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Late-Stage Functionalization by Transition Metal-Catalyzed C—H Functionalization

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1.1 Introduction

The 21st century is clearly marked by important environmental issues, global warming, expanding worldwide population, depletion of natural resources, and inflating energy needs. These issues clearly impact all domains of everyday life. However, chemistry is clearly the field that can provide real solutions to these major and urgent societal problems. Accordingly, the chemical industry has initiated the sustainable revolution, and extensive efforts are devoted to produce all types of chemicals in more sustainable manner, while decreasing the environmental footprint. However, the development of modern industrial process requires initial fundamental discoveries and the development of new synthetic tools, allowing the synthesis of desired organic products in more resource-, energy-, and step-efficient manner. Accordingly, the fundamental research in organic chemistry has been undergoing, since the last two decades, a real "sustainability revolution" [1, 2]. Various approaches have been proposed to allow more sustainable synthesis, among which visible-light-mediated photocatalysis, electrochemistry, continuous-flow reactions, and "benign solvent design" are selected examples. These strategies reached now the maturity to be considered valuable and general tools for organic synthesis. In parallel, C—H activation strategy profoundly changed the mindset of a synthetic chemist [3]. Indeed, a possibility of using non-prefunctionalized substrates in the transition-metal-catalyzed process presents a formidable advantage over the standard cross-coupling reactions. Over the past years, organic chemists have learned how to use latent and strong C—H bonds as functional motifs and directly convert them into desired functional groups. Over the years, the field of C—H activation expanded tremendously, allowing major breakthroughs and providing key improvements, such as efficient site-selectivity [4], use of abundant, cheap, and nontoxic metals [5], or the design of highly reactive catalytic systems able to promote the key C—H cleavage step under mild reaction conditions. Accordingly, C—H activation field, which was 15 years ago considered a scientific curiosity, now

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reached a totally new level of industrial applications in both production [6] and R&D industrial sectors [3c]. The C—H activation field holds, in particular, an exceptional potential for speeding up research in pharmaceutical industry [7] by unlocking the door toward rapid diversification of lead drug candidates via C—H late-stage functionalization. Indeed, if a direct C—H functionalization of a complex molecule can be done in one step, the diversity of lead's congeners can be rapidly accessed by avoiding traditional *de novo*, multistep synthesis of each product.

While the first, general example of the LSF to directly install diversity of motifs on celecoxib was reported as early as in 2011 by the group of Yu [8], over the last year, late-stage functionalization via C—H activation has advanced tremendously [9]. Indeed, over the years, academic groups have devoted considerable effort to go beyond the development of new C—H activation reactions that are compatible with benchmark substrates and to showcase the synthetic usefulness of these reactions by demonstrating their compatibility with complex molecules, such as drugs and natural products.

In parallel, industrial chemists tend to implement LSF mindset, often combined with high-throughput experimentation (HTE), to expand a chemical space. In this chapter, key achievements in the LSF via C—H activation are present. First, the LSF of aromatic compounds will be discussed, followed by the aliphatic ones. Each section is organized following the nature of the C—H transformation, including direct alkylation, arylation, alkenylation, and C—X bond formation (C—O, C—N, C—B, halogenation). Attention will also be focused on the selectivity issues and the mechanistic reasons controlling the site-selectivity. It is worth noting that while remarkable progress has been achieved in LSF of peptides [10], this topic has been covered extensively and therefore is considered out of the scope for this chapter.

1.2 Late-Stage Functionalization of Aromatic Compounds

1.2.1 LSF via Direct Alkylation

LSF of drug candidates is particularly appealing when allowing the direct introduction of small groups, impacting significantly the biological activity of a drug molecule while not altering excessively the overall structure. Accordingly, LSF methylation is particularly attractive, allowing to rapidly explore the "magic methyl effect" on a given molecule. An early example of late stage methylation was published in 2013 by Yu [11]. The catalytic system combining $Pd(OAc)_2$ catalyst together with a monoprotected amino acid ligand and Li_2CO_3 was initially optimized to perform direct C—H methylation of aryl carboxylic acids using methyl tetrafluoroborate as the methylating agent (Figure 1.1a). The potential of this strategy could be further demonstrated by synthesizing a therapeutically relevant methylated derivative of BMS-98947-0550-1. The superiority of the carboxylate function as a directing group over the ester motif warrant fully site-selectivity of this reaction, furnishing the modified compound in synthetically useful

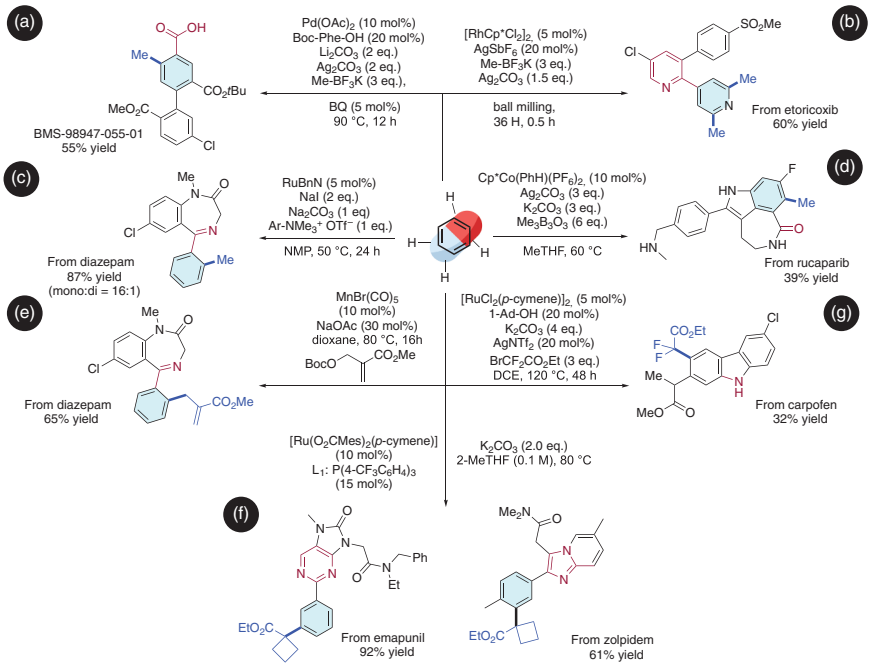

Figure 1.1 Late-stage functionalization via direct alkylation. a) Pd-catalyzed late-stage methylation of BMS-98974-0550-1 developed by Yu et al. [11] b) Rh-catalyzed methylation of etoricoxib developed by Pilarski et al. [12] c) Ru-catalyzed methylation of diazepam developed by Larrosa et al. [13] d) Co-catalyzed methylation of rucaparib developed by Johansson, Ackermann et al. [14] e) Mn-catalyzed methylation of diazepam developed by Ackermann et al. [15] f) Ru-catalyzed methylation of emapunil and zolpidem developed by Ackermann, Johansson et al. [16] g) Ru-catalyzed methylation of carprofen developed by Lan, Zhao et al. [17].

55% yield. Subsequently, Pilkarski [12] and Larrosa [13], designed, respectively, Rh and Ru-catalyzed direct methylation of phenyl pyridine and imine derivatives (Figure 1.1b, c). While RhCp* catalytic system was designed to promote direct methylation using methyl tetrafluoroborate reagent under mechanochemical, solvent-free conditions, the Ru-metallacyclic catalyst performed well in the presence of quaternary anilinium salt. Both protocols could be subsequently used for LSF of drugs, delivering, in high yields, methyl derivatives of etoricoxib and diazepam.

Regarding the great potential of LSF for R&D sector, several companies conduct their own research programs. Considering the "magic methyl effect," the researchers from AstraZeneca in collaboration with Ackermann focused on developing a general protocol for LS-methylation of complex molecules [14]. Use of HTE approach allowed them to rapidly screen hundreds of reaction conditions, aiming in a general protocol compatible with a large diversity of compounds incorporating distinctive functional groups that could play the role of DGs. This exceptional approach resulted in establishing a Co-based protocol, enhancing

direct methylation of 26 structurally very different simple aromatics. Remarkably, the same protocol allowed direct methylation of 16 drug-like molecules, clearly demonstrating its unique efficiency for the LSF of biologically active compounds. The regioselectivity in this reaction is generally controlled by a directing effect of coordinating groups (amides, carbonyl, *N*-heterocycles), thus allowing a predictable and site-selective methylation (Figure 1.1d). Although in some cases rather low yields were reached, this approach enables a tremendous research acceleration compared to the traditional *de novo* synthesis, as exemplified on rucaparib. Co-catalyzed methylation furnished the desired methylated derivative in one step in 39% yield, whereas *de novo* synthesis would require a 12-step protocol.

While methylation reactions are highly appealing from drug-design perspective, LSFs via alternative alkylation reactions have also been described. The group of Ackermann explored Mn-catalyzed direct allylation reactions (Figure 1.1e) [15]. Although initially developed for C2-functionalization of indole scaffolds with remarkable applications for peptide modifications, this transformation performed equally well using diazepam as the starting material. The desired alkylated diazepam was thus isolated in 65% yield, and the excellent site-selectivity results from *ortho*-directing properties of the imine group.

A complementary, distal *meta*-selective direct alkylation of complex molecules was recently reported by Ackermann and Johansson (Figure 1.1f) [16]. The HTE approach allowed expedient evaluation of various reaction conditions, targeting a reaction protocol compatible with a diversity of aromatic substrates. After the extensive optimization, $[Ru(O_2CMes)_2(p\text{-cymene})]$ was determined as the optimal catalyst in the presence of a monophosphine ligand **L1**, allowing direct *meta*-coupling between aromatics bearing various DGs and bromoalkanes. Remarkably, while challenging this catalytic system with several aromatic drug derivatives, the desired alkylation proceeded smoothly, providing products such as emapunil or zolpidem derivatives in remarkably high 92% and 62% yields.

An additional example of unusual site-selectivity in LSF-difluoroalkylation was disclosed by Lan and Zhao. While focusing on Ru-catalyzed direct functionalization of aniline derivatives, they discovered a unique *para*-selective transformation (Figure 1.1g) [17]. After illustrating the compatibility of this strategy with diversity of aniline derivatives, including indoline and tetrahydroquinoline, LSF of carbazole-derived drug, carprofen, was accomplished competently.

