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REVIEW

Late-stage modification of bioactive compounds: Improving druggability through efficient molecular editing

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Abstract Synthetic chemistry plays an indispensable role in drug discovery, contributing to hit compounds identification, lead compounds optimization, candidate drugs preparation, and so on. As Nobel Prize laureate James Black emphasized, "the most fruitful basis for the discovery of a new drug is to start with an old drug"[1]. Late-stage modification or functionalization of drugs, natural products and bioactive compounds have garnered significant interest due to its ability to introduce diverse elements into bioactive compounds promptly. Such modifications alter the chemical space and physiochemical properties of these compounds, ultimately influencing their potency and druggability. To enrich a toolbox of chemical modification methods for drug discovery, this review focuses on the incorporation of halogen, oxygen, and nitrogen—the ubiquitous elements in pharmacophore components of the marketed drugs—through late-stage modification in recent two decades, and discusses the state and challenges faced in these fields. We also emphasize that increasing cooperation between chemists and pharmacists may be conducive to the rapid discovery of new activities of the functionalized molecules. Ultimately, we hope this review would serve as a valuable resource, facilitating the

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application of late-stage modification in the construction of novel molecules and inspiring innovative concepts for designing and building new drugs.

1. Introduction

The development of drug discovery has been accelerated by the emergence of new strategies and technologies, such as combinatorial chemistry, large compound libraries, high-throughput screening, cheminformatics, omics, and artificial intelligence[2−6]. However, organic synthesis remains a rate-limiting factor in drug discovery, despite decades of groundbreaking research in academia[7−9]. Recently, late-stage modification (LSM), or called late-stage functionalization (LSF) of drugs, natural products and bioactive compounds has attracted more and more attention from pharmaceutical chemists. As Nobel Prize winner James Black highlighted, "the most fruitful basis for the discovery of a new drug is to start with an old drug"[1]. In the field of pharmaceutical science, LSM enables the rapid generation of efficient tool molecules for the investigation of structure−activity relationship (SAR) and optimization of druggability by modifying numerous analogs of bioactive compounds and natural products without resorting to *de novo* synthesis[10,11].

LSM of bioactive compounds offers the opportunity to introduce new effects that were either designed or previously unanticipated. This approach can modulate the physicochemical properties, such as solubility, acidity coefficient (pK_a), and oil-water partition coefficient (log*P*), by incorporating different polarity groups into bioactive compounds. Moreover, adjusting the shape and size of substituent groups can optimize their fit within target cavities. Halogen, oxygen, and nitrogen are common elements in pharmacophore groups and are frequently found in marketed drugs. Particularly, the groups containing halogen, oxygen, and nitrogen elements can form halogen and hydrogen bonds with amino acid residues, and may enhance binding affinity and retention time with targets[12]. Analysis of US Food and Drug Administration (FDA) approved drugs from 2015 to 2020, reveals that nitrogen or oxygen elements are present in most drugs, while nearly half of them also contain halogen elements[13]. In this review, we will expound on the importance of introducing halogen, oxygen, and nitrogen elements here individually, emphasizing their potential for influencing potency and druggability with target molecules. While other functionalization of bioactive compounds are the same important in LSM, such as methylation[14−16], trifluoromethylation[17−19], and so on, some excellent articles have summarized this field well.

For instance, metabolic instability mediated by P450 enzymes poses a significant challenge in drug discovery[12]. Thus, blocking susceptible metabolic sites of bioactive compounds with fluorine atoms has emerged as an effective strategy in the early stage of drug discovery[20−22]. Ibuprofen is a famous non-steroidal anti-inflammatory drug, that works as an inhibitor of cyclo-oxygenases. When introducing a fluorine atom on the active benzyl site, its metabolic stability will be increased. The clearance was decreased from 19 to 12 μg/(min·mg) protein in human microsome and from 71 to 39 μg/(min·mg) protein in rat microsome (Fig. 1)[23]. Terfenadine, a non-sedating antihistamine withdrawn due to high cardiotoxicity, underwent a remarkable transformation. Its carboxylic acid metabolite, Fexofenadine[24,25], was proven safe after oxygen atom incorporation, paving the way for its emergence as a second-generation antihistamine (Fig. 1)[26,27]. There was a typical case to show the application of introducing nitrogen elements in drug discovery. Pioglitazone is a strong and selective PPARγ agonist, which was approved for diabetes by FDA in 1999[28], and applied to treat other metabolic diseases in clinical later[29,30]. In 2013, Baran introduced azide group with a linker into this drug, and then the new derivative could occur click reaction and be applied in other situations (Fig. 1)[31].

2. Halogenation of bioactive compounds

The inclusion of halogen atoms in a molecule can significantly alter its properties. The varying sizes and electronegativities of different halogens result in distinct changes in the physicochemical characteristics of bioactive compounds[32]. Introducing halogen atoms would raise the log*P* and reduce the solubility of benzene (Table 1), consequently influencing the pharmacokinetic properties and binding affinity of halogenated bioactive compounds. For example, Deschloroketamine, which is an analog of Ketamine without chlorine, has a lower log*P* than Fluoroketamine, Ketamine, and Bromoketamine[33]. And when a halogen atom was removed in a non-nucleoside reverse transcriptase inhibitor (NNRTI) presented by Anderson, its solubility was enhanced obviously[34].

