-stage oxidation of aliphatic C–H bonds in amide-containing molecules. J Am Chem Soc. 2017 November 18;139(41):14586–14591.
60. Zhao J, Nanjo T, de Lucca EC, et al. Chemoselective methylene oxidation in aromatic molecules. Nature Chem. 2019 March 01;11(3):213–221.
61. Zhang Z, Tang W. Drug metabolism in drug discovery and development. Acta Pharm Sin B. 2018 September 01;8(5):721–732.
62. Börgel J, Tanwar L, Berger F, et al. Late-stage aromatic C–H oxygenation. J Am Chem Soc. 2018 November 28;140(47):16026–16031.
63. Marcelo Zaldini H, Suellen Melo TC, Diogo Rodrigo MM, et al. Halogen atoms in the modern medicinal chemistry: hints for the drug design. Curr Drug Targets. 2010;11(3):303–314.
64. Martin YC, Dunn WJ. Utility of the topliss schemes for analog synthesis. J Med Chem. 1973 May 01;16(5):578–579.

65. Yamamoto K, Li J, Garber JAO, et al. Palladium-catalysed electrophilic aromatic C–H fluorination. Nature. 2018 February 21;554:511. online.
66. Meanwell M, Adluri BS, Yuan Z, et al. Direct heterobenzylic fluorination, difluorination and trifluoromethylthiolation with dibenzenesulfonamide derivatives. Chem Sci. 2018;9(25):5608–5613.
67. Campos KR, Coleman PJ, Alvarez JC, et al. The importance of synthetic chemistry in the pharmaceutical industry. Science (New York, NY). 2019 Jan 18;363:6424.
•• **Review of the impact of synthetic chemistry on the pharmaceutical industry.**