1.2.2 LSF via Alkenylation

Direct alkenylation, i.e., oxidative Heck reaction, is one of the most developed direct functionalizations. Thus, non-surprisingly, several examples of such C—H functionalization performed on drug molecules have been reported. In 2019, Zhu disclosed direct *ortho*-selective olefination of free phenol derivatives [18]. Considering the ubiquitous presence of phenol rings in medicinal chemistry, the potential of the newly discovered protocol was rapidly validated in LSF (Figure 1.2a). Not only alkenylated estrone and estradiol but also ethinylestradiol could be obtained. The *ortho*-selectivity of this reaction is clearly controlled via coordinating

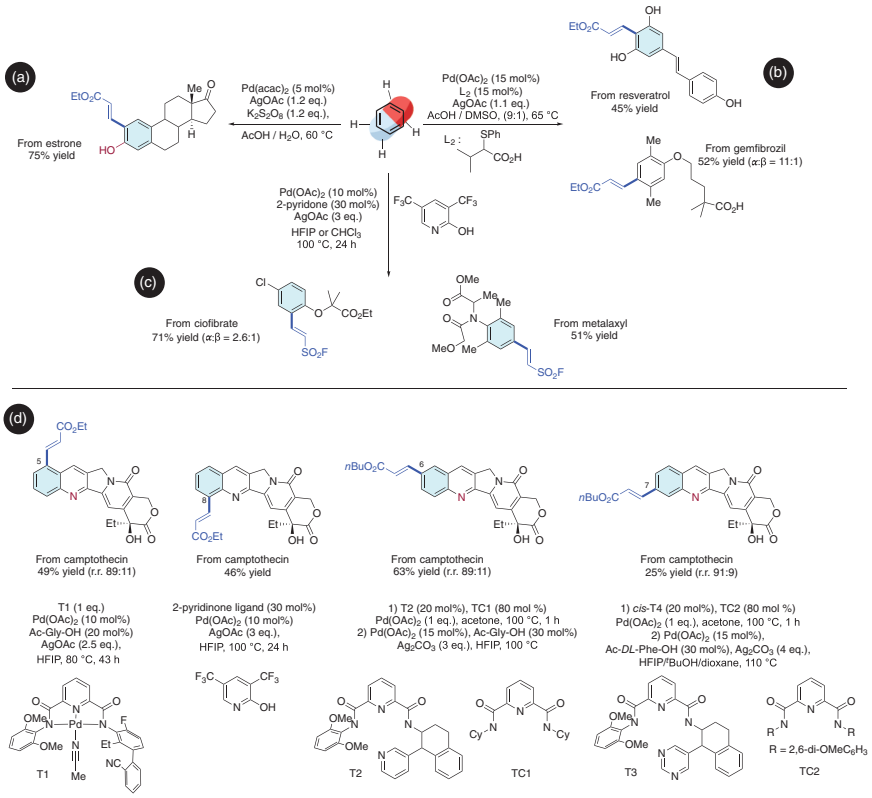

Figure 1.2 LS olefination of aromatic drug-type molecules (r.r. = regioisomeric ratio).
a) Pd-catalyzed late-stage olefination of estrone developed by Zhu et al. [18]
b) Pd-catalyzed late-stage olefination of resveratrol and gemfibrozil developed by Wu, Yao et al. [19] c) Pd-catalyzed late-stage olefination of metalaxyl and ciofibrate developed by Wang, Yu et al. [21] d) Pd-catalyzed late-stage olefination of camptothecin developed by Yu et al. [22, 23] and Yu, Houk et al. [24].

properties of the hydroxyl group, exercising the role of the DG and "preinstalling" the metal in proximity at the *meta*-positions.

An alternative example of LSF of phenol derivatives was reported in 2023 by Wu and Yao [19]. Capitalizing on the arylthiol acid ligands **L2** designed by Fernández-Ibáñez [20], they reported the undirected functionalization of several phenol- and ether-containing natural products and drug derivatives. The C—H activation occurs in general at the electronically favored positions, such as *ortho*- and *para*-positions, while steric effects cannot be obviated. For example, fully selective olefination of resveratrol was reached, while the mixture of regioisomeric products was isolated in the case of gemfibrozil (Figure 1.2b).

Non-directed olefination of phenol derivatives is not limited to the use of acrylates as coupling partners. Wang and Yu extended the applicability of this methodology to the use of vinyl sulfonyl fluorides [21]. The Pd-based catalytic system request addition of the 2-pyridinone ligand to warrant sufficient reactivity and the selectivity

of the reaction if controlled by the combination of steric and electronic factors. Accordingly, metalaxyl derivative could be isolated regioselectively in 51% yield, while olefination of ciofibrate led to the formation of the regioisomeric mixture of products in 71% yield (Figure 1.2c).

Reaching alternative site-selectivities in the C—H activation reactions is often a formidable challenge. Several approaches, including the design of long, U-shaped Directing Groups, as well as Ru-catalyzed C—H functionalizations have been found in the literature. However, the use of U-shaped DG is tedious and difficult to predict, while meta-selective Ru-functionalizations are mainly limited to alkylation reactions. To expand the chemical space of compounds obtained via C—H activation, the group of Yu focused on alternative strategies promoting functionalizations at distant positions. In early 2017, they described a Pd-catalyzed *meta*-selective olefination [22]. The site-selectivity was dictated by the presence of an external, bifunctional nitrile template **T1**, used in a stoichiometric amount (Figure 1.2d). Such a bicoordinating template **T1** plays a double role of coordination to the DG, directing the metal to the distal position while rendering the Pd-catalyst as a sufficiently reactive catalyst. After demonstrating the potential of this protocol on various aza-aromatic compounds, direct olefination of camptothecin was attempted. Remarkably, selective functionalization at remote C5 benzocyclic position was thus achieved. Interestingly, a reversed site-selectivity was observed while exploring the potential of an alternative Pd-based catalytic system developed by the same group [23]. Interestingly, C8-selectivity, i.e., the functionalization at the most reactive, electronically driven position could be completed selectively while using "non-directed approach." In this case, the key difficulty lies in selecting a ligand providing the Pd-catalyst sufficient reactivity. Intensive optimization by the group of Yu established 2-pyridone **L2** as such privileged ligand for non-directed olefination of aromatics. Accordingly, the acrylate function could be introduced at the C8-position of camptothecin in excellent selectivity. Noteworthy, this non-directed functionalization could also be used to diversify other complex molecules, including fenofibrate, caffeine, estrone-OMe, and viloxazine-NTs.

Selective functionalization of C6 and C7 positions of a quinoline scaffold, such as in camptothecin, presents an additional tremendous challenge, resulting from the chemical inertness and electronic similarity of these two C—H bonds. Exceptional regiochemical precision toward functionalization of these distant yet non-activated positions were attained by Yu and Houk by designing two conceptually distinct directing templates [24]. The concept is based on the (1) initial coordination between the N-atom of the substrate and Pd-coordinated template, followed by the coordination of the second Pd-atom on the pyridine motif of the template, thus delivering the metal catalyst near the C—H bond to be cleaved. The discrimination between different positions is thus achieved via very precise spatial and chiral recognition. Accordingly, C7 position of camptothecin underwent oxidative Heck reaction in the presence of chiral **T2** and **TC1** (template chaperon used to turn over the directing template that now can be used in "catalytic" amount), while C7 functionalization required the use of **T3** template.

While the above present work perfectly illustrates the potential of LSF for site-selective functionalization of drug derivatives, the incredible challenge associated with the meticulous regioselectivity control is evident.

1.2.3 LSF via Arylation

Ortho-directed C—H arylation is certainly among the most developed C—H functionalization reactions. Therefore, it is not surprising that this approach has also been successfully used for the late-stage diversification of complex molecules. In 2018, Larrosa reported the cyclometallated Ru-complex-catalyzed direct arylation (Figure 1.3a) [25]. While the catalyst optimization and the mechanistic studies were conducted using largely explored phenyl pyridine substrate, the catalytic cycle turned out to be equally efficient for several complex molecules, featuring aza- or imine functionalities that can be used as directing groups. Accordingly, direct diversification of scaffolds such as zolimidine, flurazepam, or sulfaphenazole could

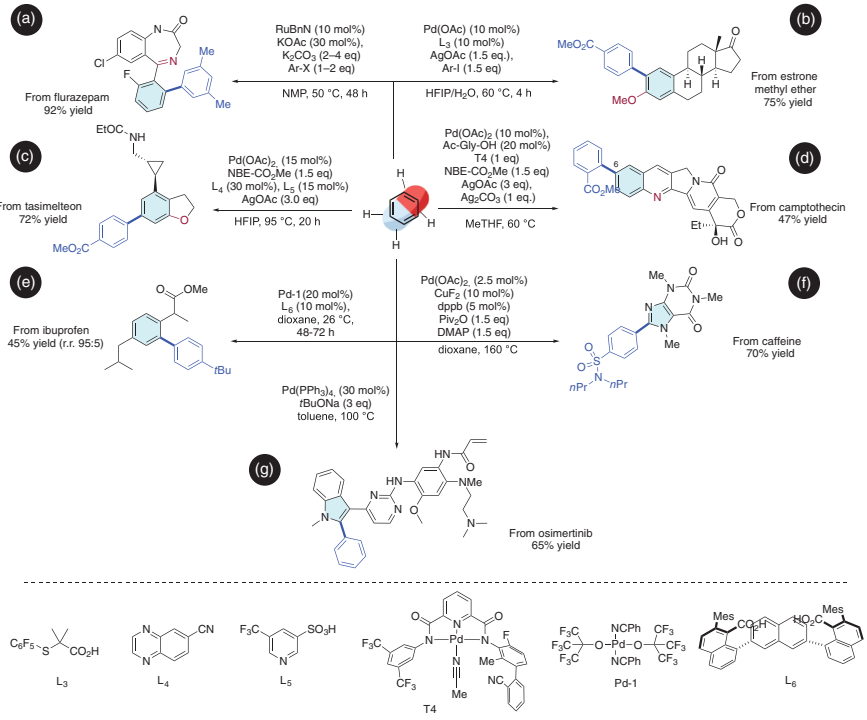

Figure 1.3 LSF of aromatic compounds via direct arylation. a) Ru-catalyzed late-stage arylation of flurazepam developed by Larrosa et al. [25] b) Pd-catalyzed late-stage arylation of estrone methyl ester developed by Fernández-Ibáñez et al. [26] c) Pd-catalyzed late-stage arylation of tasimelteon developed by Yu et al. [27] d) Pd-catalyzed late-stage arylation of camptothecin developed by Houk, Yu et al. [28] e) Pd-catalyzed late-stage arylation of ibuprofen developed by Čorić et al. [30] f) Pd/Cu-catalyzed late-stage arylation of caffeine developed by Hong, Szostak et al. [31] g) Pd-catalyzed late-stage arylation of osimertinib developed by Li, Zhang, Gao et al. [32].

be reached under very mild reaction conditions (at a temperature of 35 °C) and with excellent yields.

Ortho- and *para*-directed effect of OR group in electrophilic substitution is evident; however, accessing sufficiently reactive catalysts to promote direct metalation of phenol-derivatives is far from evident. Very recently, Fernández-Ibáñez reported an elegant example of non-directed C—H arylation of alkoxy aromatics. In this case, the use of S,O-ligand **L3** allowed to generate highly reactive Pd-species, prompt to promote electronically favored *ortho*-arylations (Figure 1.3b) [26]. The potential of this strategy toward LSF of complex molecules was illustrated while challenging the catalytic system with estrone methyl ether as a substrate.