2.1. *Fluorination of bioactive compounds*

The incorporation of fluorine atoms into bioactive compounds has been a prominent strategy in drug discovery, with several approved drugs containing fluorine atoms. Such as Tivicay[40,41], Verzenio[42], Isentress[43,44], and so on, contain at least one fluorine atom among the top 200 small molecule drugs sold[45−47]. This part explores the effects of introducing fluorine elements on the characteristics and potency of these molecules. The primary goal was to prevent *in vivo* metabolism by incorporating fluorine atoms into drug candidates[47,48]. The similarity in size between fluorine (atomic radius 0.42 Å), hydrogen (atomic radius 0.53 Å), and oxygen atoms (atomic radius 0.48 Å) allows for seamless replacement[49], blocking active sites without significant steric effects[50,51]. Moreover, the introduction of fluorine atoms can predictably enhance potency, primarily through the formation of new hydrogen bonds and the electron-withdrawing effect[52,53]. These interactions improve binding affinity with targets and enhance the

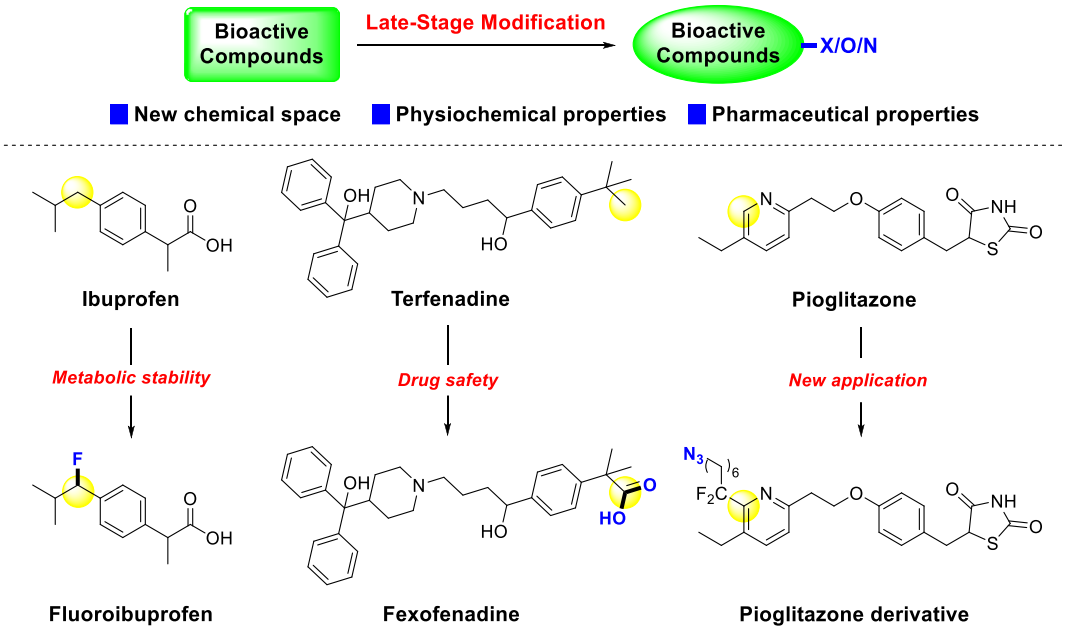


Figure 1 Influences after introducing 'X', 'O', and 'N' into bioactive compounds. Therefore, LSM has been a convenient and powerful strategy for incorporating 'X', 'O', and 'N' into bioactive compounds. This review would explore the role of LSM in the generation of new molecules from the insight of pharmaceutical science. Specifically, late-stage halogenation, oxygenation, and nitrogenation strategies will be expounded along the logic of conversion of functional groups.

$\pi-\pi$ stacking effect of benzene rings[52,53]. Additionally, the aryl C−F moiety serves as a hydrophobic isostere, mimicking the pyridone carbonyl moiety and improving bioavailability[54].

The incorporation of fluorine atoms into bioactive compounds also has significant effects on their physicochemical properties, such as lipophilicity and membrane permeability[55,56]. Moreover, different moieties containing fluorine atoms can influence membrane permeability in distinct ways, with aryl, vinyl, and alkyl fluorine playing varying roles[48,57]. While the proximal fluorine atoms might change the log*P* of molecules containing amine groups, due to the interaction of fluorine and the nearby N−H[58,59].

Therefore, the strategic introduction of fluorine atoms into bioactive compounds in late-stage by rational design may increase the potency and improve the pharmacokinetic properties, thus facilitating drug discovery and development. Furthermore, trifluoromethylation is also a fantastic strategy for introducing fluorine atoms into bioactive compounds, there were several good reviews described this field from different perspectives[17−19].

Table 1 Selected properties of substrate and product in halogenation.