While non-directed C—H activation generally occurs at *ortho*- and *para*-positions, alteration of this native reactivity of electron-rich alkoxy aromatics to reach *meta*-selectivity is extremely challenging. Elegant example of such non-directed *meta*-selective C—H arylation was reported in 2019 by Yu [27]. The key to reverse the conventional selectivity lies in the use of norbornene additive, able to displace the site-selectivity from the *ortho*- to the *meta*-position, as initially used in the Catellani reaction [28] (Figure 1.3c). Following this concept, a large diversity of biaryl phenol derivatives could be prepared using a complex catalytic system composed of $Pd(OAc)_2$, norbornene, and dual ligand system (quinoxaline derivative **L4** together with pyridine sulfonic acid derivative **L5**). Remarkably, direct *meta*-selective arylation of tasimelteon proceeded smoothly, delivering the desired product in 72% yield.

An additional example of a brilliant use of norbornene mediator to modify the selectivity of the C—H activation was reported by the same group in 2020 [29]. In this case, direct arylation of quinoline was investigated. While the use of the bifunctional template approach allows to selectively address C5 position, the functionalization could be displaced by one carbone, thus occurring at the C6 position, in the presence of a norbornene additive. This approach thus warrants access to the C6-arylated camptothecin in 47% yield (Figure 1.3d).

An additional interesting concept for controlling site-selectivity in non-directed C—H activation was proposed by Čorić in 2020 [30]. The author speculated that a fine design of carboxylic acid anionic ligand can allow spatial control over the regioselectivity, the metalation event. Accordingly, naphthyl-derived biscarboxylic acid **L6** was designed and explored in Pd-catalyzed direct arylation using hypervalent iodines as coupling partners (Figure 1.3e). While high reactivity was observed for various substrates under mild reaction conditions (room temperature), only moderate regioselectivity was generally observed. However, in the case of ibuprofen methyl ester as a substrate, featuring two sterically different substituents, selective diversification occurred, delivering the functionalized compound in 45% yield and high selectivity.

Selective non-directed C—H activation can frequently be achieved in case of heterocyclic compounds. Elegant example of LSF of caffeine was achieved by Hong and Szostak [31]. Bimetallic catalytic system composed of Cu and Pd was thus used to allow decarboxylative arylation of N-heterocyclic compounds. The key C—H activation step results from coordination of a heterocyclic substrate by Cu, followed

by migration occurring via the C—H activation step, while the Pd-catalyst promotes the activation of the second aromatic partner via decarboxylation (Figure 1.3f). Under such finely designed catalytic conditions and using probenecid acid derivative as the coupling partner, direct arylation of caffeine was achieved in 70% yield.

The importance of LSF of heteroaromatic cores was also clearly demonstrated in the recent study by Li, Zhang, and Gao who explored LSF of osimertinib (Figure 1.3g) [32]. Fine optimization of the reaction conditions allowed determining a selective protocol for C2 functionalization of the indole core. A large library of the arylated osimertinib derivatives could thus be afforded, and their biological activity was directly evaluated.

1.2.4 LSF via C—O Bond Formation

LSF via introduction of O-atom may have a critical impact on the biological properties, including increased solubility and decreased *logP*. Besides, binding affinity of the oxygenated derivatives may also be improved, as new interactions may now be expected. Therefore, development of LS reactions allowing direct conversion of C—H bonds into C—O bonds seems extremely appealing. Following this analysis, the group of Yu developed carboxylate-directed hydroxylation of benzoic acid derivatives [33]. Newly designed pyridine-pyridone ligand **L7** showed exceptional reactivity in such reactions, featuring strong *ortho*-directed effect with respect to the carboxylate directing group, even in the presence of potentially stronger directing groups. Accordingly, not only a large platform of innovative phenol congeners, previously difficult to access, could be obtained in a single step, but also a LS diversification of a biologically active probenecid occurred smoothly, delivering the desired product in 60% yield (Figure 1.4a). Despite the fundamental importance of this methodology, the use of BQ oxidant together with O_2 are far from optimal. Seeking more industrially relevant transformation, the same group shortly after an additional protocol is compatible with the use of H_2O_2 as the privileged source of the hydroxyl group [34]. A modified carboxy-pyridone ligand (**L8**) generates sufficiently reactive catalytic cycle to promote direct hydroxylation of a bench of benzoic acids as well as phenylacetic acids. Remarkably, while implementing this strategy for the LSF of ibuprofen, remarkably scale up of the reaction (>200 g) was conducted efficiently using only 1 mol% of the Pd-catalyst at room temperature. Considering the diversity of phenylacetic acid motif in drug design, the optimized protocol could be rapidly evaluated against a bench of biologically active scaffolds, including loxoprofen, itanapraced, and ketoprofen (Figure 1.4b). It is also worth mentioning that high selectivity of this protocol toward carboxylate directing group warrants good functional group tolerance.

Ortho-directed Pd-catalyzed hydroxylation may also be conducted using oxime ether as a directing group, as reported by Jiao [35]. The use of simple PPh_3 or DEAD as ligand generated a catalytic system compatible with the use of oxone as the coupling reagent (Figure 1.4c). Under the optimized reaction conditions, various hydroxylated compounds, including zaltoprofen, were afforded in good yields and excellent site-selectivity.

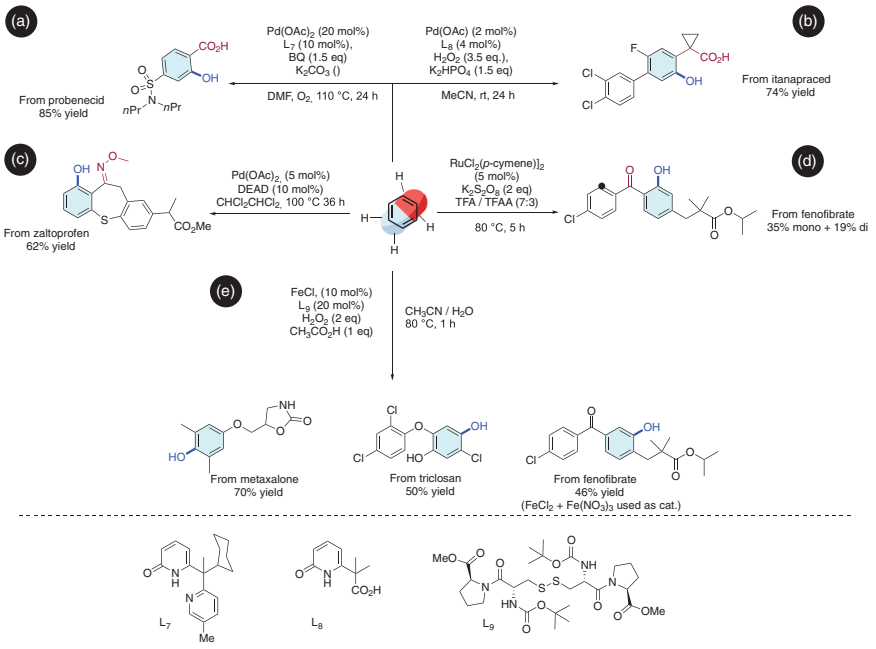

Figure 1.4 LSF of aromatics via direct C—O bond formation. a) Pd-catalyzed late-stage hydroxylation of probenecid developed by Yu et al. [33] b) Pd-catalyzed late-stage hydroxylation of itanapraced developed by Yu et al. [34] c) Pd-catalyzed late-stage hydroxylation of zaltoprofen developed by Jiao et al. [35] d) Ru-catalyzed late-stage hydroxylation of fenofibrate developed by Rao et al. [36] e) Fe-catalyzed late-stage hydroxylation of metaxalone, triclosane and fenofibrate developed by Han et al. [37].

The *ortho*-hydroxylation is not limited to Pd-catalyzed reactions. While interesting example of Ru-based catalytic system was reported for ketone-directed functionalization, the control of the monohydroxylation vs. dihydroxylation is far from trivial, as exemplified by the synthesis of fenofibrate-derivatives as a mixture of monohydroxy and dihydroxy products (Figure 1.4d) [36].

While noble metals proved their excellent reactivity in diversity of C—H activation reactions, their poor abundance, extreme costs, and often encountered high toxicity issues clearly impact the transfer of this chemistry from academic laboratories toward industry. Therefore, the design of 3d-metal-catalyzed transformations is extremely important. An attractive example of Fe-catalyzed direct hydroxylation was disclosed in 2021 by Han (Figure 1.4e) [37]. The authors discovered that this extremely cheap metal, while coordinated with cysteine-derived ligand **L9**, is prompt to promote efficient non-directed hydroxylation of a diversity of aromatics using hydrogen peroxide as the terminal oxidant. Excellent functional group tolerance and quite mild reaction conditions render this strategy a perfect solution for LSF, as illustrated by the synthesis of hydroxy metaxalone or triclosane for example, as well as a regioisomer of the previously described fenofibrate derivative.

1.2.5 LSF via C—N Bond Formation

Nitrogen atom has a pivotal role in nature, and therefore it is not surprising that the majority of drug candidates contain at least one N-atom. Indeed, nitrogen participates readily in diversity of interactions, warranting specific recognition between a drug candidate and an enzymatic pocket, for example. Accordingly, the introduction of N-atom at a late stage on a structurally complex molecule present not only a tremendous opportunity but also a great challenge. While first examples of LS nitrogenation for direct diversification of drug-like molecules were developed using mainly Cu-based catalyst, the introduction of an external directing group, such as oxazoline or oxime ether motif, was necessary [38]. In contrast, a more general strategy toward C—H amidation, compatible with several different DGs, was reported by Loh [39]. While the protocol for $Rh^{(III)}$-catalyzed direct C—N bond formation was optimized using N-heterocycle-based DG, alternative coordinating groups such as amine, amide, and ketones also showed their efficiency to direct the desired functionalization at the *ortho*-position. Interestingly, the use of hypervalent iodine reagent containing I—N bond (Zhdankin's reagent) turned out to be particularly appealing, granting the amidation event to occur under relatively mild reaction conditions (Figure 1.5a). Remarkably, thanks to the compatibility of this protocol with various DGs, it could be efficiently used for the direct nitrogenation of camptothecin *N*-oxide, delivering the desired compound in 70% yield.

Introduction of N-based functionality can also be a perfect opportunity to directly convert a desired molecule into a conjugate for target drug delivery, "PROTAC

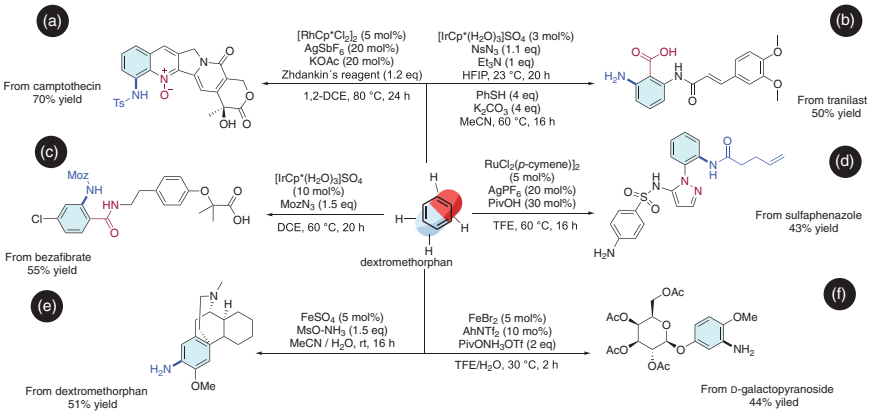

Figure 1.5 Late-stage direct C—N bond formation. a) Rh-catalyzed late-stage nitrogenation of camptothecin developed by Loh et al. [39] b) Ir-catalyzed late-stage nitrogenation of tranilast developed by Johansson, Martin-Matute et al. [40] c) Ir-catalyzed late-stage nitrogenation of bezafibrate developed by Johansson, Martin-Matute et al. [41] d) Ru-catalyzed late-stage nitrogenation of sulfaphenazole developed by Ackermann, Johansson et al. [42] e) Fe-catalyzed late-stage nitrogenation of dextromethorphan developed by Morandi et al. [43] f) Fe-catalyzed late-stage nitrogenation of D-galactopyranoside developed by Jiao et al. [44].

synthesis," or introduction of a fluorescent motif. This overall goal motivated a collaborative project between the group in AstraZeneca led by Johansson and Martin-Matute to explore direct amidation of carboxylic acid derivatives [40]. Implementation of HTE approach guaranteed rapid optimization of the reaction conditions and determination of the reaction protocol, allowing not only a high yielding reaction on a benchmark substrate but also important functional group tolerance (evaluated via the screening of various additives). IrCp*-based catalyst showed the best reactivity, thus allowing direct C—N bond formation under remarkably mild reaction conditions (Figure 1.5b). The compatibility of this protocol with various carboxylate-containing drugs was further validated, allowing the synthesis of amino-derivatives of molecules such as flavoxate and tranilast (*in situ* deprotection can be achieved). Shortly after, the same consortium further extended the generality of direct nitrogenation reactions by focusing on substrate bearing various directing groups [41]. HTE-technology was one more time the key to success to rapidly discover a modified catalytic system, able to promote the *ortho*-amidation of various building blocks, including N-heterocycles containing DGs, amides, imines, benzamides, etc. The impressive generality of this approach unlocked the door toward LSF of large panel of drug-like molecules (12 examples), including bezafibrate, levamisole, and protelivir (Figure 1.5c).

While $Ir^{(III)}$ and $Rh^{(III)}$ catalysts are recognized for their potential in direct C—N bond formation, the high cost associated with their usage may clearly hamper the industrial applications. In contrast, although Ru is a noble metal as well, its larger availability and significantly reduced costs make Ru a highly appealing alternative. Indeed, Ackermann and Johansson focused on implementing this alternative catalytic system for LSF of diversity of drug-like products [42]. In addition, dioxazolone reagents were selected as desirable aminating agents (Figure 1.5d). Under extensive high-throughput optimization, two sets of the reaction conditions were determined to promote the expected *ortho*-nitrogenations in the presence of various directing groups. The desired transformation turned out to be highly general and easily applicable to diversity of drug-like molecules. Although the yields of this LS amination are not always very high, the synthetic simplicity and rapidity of this strategy, obviating the need of the *de novo* construction of each derivative, clearly illustrate the exceptional importance of this approach. In addition, compatibility of this transformation with bifunctional dioxazolones allows LS linker installation for possible applications in PROTAC systems.

While the previous examples were based on directed approaches, benefiting for the native coordinating groups to direct the nitrogenation at the *ortho*-position, an alternative approach toward direct introduction of the nitrogen function may relay on the electrophilic activation of an aromatic ring followed by Fe-catalyzed functionalization. In 2016, Morandi disclosed an efficient and straightforward strategy for non-directed amination of electron-rich aromatics [43]. Remarkably, combination between cheap $FeSO_4$ and protonated hydroxylamine N-source warrants direct access to the primary amine derivatives without a need for additional functional group interconversions. Besides, as the aromatic substrates are used as the limiting agents, this protocol offers a unique potential for the late stage amination of drug

candidates, including flurbiprofen and dextromethorphan (Figure 1.5e). Almost simultaneously, the group of Jiao reported a conceptually similar approach toward undirected, electrophilic amination of electron-rich arenes [44]. In their case, a more complex aminating agent, $PivONH_3OTf$, was finally used as the aminating agent in the presence of Fe as a catalyst and Ag-salt as a co-catalyst (Figure 1.5f). The reaction proceeded smoothly not only on a diversity of electron-rich aromatic compounds but also several applications toward LSF of complex molecules were showcased, including the synthesis of amine-derived compounds bearing D-galactopyranoside. Finally, undirected Fe-catalyzed direct amination can also be run in HFIP as solvent [45].

1.2.6 LSF via C—B Bond Formation

Direct C—H borylation, pioneered by Smith [46] and tremendously expanded by Hartwig [47, 48], is among the early and also the most powerful direct C—H activation reactions. Indeed, direct conversion of a latent C—H bond into synthetically useful C—B bond presents an extraordinary potential, paving the way toward subsequent conversion into variety of other functional groups. Therefore, selective borylation reactions warrant straightforward access to a diversity of molecular scaffolds [49].

The initial examples of direct borylations were mainly based on the use of an Ir-catalyst in combination with B_2pin_2 as the coupling partner. As heterocyclic compounds are particularly appealing in such transformations, site-selectivity was primarily controlled via combination of steric and electronic reasons, thus obviating a need for preinstallation of a directing group. Thus, non-directed direct borylation turned out to be extremely powerful and reliable strategy to afford diversity of heterocyclic building blocks [50]. One of the early elegant examples of two-step direct functionalization of complex drug-type molecules was disclosed by Hartwig in 2014 [51]. Careful evaluation of the regioselectivity of the borylation of various heterocyclic substrates allowed establishing reactivity rules, thus unlocking the door toward predictable non-directed functionalization of drug-like compounds (Figure 1.6a). The synthetic importance of this approach was beautifully illustrated while functionalizing c-Met kinase inhibitor. The site-selective C—B bond formation occurred selectively on benzoxazole moiety, thus affording an activate intermediate for a sequential Suzuki coupling. The two-step protocol of borylation followed by cross-coupling thus allowed formation of an interesting pyridine-derived drug candidate. Another attractive illustration of the synthetic importance of direct borylation of heterocycles was disclosed a few years later. Focusing on substrates bearing thiophene or pyridine-derived scaffolds, regioselective Ir(cod)-catalyzed borylation followed by copper-catalyzed methylation furnished rapidly methylated congeners of drugs such as clopidogrel or loratadine (Figure 1.6b) [52].

The excellent reactivity of the Bpin motif in various metal-catalyzed cross-coupling reactions renders this group extremely useful in synthetic chemistry and drug development. This concept was clearly demonstrated by Segawa and Itami while exploring direct borylation of strychnine (Figure 1.6c) [53]. Remarkably, the

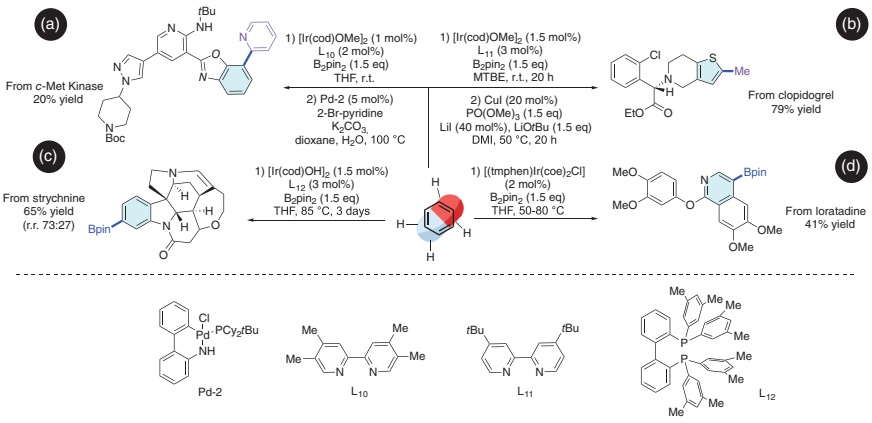

Figure 1.6 Direct borylation via LSF. a) Ir-catalyzed late-stage borylation of c-Met kinase inhibitor developed by Hartwig et al. [51] b) Ir-catalyzed late-stage borylation of clopidogrel developed by Hartwig et al. [52] c) Ir-catalyzed late-stage borylation of strychnine developed by Segawa, Itami et al. [53] d) Ir-catalyzed late-stage borylation of loratadine developed by Tu, Shekhar, Hartwig et al. [54].

Ir-based catalytic system, in combination with a finely designed diphosphine ligand **L12**, allowed direct conversion of C—H bond at C3 position of the indole motif into the desired C—B moiety. The newly accessed compound could thus be used as a starting material in a variety of reactions. Therefore, direct borylation step combined with an additional catalytic event led to the formation of a library of 15 C3-substitiuted strychnine derivatives, compounds that would be extremely difficult to access via *de novo* synthesis.

While $[Ir(cod)OMe]_2$, combined with N-based ligands, such as bipyridine- or phenantroline-derived ligands turned out to be the privileged catalysts for direct C—B bond formation, the air sensitivity of this catalytic system renders the reactions poorly reproducible and difficult to handle at larger scale. Accordingly, the design of more user-friendly catalysts has gained significant attention of the scientific community. In 2024, single-component, air-stable, and easy-to-handle Ir-catalyst has been reported by Tu, Shekhar, and Hartwig [54]. The air-stable Ir-catalyst bearing trimethylphenantroline ligand promotes the desired borylation reactions with comparable selectivities and efficiencies. Notably, its inherent stability allows direct functionalizations to be conducted, if requested, also on submicromolar scale, for applications in HTE, for example. While implementing this improved catalytic system, direct C—B functionalization of loratadine was reached in 70% yield (Figure 1.6d).