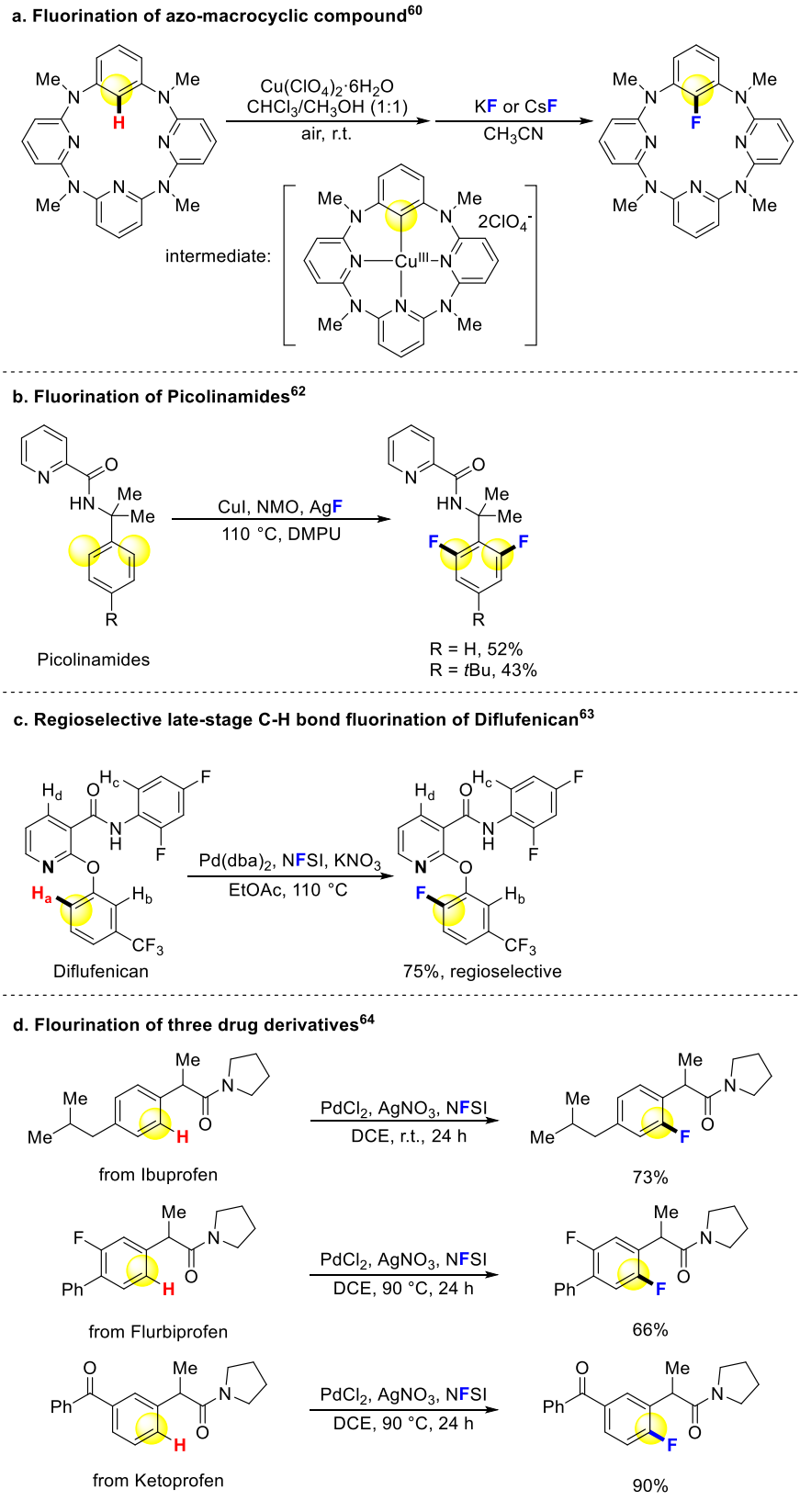
Substrate	Product	Substrate/Product	
		Log*P*[a]	S_w (mg/L)[a]
		2.13/2.27	1789/1550
		2.13/2.81	1789/472
		2.13/2.81	1789/472
		2.13/2.99	1789/410

[a]Data from references[35−39]; log*P*: octan-1-ol/H_2O partition coefficient; S_w: aqueous solubility at 25 °C, mg/L.

2.1.1. *Conversion of C−H bond to C−F bond*

The development of C−H bond functionalization based on transition-metal catalysis has opened up new possibilities for the fluorination of aromatic bioactive molecules. This review discusses notable examples of C−H bond fluorination strategies reported in recent two decades. Wang and coworkers successfully fluorinated an azo-macrocyclic compound through aryl−Cu(III) complex intermediate (Scheme 1a)[60]. Daugulis reported site-selective sp^3 C−H arylation directed by 8-animoquinoline and picolinic acid auxiliaries in 2005[61]. In 2013, this strategy was developed for *o*-fluorination of benzoic acid and some heterocyclic carboxylic acids with high selectivity of monofluorination and diflourination in different conditions[62]. Picolinamides, a PARP inhibitor, could be fluorinated with moderate yield under this condition (Scheme 1b)[62]. Xu and coworkers demonstrated an *o*-fluorination strategy for phenols, where the directing group pyridine could be removed after modification of molecules. Intriguingly, the pesticide Diflufenican and bioactive 2-phenoxyl nicotinic acid derivatives could be regioselective and late-stage modified smoothly, even with the presence of other potential sites (Scheme 1c)[63]. In 2018, Xu group presented a nitrate-promoted Pd-catalysis method for the fluorination of three drug derivatives (Scheme 1d)[64]. Although the presented examples are limited due to the existence of directing groups that restrict substrate structures, they highlight the potential of C−H bond fluorination in the synthesis of bioactive compounds.