While the initial efforts on direct borylation focused mainly on transformations governed by electronic and steric properties of substrates, fine design of alternative catalytic systems to address selectively *ortho*-, *meta*-, and *para*-positions rapidly caught attention of the scientific community. Various systems have thus been designed to allow selective DG-controlled introduction of the Bpin motif [51b]. Very elegant example of the synthetic utility of the ligand-free borylation occurring under

directing-group selectivity control was reported in the context of the medicinal chemistry project in 2020 by Scott et al. [55]. The authors focused on the LS diversification approach to generate fluorinated analogs of the drug-candidate AZD9833. Several conceptually different routes have been envisioned to introduce the F-atom at the different positions of the advanced molecules. In particular, direct borylation/fluorination sequence was designed to introduce the halogen atom at the C6 position of the indazole core. The presence of the pyridine motif was expected to warrant high regioselectivity via the initial pre-coordination of the Ir-complex. As expected, the desired transformation occurred smoothly under rather mild reaction conditions, delivering the expected borylated product in synthetically useful yield of 64% (Figure 1.7a). Although the further steps including amination and fluorination turned out to be more challenging, this study clearly illustrates the potential of the directed borylation using inherently present functionalities of an advanced molecule.

More systematic study of ligand-free DG-controlled *ortho*-LS borylation was reported in 2022 by Sunoj and Chattopadhyay [56]. The authors discovered that while $[Ir(cod)OMe]_2$ is used in the absence of any specific ligand, *ortho*-directing effect can be observed for several classes of substrates, including 2-phenylpyridines, 2-anilinpyridines, and benzylamines. Accordingly, this operationally simple protocol could be efficiently implemented for the LS borylation of several drug type scaffolds, including dapoxetine and sertraline (Figure 1.7b). Remarkably, the desired compounds were isolated in very high yields, thus rapidly furnishing important building blocks for further modifications.

While interesting examples can be obtained using simple $[Ir(cod)OMe]_2$, the design of significantly more general catalysts, featuring high reactivity

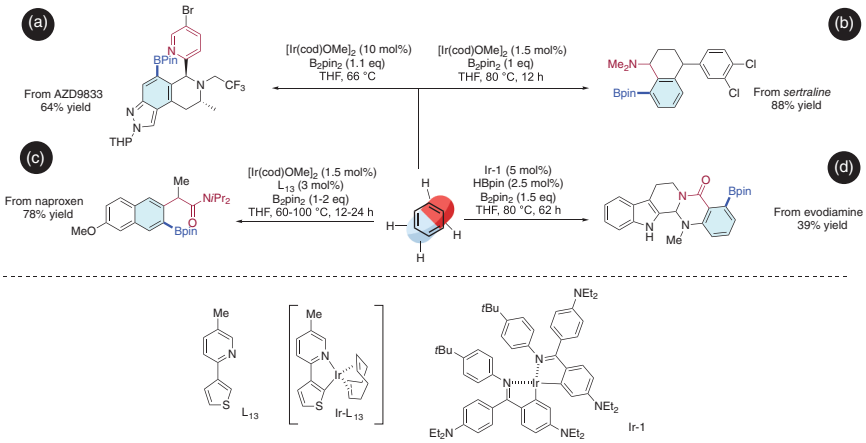

Figure 1.7 Late-stage direct C—H borylation. a) Ir-catalyzed late-stage borylation of AZD9833 developed by Scott et al. [55] b) Ir-catalyzed late-stage borylation of sertraline developed by Sunoj, Chattopadhyay et al. [56] c) Ir-catalyzed late-stage borylation of naproxen developed by Chattopadhyay et al. [58] d) Ir-catalyzed late-stage borylation of evodiamine developed by Ackermann, Smejkal, Wencel-Delord et al. [59].

and *ortho*-selectivity in the presence of structurally very different substrates, seems extremely appealing from medicinal chemistry perspective. Following this goal, Chattopadhyay proposed an original *in situ*-generated metalacyclic [57] Ir-C(thienyl) and Ir-C(furyl) anionic complexes [58]. These new catalysts feature excellent directing group compatibility, thus allowing *ortho*-selective borylation of aromatics bearing functional groups such as amides, esters, ketones, imines, ethers, amines, thioethers, and carbamates. Although relatively harsh reaction conditions are requested (at temperatures typically between 60 and 100 °C), the generality of this protocol renders it particularly suited for LS borylation, as illustrated on several examples including sertraline and naproxen (Figure 1.7c).

Following the concept of metalacyclic complexes for robust and general C—H activation, bis-cyclometallated Ir-complexes bearing imine ligands were designed by a collaboration between Smejkal from Syngenta and the groups of Ackermann and Wencel-Delord [59]. While the bis-cyclometallated complex structure is quite surprising, such Ir-species turned out to be remarkably stable and easily isolable, thus facilitating catalyst's handling. In addition, high reactivity of this complex in several different solvents, including Me-THF, octane, *i*PrOAc, CPME, and eucalyptol, under moderate reaction temperature (50 °C) and its compatibility with DGs, including amides, ketones, esters, ethers, oximes, etc., renders it highly appealing for various late stage applications, as illustrated via direct borylation of evodiamine (Figure 1.7d).

Considering the key importance of the late stage borylation for rapid expansion of the molecular complexity of advanced scaffolds, recently HT approach has attracted growing scientific interest. In a collaborative effort from researchers from Syngenta, AstraZeneca, and the group of Wencel-Delord, HT borylation of various drug-like molecules was explored, using several standard protocols, including ligand-free protocol using $[Ir(cod)OMe]_2$ precursor, $[Ir(cod)OMe]_2$ in combination with phenanthroline ligand, bipyridine ligand, and **L13**, as well as **Ir-1** [60]. Miniaturization study combined with HT technic allowed to rapidly evaluate the efficiency of such various reaction conditions for direct borylation of 45 complex drug molecules. While the reactions performed poorly or with low selectivity for 21 examples, 24 compounds furnished the functionalized structures. Even though the isolation of the borylated drugs often turned out to be highly challenging and additional derivatization steps were required, this study unambiguously illustrates the high potential of the LS borylation. The regioselectivity of the reactions appears highly substrate-dependent; in some cases, such as donepezil or tamibarotene, *ortho*-effect of the inherently present coordinating groups is evident, while in other cases, including flumazenil or olaparib, the site-selectivity seems to be controlled by steric and electronic properties of the substrate. In some cases, following the reaction conditions used, an interesting regioselectivity switch was evidenced. While this advanced study does not allow yet to predict the outcome of the direct borylation at the advanced structures, it clearly indicates the reactivity trends and selectivity/reactivity relationship depending on the nature of the catalytic system used.

Following the same objective of the rationalization of the LS borylation, the researchers from Roche, in collaboration with Konrad and Schneider, endeavored

combining HTE approach for direct borylation with deep machine learning [61]. Selection of 23 drug compounds, 12 drug-like structures, and 5 frequently occurred substrates was settled as library. Standard reaction conditions, i.e., the use of $[Ir(cod)OMe]_2$ precursor in different solvents, were selected as parameters, designing a set of 956 experiments that were subsequently used as database for machine learning. The deep learning approach fructified in establishing a model able to predict reaction yield for a known reaction with an absolute error margin of 4–5%. The reactivity prediction for a new reaction was slightly less efficient but still reached the level of 92–67%, and the regioselectivity of the major product could be generally adequately foreseen.

1.2.7 LSF via C—X Bond Formation

Introduction of a Fluor atom on drug candidates can have a critical impact on the biological properties, increasing the lipophilicity, modifying pharmacokinetics and dynamic properties of a molecule, and enhancing its solubility [62]. Accordingly, approximately 20% of the commercialized pharmaceuticals and 50% of agrochemicals contain at least one fluor atom. Therefore, a late-stage fluorination of advanced drug candidates is extremely important [63].

One of the early examples of the direct fluorination of a complex molecule was described in 2015 by Xu and Xu [64]. The authors developed an efficient, Pd-based catalytic system for C—H/C—F exchange benefitting from a removable 2-pyridyloxy group. While direct fluorination is believed to be particularly challenging due to slow and unfavorable C—F bond forming reductive elimination, the use of NFSI as both the fluorinating agent and a strong oxidant warrants the desired reaction to occur smoothly for a diversity of phenol-containing substrates. Particular attention should be paid on direct fluorination of diflufenican, where high site-selectivity could be reached owing to the coordinating properties of the pyridine ring (Figure 1.8a). Use of NFSI as both, the oxidant and the fluorinating agent, was also the solution of choice to promote direct fluorination of benzamides and benzeneacetamides [65]. Slightly modified reaction protocol, using $PdCl_2$ together with $AgNO_2$, thus allowed the synthesis of diversity of fluorinated compounds, including drug derivatives such as ketoprofen and flurbiprofen, in 90 and 66% isolated yields, respectively (Figure 1.8b).

While the previous examples correspond to the traditional C—H activation scheme, occurring via insertion of a metal catalyst into a C—H bond, a conceptually very different approach toward direct fluorination of arenes was disclosed by Ritter [66]. In this case, a finely designed Pd-catalyst is used to catalytically generate, *in situ*, a highly reactive electrophilic fluorinating agent, prompting to undergo electrophilic aromatic substitution. Remarkably, this transformation offers alternative selectivity pattern, as the functionalization occurs at the electronically activated positions. The reaction features important functional group tolerance, thus paving a way toward direct diversification of a few compounds, including ciprofibrate and nateglinide derivatives (Figure 1.8c).

While direct fluorination allows to strongly impact the biological properties of drugs, the presence of other halogen atoms, in particular, chlorine, can also be an

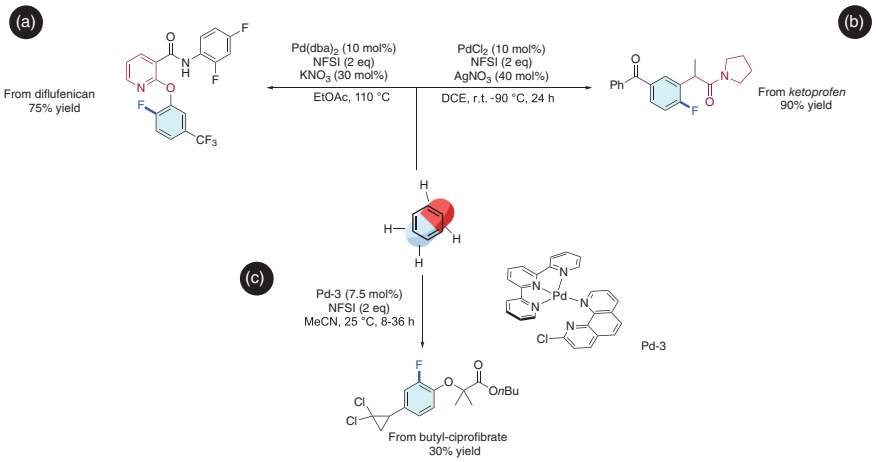

Figure 1.8 Late-stage direct fluorination. a) Pd-catalyzed late-stage fluorination of diflufenican developed by Xu, Xu et al. [64] b) Pd-catalyzed late-stage fluorination of ketoprofen developed by Lou, Xu et al. [65] c) Pd-catalyzed late-stage fluorination of ciprofibrate developed by Ritter et al. [66].

interesting tool toward improved pharmacological profile. Similarly to the late-stage fluorination directed by 2-pyridyloxy group, a direct introduction of Cl-atom can also be achieved via this Pd-catalyzed transformation [67]. The use of NCS as the chlorinating agent turned out to be optimal, allowing *in situ* generation of high oxidation state Pd(IV) intermediates, thus facilitating the challenging reductive elimination C—Cl bond formation step. This synthetic potential of this protocol toward late stage chlorination was demonstrated using diflufenican substrate, yielding the desired halogenated congener in remarkably 94% yield (Figure 1.9a).

A very interesting combination of LS functionalization and the concept of transient directing group toward direct chlorination of complex structures was reported in 2019 by Zhang [68]. While using inherently present aldehyde, combined with *p*-trifluoroaniline additive (to generate the imine directing group *in situ*), in the presence of Pd-catalyst and pyridone ligand **L14**, the *ortho*-methoxylation and chlorination occurred efficiently. When challenged with a complex structure,

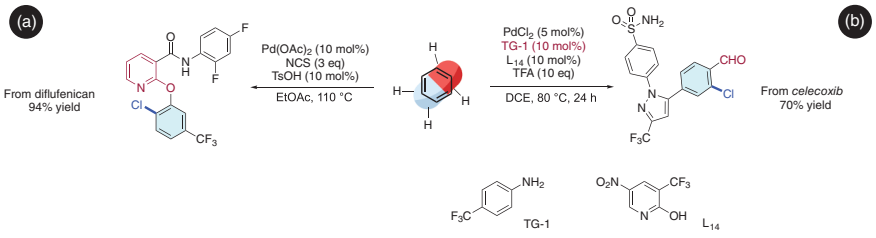

Figure 1.9 Late-stage direct chlorination. a) Pd-catalyzed late-stage chlorination of diflufenican developed by Wu, Wu et al. [67] b) Pd-catalyzed late-stage chlorination of celecoxib developed by Zhang et al. [68].

such as celecoxib, the catalytic system performed efficiently, delivering the halogenated compound in 70% yield and high 5:1 mono-functionalization vs. di-functionalization (Figure 1.9b).

1.2.8 LSF via C—D Bond Formation

Isotopically labeled compounds are of prime importance for the pharmaceutical industry [69]. Indeed, they are crucial for the elucidation of biological activity, thus being commonly used to perform ADME studies required for registration. Besides, a selective introduction of deuterium can also alter metabolic properties of a given drug candidate. Therefore, development of sustainable and straightforward hydrogen isotope exchange (HIE) reactions is highly appealing. In this context, metal-catalyzed C—H activation, in particular, LSF offers a unique route to rapidly prepare deuterated compounds while obviating the need for *de novo* synthesis with numerous synthetic steps and deuterated building blocks.

While several examples of late-stage deuteration of drug candidates have been developed using Ir-based Crabtree's catalyst [70] as well as Kerr's Ir–NHC complex [71], and other Ir-based catalysts [72], the development of alternative routes compatible with less expensive catalyst was highly appealing [73].

Elegant and sustainable strategy toward hydrogen isotope exchange was proposed by Chirik in 2016, focusing on Fe-based catalyst. Following their work on Fe-catalyzed hydrogenation of non-activated alkanes, they discovered that bis(arylimidazol-2-ylidene)pyridine iron bis(dinitrogen) complex **Fe-1** shows exceptional reactivity in hydrogen/deuterium exchange [74]. Remarkably, gaseous $^{2}H_{2}$ can be used under moderate overpressure (4 atm) and mild reaction conditions (45 °C). The selectivity of this reaction is controlled by the steric factors, with the preferential functionalization occurring at the most accessible position. The reaction is also favored in the case of electron-poor substrates and is compatible, as well, with various heterocyclic substrates. While challenging this catalytic system with complex substrates, including drug derivatives, several deuterated congeners could be directly accessed, including paroxetine, loratadine, and flumazenil (Figure 1.10a). An additional unique advantage of this protocol is its compatibility with tritiation. Indeed, under only subatmospheric pressure of $^{3}H_{2}$, tritium labeling occurred smoothly, warranting expedient access to the tritium-labeled drugs, such as souvorexant, cinacalcet, and flumazenil. While this strategy offers an interesting route toward important scaffolds, extreme water and air sensitiveness of the catalyst makes these transformations not easily applicable for less experienced practitioners.

Few years later, the same research groups focused on Ni-based catalysts for hydrogen isotope exchange. By developing nickel hydride precatalyst (**Ni-1**), they succeeded in establishing an operationally simple and highly efficient protocol for direct deuteration and tritiation of various heterocyclic substrates, using gaseous $^{2}H_{2}$ and $^{3}H_{2}$ [75, 76]. Compared to the previous Fe-based system, Ni-complex shows improved reactivity toward electron-rich heteroarenes, including pyrroles and indoles, without a need of an N-directing group. The isotope exchange occurs preferentially at positions adjacent to the nitrogen atom for N-heterocyclic

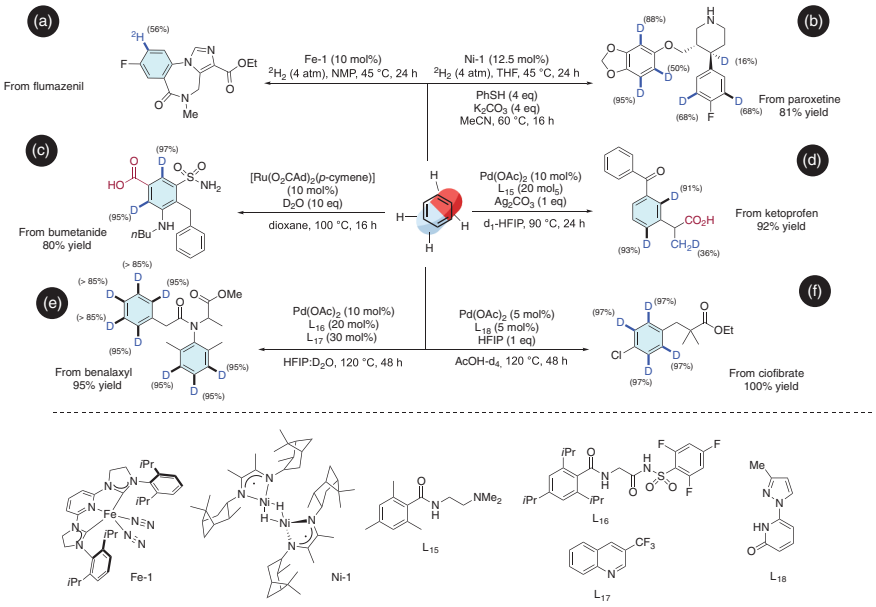

Figure 1.10 Direct hydrogen isotope exchange for the synthesis of deuterated drugs.
a) Fe-catalyzed late-stage deuteration of flumazenil developed by Chirik et al. [74]
b) Ni-catalyzed late-stage deuteration of paroxetine developed by Chirik et al. [75]
c) Ru-catalyzed late-stage deuteration of bumetanide developed by Ackermann et al. [77]
d) Pd-catalyzed late-stage deuteration of benaalaxyl developed by van Gemmeren et al. [79] e) Pd-catalyzed late-stage deuteration of clofibrate developed by Joo et al. [80]
f) Pd-catalyzed late-stage deuteration of ketoprofen developed by van Gemmeren et al. [78].

substrates and at the sterically most available positions for aromatic compounds. This Ni-based catalytic system thus paved a way toward isotopically labeled entities, such as etoricoxib, papaverine, or paroxetine (Figure 1.10b).

While Chirik's Fe- and Ni-based complexes showed particular efficiency in hydrogen isotope exchange at sterically available positions, alternative regioselectivity trend was observed by Ackermann, while establishing Ru(II)-catalyzed protocol [77]. Benefiting from high reactivity of ruthenium biscarboxylate complexes and reversibility of the C—H activation step, the group succeeded in developing fully *ortho*-selective hydrogen isotope exchange protocol, using carboxylate as largely present in nature DG. The use of D_2O as deuterium source further increases the operational simplicity of this methodology, even though high reaction temperature (100 °C) is required to reach full conversion. The high potential of this hydrogen isotope exchange approach was further highlighted via LS deuteration of several pharmaceutical drugs and biological active sulfonamides, including repaglinide, bumetanide, and telmisartan (Figure 1.10c).

An alternative protocol toward deuteration of carboxylic acids was reported one year later by the group of van Gemmeren [78]. Benefiting from the coordinating properties of the carboxylate DG, combined with the addition of an amide type ligand **L15** in charge of promoting the CMD (concerted metalation-deprotonation)

C—H cleavage step, reversible C—H metalation and the following *ortho*-selective deuteration were performed successfully. While the silver salt was often necessary to reach high conversion, both d_1-HFIP and D_2O could be used as the deuterating agents. Interestingly, the reaction protocol tolerates both, aliphatic and aromatic substrates, allowing direct deuteration of structurally different compounds. As the benzyl carboxylate motif is largely present in various natural products and drugs, the compatibility of this reaction with LS deuteration was demonstrated using substrates such as ketoprofen, ciofibric acid, and ciprofibrate (Figure 1.10d). While developing this Pd-based system, the authors also discovered that under slightly modified reaction conditions undirected deuteration can be promoted [79]. Indeed, in the presence of two catalysts, i.e., bicoordinating amide **L16** combined with a pyridine-based ligand **L17**, general deuteration of the aromatic rings was observed at various aromatic positions. In case of pharmaceutically relevant scaffolds, such as benalaxyl or praziquantel, high level of D-insertion was observed at all aromatic positions using HFIP/D_2O as solvent mixture under harsh conditions (at a temperature of 120 °C) (Figure 1.10e).

Conceptually, closely related per deuteration of aromatic substrates was reported in 2023 by Joo. Capitalizing on the privileged $Pd(OAc)_2$ catalyst, they designed an alternative catalytic cycle using pyrazolopyridone (**L18**) ligand [80]. The pyridine motif acts as an internal base during the C—H cleavage step, warranting reversibility of this event and thus promoting efficient hydrogen isotope exchange. The reaction conditions remain harsh, with the reaction temperature of 120 °C and the use of acetic acid as the deuterium source, but they are still applicable for the synthesis of labeled drugs, including fenofibrate and clofibrate (Figure 1.10f).