In addition to directed fluorination strategies, non-directed methods have also been explored for the modification of aromatic bioactive molecules. In 2013, Hartwig reported that the 2-fluorination of a broad range of substituted pyridines occurs with AgF_2, and some medicinally relevant compounds can also be fluorinated using this method (Scheme 2a)[65]. In mechanism, the Ag atom is firstly coordinated with the nitrogen atom of pyridine, then the [Ag]-F bond is added to the π system of pyridine, and a

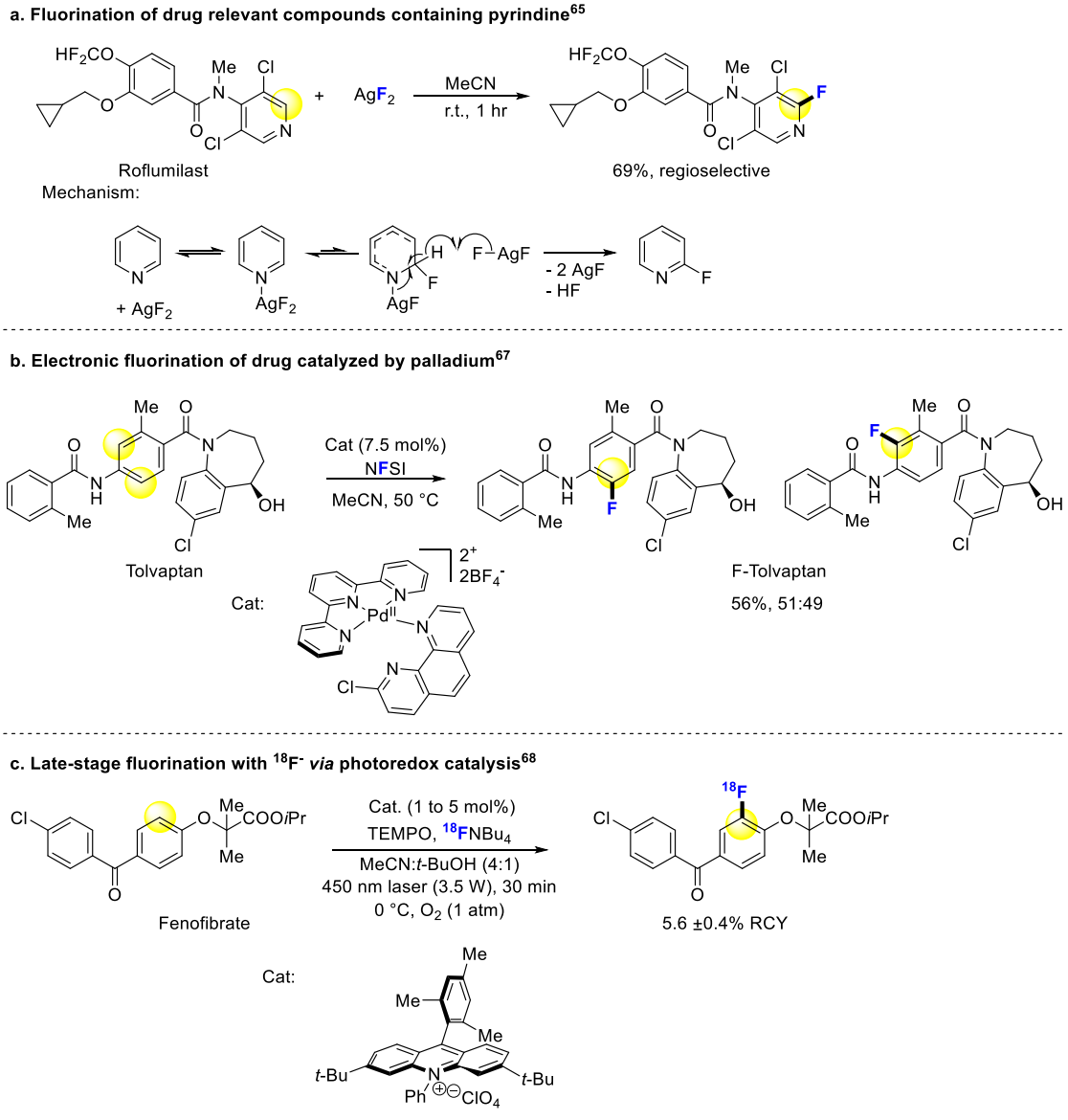


Scheme 1 Directed fluorination of arenes.