1.3 Late-Stage Functionalization of Aliphatic Compounds

While LS functionalization of aromatic compounds has reached some level of maturity, direct introduction of functional groups on aliphatic parts of a complex molecule is infinitely more challenging. Indeed, C(sp^3)—H bonds are considerably less reactive in inner-sphere C—H activation type reactions. In addition, in most cases, derivatization of an advance molecule to introduce a specific DG is requested, as exemplified by a work of Chang [81]. The elegant Ir-catalyzed strategy has been reported for direct amidation of unactivated methyl group. As oxime was necessary as DG, direct functionalization of complex molecules such as friedelin or lanosterol could be achieved, but prior conversion of ketones or secondary alcohol motifs into the desired ketoxime was essential. In addition, inner-sphere metal-catalyzed protocols are generally limited to the sterically accessible positions, thus significantly limiting the diversity of possible substrates.

Alternative strategy toward metal-catalyzed direct functionalization of C(sp^3)—H bonds implies outer-sphere C—H activation strategies, particularly suited for C—N and C—C bond formation via nitrenoid and carbenoid intermediates. Drawing inspiration from nature, spectacular direct oxidation type

transformations have been reported using finely designed Fe- and Mn-based complexes [82]. In this case, minor modifications of the ligand structure allows precise control of the regioselectivity of the direct oxidation, thus allowing direct installation of an O-atom in a precise and predictable manner [83].

1.3.1 LSF of Aliphatic Substrates via Direct C—C Bond Formation

While Pd-catalyzed direct C—H activation typically requires the use of a DG to pre-coordinate the catalyst to the substrate and promote regioselective direct arylation, carboxylic acid, often encountered motifs in natural products and drugs, can play this role and being used as an inherent directing group. This concept has been elegantly used by Yu for direct C—H arylation of activated aliphatic substrates, i.e., cyclopropanes, in 2019 [84]. The careful design of the amino acid-derived ligand **L19** allowed not only to reach high reactivity in this C—H activation reaction, but also enantioselective outcome of this arylation was achieved, delivering the arylated cyclopropanes in high ees. While challenging the catalytic system with itanapraced, cyclopropane-containing drug, the LS arylation occurred smoothly, delivering the arylated congener in excellent yield and 94% ee (Figure 1.11a). Few years later, the concept of the carboxylic acid-directed transannular C—H arylation was extended toward a large diversity of cycloalkanes [85]. Addition of the quinuclidine-pyridone ligand (**L20**) allowed transannular γ-methylene C—H activation that was successfully exploited for a diversity of cyclobutene, cyclopentane, cyclohexane, cycloheptane, and cyclooctane substrates. Remarkably, this protocol could also be exploited in the context of direct arylation of isosteviol, where the regioselectivity is perfectly controlled by the geometry of the metalacyclic intermediate (Figure 1.11b).

An alternative example of the applications of native functional groups as DG for C—H activation was reported by Gaunt et al. in 2020 [86]. The authors discovered that tertiary amines are able to coordinate the Pd catalyst, directing the C—H activation toward γ-position via generation of 5-membered metalacyclic intermediate. Addition of an external ligand, such as monoprotected amino acid, was crucial to enhance the C—H cleavage step, and simple *N*-acetyl *t*-leucine (**L21**) turned out to be the optimal additive to efficiently trigger the CMD-type metalation event. Under the optimized reaction conditions, the desired arylation could thus be conducted using diversity of propylamine derivatives. Interestingly, benefiting from the inherent structure of trimipramine, this direct arylation reaction could be implemented to directly furnish several aromatic derivatives of this antidepressant drug (Figure 1.11c). It is also worth noting an elegant work of Sanford, where transannular arylation of cyclic amines could be achieved using Pd-catalyst. However, installation of precise directing group was necessary to promote LS functionalization of varenicline derivative [87].

A conceptually and mechanistically very different example of LS functionalization of aliphatic substrates was reported by Davies and Beckwith [88]. Outer sphere Rh-catalyzed strategy was used to diversify alkaloids, including brucine. The reactivity of Rh-carbenoid insertion of donor/acceptor diazo coupling partner

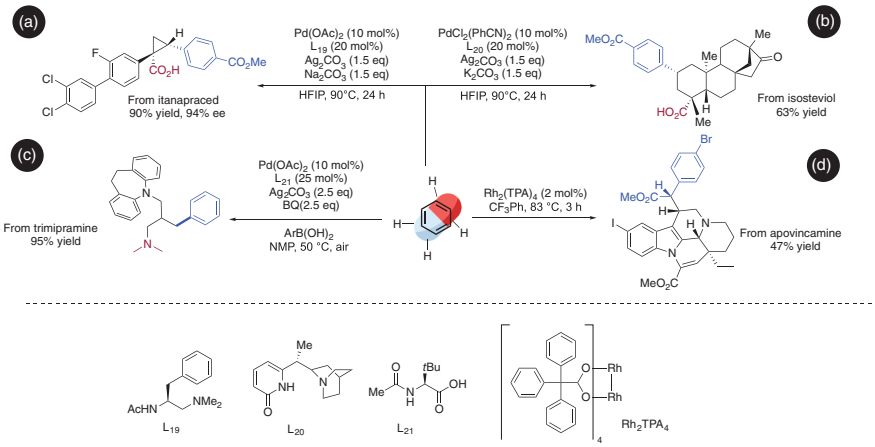

Figure 1.11 Late-stage diversification of aliphatic substrates via C—C bond formation.
a) Pd-catalyzed C(sp^3)-H late-stage arylation of itanapraced developed by Yu et al. [84]
b) Pd-catalyzed C(sp^3)-H late-stage arylation of isosteviol developed by Yu et al. [85]
c) Pd-catalyzed C(sp^3)-H late-stage arylation of trimipramine developed by Gaunt et al. [86]
d) Pd-catalyzed C(sp^3)-H late-stage alkylation of apovincamine developed by Davies, Beckwith et al. [88].

favors functionalization at electronically enriched positions, i.e., benzylic, allylic, α-atom to heteroatom, or tertiary positions. In addition, fine-tuning of the ligand allows to further control site, and if relevant, stereoselectivity of the reaction. Benefiting from such a high selectivity of the $Rh^{(II)}$-carbenoid insertion, the authors succeeded in designing three catalytic systems amenable to differentiate very similar C(sp^3)—H bonds, thus delivering selectively three different regioisomers of the functionalized compound. The reaction could be further extended toward other alkaloid-type substrates, including securinine and apovincamine (Figure 1.11d). Over the following years, additional examples of $Rh^{(II)}$-catalyzed insertion reactions have been used to allow direct synthesis of complex natural products and derivatization of drugs [89].

1.3.2 LSF via C—O Bond Formation

Direct oxidation of aliphatic compounds is one of the key processes in nature. Therefore, it is not surprising that development of similar strategies to direct installing oxygen atom on a complex molecule is a rapidly evolving research field.

Among the catalytic systems that have attracted key scientific attention, Fe-based complexes are particularly interesting. Following the excellent work of White group [83], exceptional reactivity of Fe(PDP)-catalyst was discovered, allowing non-directed but highly selective direct oxidation of aliphatic substrates. Indeed, this catalyst features a unique capability of being able to differentiate even very similar C(sp^3)—H bonds based on their electronic (activation by electron-donating groups), steric (favored functionalization of 3° site), and stereoelectronic properties (conformational effects are contributing factors to

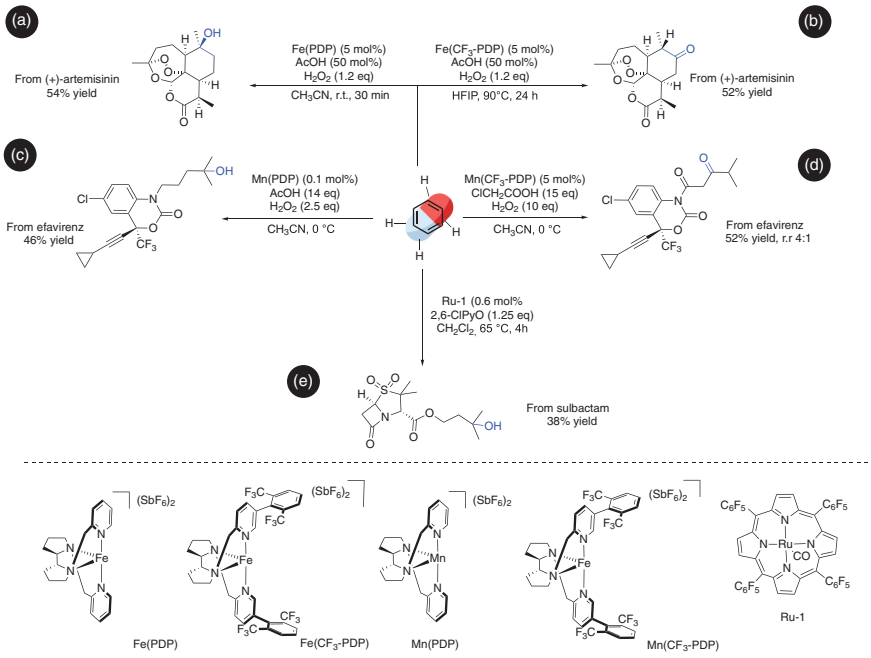

Figure 1.12 LS oxygenation of aliphatic complex molecules. a) Fe-catalyzed C(sp^3)-H late-stage oxidation of artemisinin developed by White et al. [91] b) Fe-catalyzed C(sp^3)-H late-stage oxidation of artemisinin developed by White et al. [92] c) Mn-catalyzed C(sp^3)-H late-stage oxidation of efavirenz developed by White et al. [93] d) Mn-catalyzed C(sp^3)-H late-stage oxidation of efavirenz developed by White et al. [93] e) Ru-catalyzed C(sp^3)-H late-stage oxidation of sulbactam developed by Hartwig et al. [94].

the product distribution). The detailed analysis of the combination of these parameters allows highly predictable transformations, even when using complex substrates, including dihydropleuromutilone [90] or artemisinin (Figure 1.12a) [91]. Remarkably, precise modification of the ligand's structure impacts significantly its chemical behavior, altering the selectivity of the oxidation step. Indeed, introduction on the external part of the ligand two aromatic units bearing sterically demanding and electron-withdrawing CF_3 motifs contributes to the increased sensitivity of the catalyst toward steric hindrance of a substrate. Accordingly, the newly designed Fe(CF_3-PDP) catalyst promotes oxidation of the 2°-positions, delivering regiomeric products compared to the standard Fe(PDP) system (Figure 1.12b) [92].

Extending the work of Fe(PDP), White et al. investigated a closely related Mn(PDP)-complex [93]. This new catalyst also showed important reactivity toward direct C—O bond formation at 3°-position, and it tolerates well the presence of nitrogen motifs on complex molecules. Accordingly, the LS functionalization of efavirenz was achieved selectively in a synthetically useful yield, using very low catalyst loading of 0.1 mol% (Figure 1.12c). Following the same trend as in case of the Fe-complexes, more sterically accessible Mn(PDP) promotes selective oxidation at the 3°-position, while the use of more sterically hindering (CF_3-PDP) gives

access to the regiomeric products with the oxygen being installed at the 2°-position (Figure 1.12d).