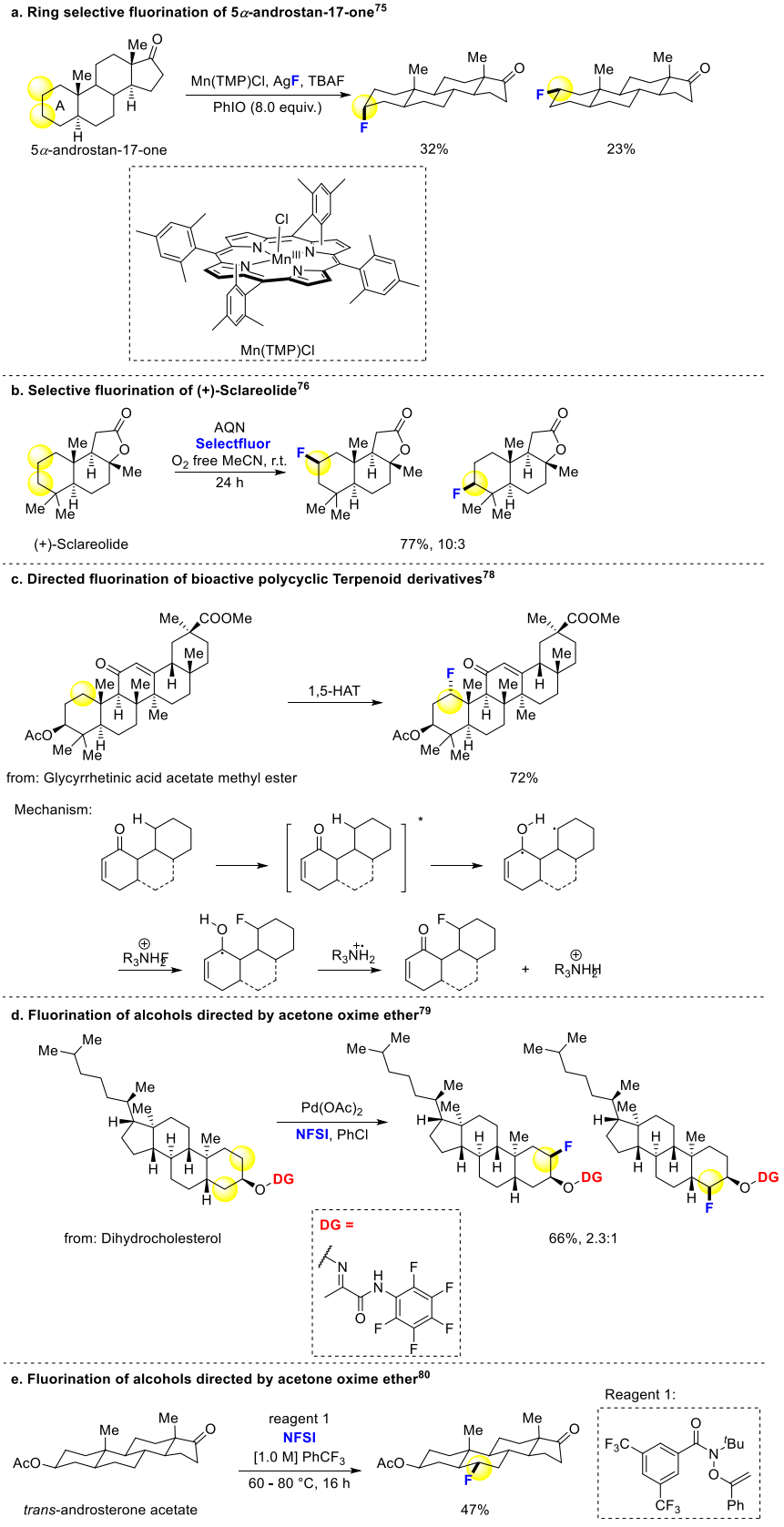
second equivalent of AgF_2 is abstracted from the hydrogen-atom to form product (Scheme 2a)[65]. Subsequently, they added nucleophilic reagents and bases into this system to further convert to 2-fluoropyridines[66]. Notably, Ritter's group has made a breakthrough in direct aromatic C−H fluorination with a broad substrate scope. The aromatic rings with all kinds of electron-donating groups and a few electron-withdrawing groups could be fluorinated by designed palladium catalyst, including some bioactive compounds. This reaction would be a practical tool for LSM, while overcoming its limitation of regioselectivity in the future (Scheme 2b)[67]. Li and Nicewicz utilized organic photoredox catalysis to introduce ^{18}F atoms into aromatic molecules with excellent substrate tolerance, and the steric effects might be the main factor to influence site-selectivity. Excitingly, numerous bioactive compounds were fluorinated through this method within a short time, and might be a great supplement for PET (Scheme 2c)[68]. The main challenge in non-directed strategies is achieving selectivity, as current approaches rely on the electronic properties of substituents on aromatic rings, but precise control remains elusive.

Although directed aryl fluorination has made significant progress in recent twenty years, challenges remain for chemists due to the strong metal−fluorine bond hindering reductive elimination[69–71] and the limited substrate scope imposed by directing groups. Conversely, non-directed fluorination of arenes, particularly heteroaromatics, often lacks regioselectivity. Despite these challenges, many commercially available small molecule drugs feature aryl fluoride moieties, such as Invega[72], Lynparza[73], and Erleada[74]. The development of improved aryl fluorination methods could enable the late-stage fluorination of more bioactive compounds, leading to their rapid progression as potential drug candidates.

No-aromatic fluorination has also been developed by chemists over the past two decades. In 2012, Groves and coworkers reported the aliphatic C−H bond fluorination strategy catalyzed by manganese porphyrin for the first time. The secondary carbon



Scheme 2 Non-directed fluorination of arenes.



Scheme 3 Direct fluorination of alkanes.

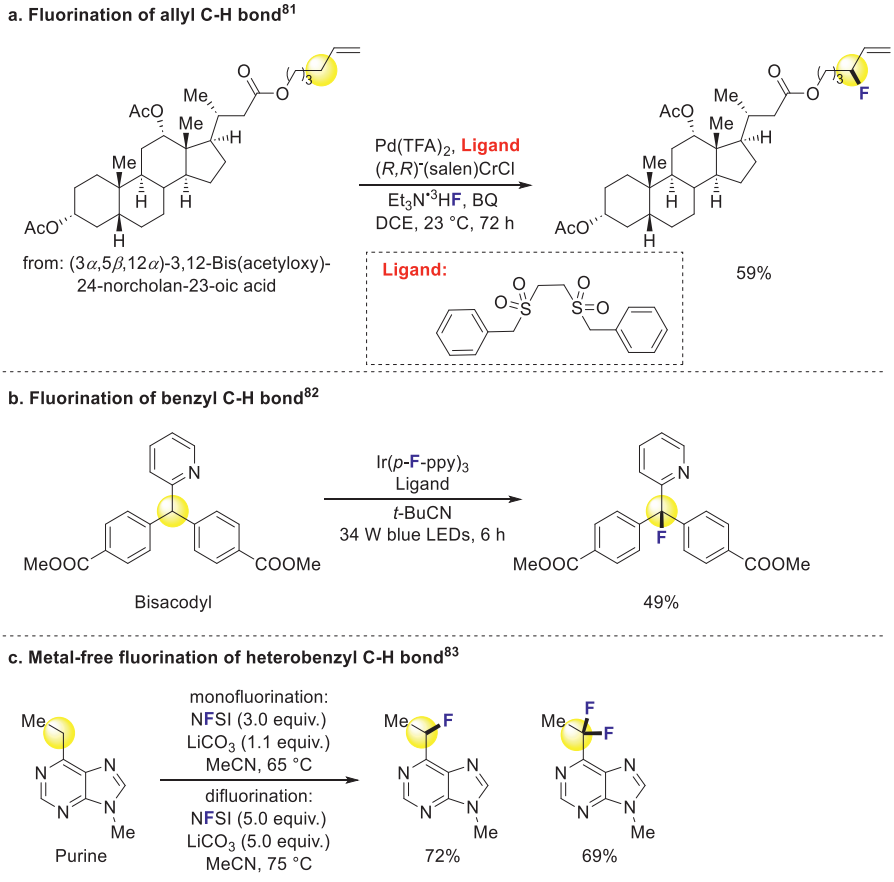
could be fluorinated more easily than primary and tertiary carbons slightly, and a kind of androgen was selectively fluorinated on A-ring under this condition (Scheme 3a)[75]. Tan and coworkers presented a new strategy of fluorination for unactivated secondary alkyl C−H bonds *via* photocatalysis, and (+)-Sclareolide, a terpenoid from plants, was subjected to this fluorination method (Scheme 3b)[76]. Lectka demonstrated a photocatalytic approach that selectively fluorinates peptides containing phenylalanine-like residues[77], and in another work the bioactive polycyclic terpenoid derivatives with α,β-unsaturated ketones could be regioselectively fluorinated *via* 1,5-hydrogen atom transfer process (Scheme 3c)[78]. In 2018, Xu, Luo and coworkers used acetone oxime ether as a removable directing group to achieve the fluorination of the β-C position of hydroxyl groups, facilitating the conversion of steroid molecules into the desired products (Scheme 3d)[79]. In 2022, Alexanian and coworkers developed an aliphatic C−H functionalization strategy, including fluorination, through radical chain transfer mechanism. Many kinds of C−H bonds could be functionalized in mild to good yields, and some bioactive compounds could be fluorinated with good regioselectivity (Scheme 3e)[80].

As we know, the methylene C−H bonds of alkyl bioactive molecules are often indistinguishable to fluorination reagents, unless the directing group takes effect. In addition, chirality is also an important factor in drugs. Enhancing the stereoselective fluorination of aliphatic C−H bonds, particularly those in aliphatic heterocycles, would greatly facilitate the application of late-stage fluorination in drug discovery. This would enable the selective introduction of fluorine atoms while preserving the desired stereochemistry of bioactive compounds.