Very recently, a new approach toward direct hydroxylation of various compounds, including natural products and drug derivatives, was disclosed by Hartwig [94]. Ru-porphyrine complex turned out to be extremely reactive toward direct C—O bond formation at 3° site, featuring, in addition, extensive functional group compatibility, including nitrogenated heterocycles, halogen substituents, nitro groups, and Bpin motifs. Considering the generality of this approach and its potential toward LS functionalization was rapidly evidenced, using diverse natural products and drug derivatives, including fenofibrate, sulbactam, and thalidomide (Figure 1.12e). In all cases, high yielding reaction was conducted in the presence of only 0.6 mol% of the Ru-catalyst.

1.3.3 LSF via C—N Bond Formation

While considering outer-sphere C—H functionalization of C(sp^3)—H bonds, $Rh^{(II)}$-based catalytic systems, largely explored by Du Bois [95], Dauban [96], and others [97], are frequently considered benchmark strategy toward direct amination of aliphatic substrates. However, the initial work of Du Bois showed that this approach might be poorly efficient while challenged with complex molecules, in particular containing several nitrogen atoms. The remarkably breakthrough toward more general amination approach, compatible with LSF mindset, was reported in 2018 by Du Bois [98]. Precise selection of solvent, namely, *t*BuCN, turned out to be crucial to allow, on the one hand, solubilize densely functionalized compounds and, on the other hand, stabilize the dirhodium catalyst. Under the optimized reaction conditions, this protocol could thus be used toward highly regioselective direct amination of variety of compounds, including drugs such as tadalafil. The regioselectivity is controlled by the inherent reactivity of the substrate and thus positions into N-atom or 3°-position (Figure 1.13a).

Following the same conceptual approach as Fe- and Mn-catalyzed direct oxidation, amination of aliphatic C(sp^3)—H bonds can be efficiently conducted in the presence of a Fe- and Mn-based catalyst. While H_2O_2 was commonly used in case of the oxidation reactions, direct amination can frequently benefit from the application of iminoiodinane as the aminating agents [99]. While iminoiodinane can be generated *in situ* while reacting sulfamate and $PhI(OPiv)_2$, this reaction may be slow. Therefore, addition of a preformed iminoiodinane is frequently a solution of choice. Detailed catalytic system's optimization revealed that a polychlorinated porphyrine Mn-based catalyst outcompetes other catalysts. Contrary to the direct oxidation reaction, the C—N bond formation occurs preferentially at the benzylic position. The catalyst shows, however, strong steric preferences with the functionalization occurring at more accessible position and more electron-rich positions are addressed first. As an illustration of this methodology, direct nitrogenation of sulbactamb or sertraline can be indicated (Figure 1.13b).

Outer-sphere C—H activation of C(sp^3)—H bonds is also particularly suited to promote direct azidation-type transformations. In 2015, Groves demonstrated that

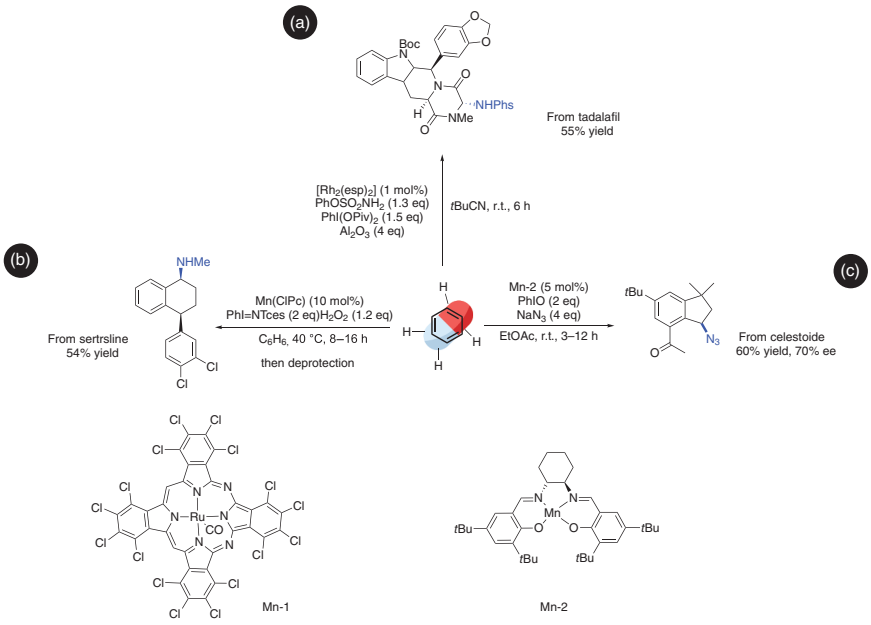

Figure 1.13 LS nitrogenation of the aliphatic substrates. a) Mn-catalyzed C(sp^3)-H late-stage nitrogenation of sertraline developed by White et al. [99] b) Mn-catalyzed C(sp^3)-H late-stage nitrogenation of celestoide developed by Groves et al. [100].

Shiff-base Mn complexes can be used successfully to install N_3-motif on various complex molecules without prior prefunctionalization [100]. The salient feature of this reaction includes the use of aqueous sodium azide solution as the coupling partner and the robustness of the catalytic system (reactions can be run under air). The azidation occurs inherently at the most reactive positions, i.e., at the benzylic or 3° site. This operationally simple protocol is thus a promising handle for the direct functionalization of a number of natural products and drugs, including artemisinin, celestoide, and papaverine (Figure 1.13c).

1.3.4 LSF via C—D Bond Formation

While metal-catalyzed direct H/D exchange can be relatively easily achieved by means of reversible C—H activation approach, the situation is significantly more complex when aliphatic C—H substrates are considered. Indeed, the metalation event, already challenging, needs to be reversible to warrant efficient H/D scrambling. One of the rare examples of LS deuteration of aliphatic carboxylic acids was reported in 2021 by van Gemmeren.[80] Combining (1) the coordinating properties of the carboxylic function inherently present on a given molecule with (2) the amine-amide ligand **L22** prone to facilitate the metalation event, efficient C(sp^3)—H activation followed by trapping with d_1-HFIP, furnished the deuterated alkanes in high efficiency. This protocol could be efficiently applied for the synthesis

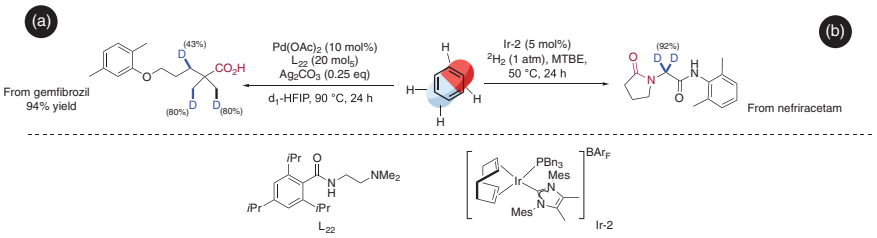

Figure 1.14 Hydrogen isotope exchange on aliphatic drug-like molecules. a) Pd-catalyzed C(sp^3)-H late-stage deuteration of gemfibrozil developed by van Gemmeren et al. [78] b) Ir-catalyzed C(sp^3)-H late-stage deuteration of nefriracetam developed by Kerr et al. [101].

of isotopically labeled complex molecules, including gemfibrozil and bezafibrate (Figure 1.14a).

An alternative protocol allowing direct hydrogen isotope exchange on amide-type substrates was reported in 2024 by Kerr [101]. The authors, capitalizing in their previous work on Ir-catalyzed H/D exchange, designed a catalytic system by promoting highly selective deuteration of C(sp^3)—H bonds in α to nitrogen atom. Excellent levels of deuterium incorporation combined with high predictability of the regioselectivity of the reaction and interesting functional group tolerance make this strategy an interesting tool to afford labeled pharmaceuticals, including laurocapram, nefriracetam, and unifiram (Figure 1.14b).

1.4 Conclusions and Perspectives

While the pioneering and sporadic examples of the use of C—H activation reactions for LSF of drug candidates have appeared in the literature at the beginning of this century, this concept has witnessed a tremendous expansion over the last few years. The diversity of newly discovered C—H activation reactions paved the way for a large panel of systems that allow direct diversification of complex molecules. Importantly, the panel of applications of LSF is extremely broad. On the one hand, diversity of functional groups can be directly introduced, including aromatic and aliphatic units, O- and N-based motifs, as well as halogen substituents (e.g., F and Cl) and boron-based groups. On the other hand, various inherently present functional groups on a drug candidate, including carboxylate or *N*-heterocycle motifs, can be used to control the site-selectivity of the reaction and promote selective *ortho*-functionalizations. Importantly, the chemical diversity of compounds can be further expanded while implementing distal C—H activation approaches to address alternative C—H positions on a molecule. However, while reaching different selectivities is relatively well known in the case of phenol derivatives, direct *meta*- and *para*-functionalization of more complex structures, without the need for preinstallation of a complex directing group, remains extremely challenging and very case-specific.

The analysis of the state-of-the-art literature also clearly shows that the vast majority of the transformations rely on the use of expensive and toxic metals. Since this step is to be used at the very end of the drug candidate synthesis, difficulty in removing traces of metal-catalysts might thus be a limitation. Therefore, development of alternative strategies, based on the use of cheap and more abundant 3d-metals, is of high demand and will certainly progress considerably in the near future. However, the difficulty toward this challenging goal lies in the common use of bis-coordinating DGs in 3d-metal-catalyzed C—H activation, which is fundamentally incompatible with the LSF approach.

Important to notice is also a real change in the perception of the LSF by the scientific community. Still, a decade ago, challenging a newly developed methodology with complex drug-like molecules was rather seldom. Currently, demonstration of a functional group tolerance and compatibility of a new reaction with complex structures is almost a standard requirement to validate the synthetic utility of a project. In addition, clear implementation of the LSF in the R&D sector in industry further highlights the importance of this topic. Importantly, the industrially driven projects also show that even poorly regioselective LSF reactions can still be of high interest as they provide direct access to several regioisomeric products, thus further expanding the chemical space.

The last decade of research in the field of C—H activation clearly evidenced that this strategy offers a unique possibility toward direct functionalization of complex molecules. However, several limitations, including selectivity toward other than *ortho*-C—H bonds, common use of Pd-, Ru-, and Ir-complexes, and compatibility issues of a given reaction with several coordinating groups present on a drug-like molecule, are still persisting challenges. However, considering the real motivation of the academic groups to showcase the synthetic utility of their new methodologies, combined with the expanding interest of industrial partners, we are strongly convinced that the field will evolve very rapidly in the near future, bringing academic research and concrete applications even closer.

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