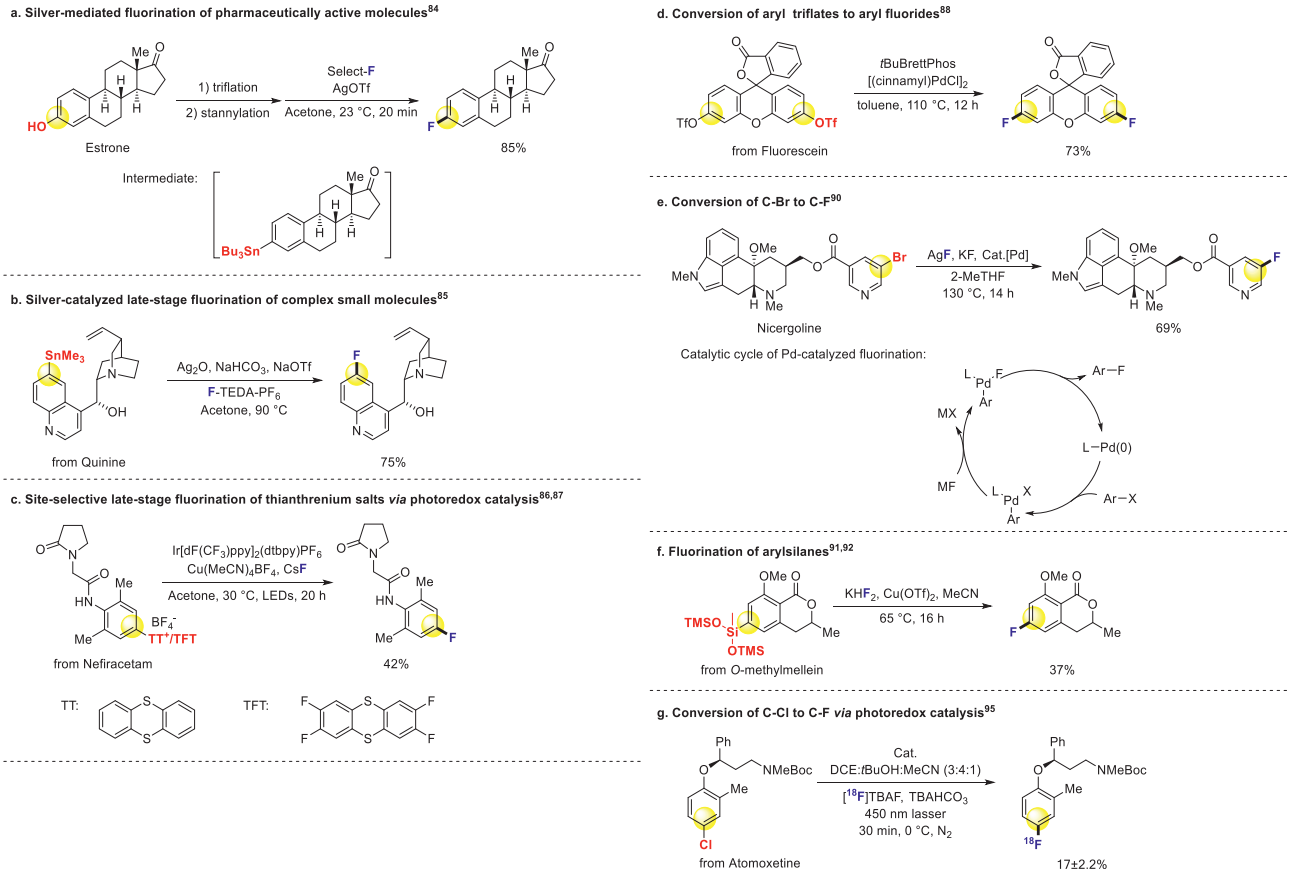
While common aliphatic C−H bonds are challenging to modify, the benzyl and allyl C−H bonds fluorination was developed leading to the emergence of several new approaches. Doyle successfully achieved allyl fluorination, demonstrating its applicability to a steroid derivative (Scheme 4a)[81]. Additionally, Doyle and coworkers developed another general strategy for benzyl C−H fluorination through photocatalysis, enabling smooth modification of various bioactive compounds and drug derivatives (Scheme 4b)[82]. Britton revealed a metal-free fluorination method for benzyl C−H bonds, offering potential applications in late-stage functionalization of bioactive molecules and positron emission tomography (PET) (Scheme 4c)[83]. Benzyl and allyl C−H bonds are appropriate fluorination sites in bioactive compounds, potentially improving their pharmacokinetic properties by blocking potential metabolic positions.

2.1.2. *Conversion of C−X to C−F bonds*

Besides the conversion of C−H bonds to C−F bonds, some works on C−X (X = B, OTf, Cl, Br, I, Si, S, Sn) to C−F bonds have been published in the last two decades. Ritter and coworkers fluorinated aryl stannanes with silver catalyst using commercial fluorination reagent Select-F[84]. By first converting hydroxyl groups to tin groups, they successfully transferred several pharmaceutically active molecules from hydroxyl to fluoride derivatives (Scheme 5a)[84]. Ritter also developed a silver-catalyzed fluorinate ion method for fluorination of many stannanes derived



Scheme 4 Fluorination of benzyl and allyl C−H bonds.



Scheme 5 Conversion of C−X to C−F.

from complex small molecules, including quinine, taxol and rifamycin S (Scheme 5b)[85]. Then, they combined photoredox catalysis with transition metal catalysis to enable site-selectivity fluorination of aryl sulfonium salts, which came from C−H bond thianthrenation of arenes. This approach allowed for late-stage modification of numerous drugs and their derivatives (Scheme 5c)[86,87].

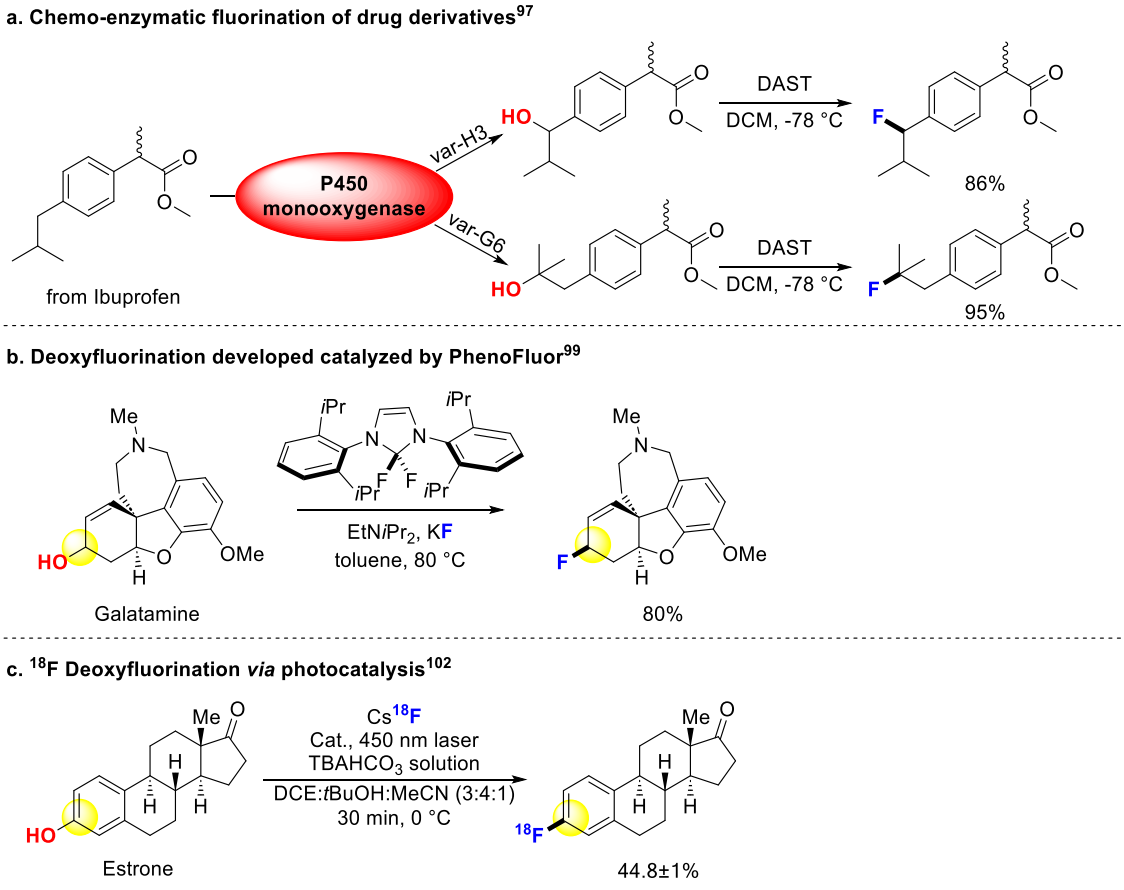
In 2009, Buchwald used palladium-catalyst to convert aryl triflates to aryl fluorides (Scheme 5d)[88]. This reaction could proceed at room temperature attributed to their new ligand AlPhos of the system[89]. Furthermore, they expanded their substrates to aryl halides (Br and I) in 2014, and the vascular disorder drug Nicergoline could be fluorinated at late-stage to provide an analog (Scheme 5e)[90].

Hartwig and coworkers have contributed to this field as well. They smoothly converted aryl trisiloxanes to aryl fluorides mediated by copper (Scheme 5f)[91,92]. Aggarwal and coworkers reported the transformation from alkyl boronates to alkyl fluorides in 2015[93]. Scott, Sanford and coworkers completed radio fluorination of pharmaceutically relevant scaffolds *via* organoboronate intermediates[94].

Nicewicz and Li cooperated to accomplish the photocatalytic method of converting C−X bonds to C−F bonds, where X can be Cl, Br, I, NO_2 and OTf groups. This approach allows for the late-stage fluorination of potential bioactive compounds with a wide substrate scope (Scheme 5g)[95]. Unlike C−H fluorination, the conversion of C−X bonds to C−F bonds is distinct because the 'X' group occupies specific positions within the molecules. This position fixed 'X' group enables the introduction of fluorine atoms without the need for challenging C−H activations.

2.1.3. *Conversion of C−O to C−F bonds*

The development of deoxyfluorination reagents has provided new strategies for converting C−OH or C−OR into C−F bonds, enabling late-stage modification of drug molecules[96]. Various methods have been established and applied to enhance the properties of pharmaceutical compounds. In 2008, Fasan combined CYP450-catalyzed oxygenation with deoxyfluorination to improve the blood−brain barrier (BBB) crossing potential[97] and metabolic stability[23] of Ibuprofen methyl ester (Scheme 6a). In 2011, Ritter group created a new deoxyfluorination reagent PhenoFluor and accomplished the direct transformation from phenol to aryl fluorides[98]. Subsequently, this commercial reagent was applied to late-stage fluorination of alcohol, and so many drugs performed well under this condition (Scheme 6b)[99]. In 2015, they further upgraded the reagent to PhenoFluorMix, which facilitated the deoxyfluorination of phenols[100]. In 2019, Ritter and coworkers utilized PhenoFluorMix to deoxyfluorinate sterides favorably[101]. Nicewicz and Li developed photocatalysis for late-stage deoxyfluorination and used it for ^{18}F isotope labeling of Estrone (Scheme 6c)[102]. Moreover, many scientists have made contributions to this field[103−107]. Deoxyfluorination has emerged as an effective approach for introducing fluorine atoms into bioactive molecules using readily available alcohols and phenols as starting materials.



Scheme 6 Conversion of C−O to C−F.

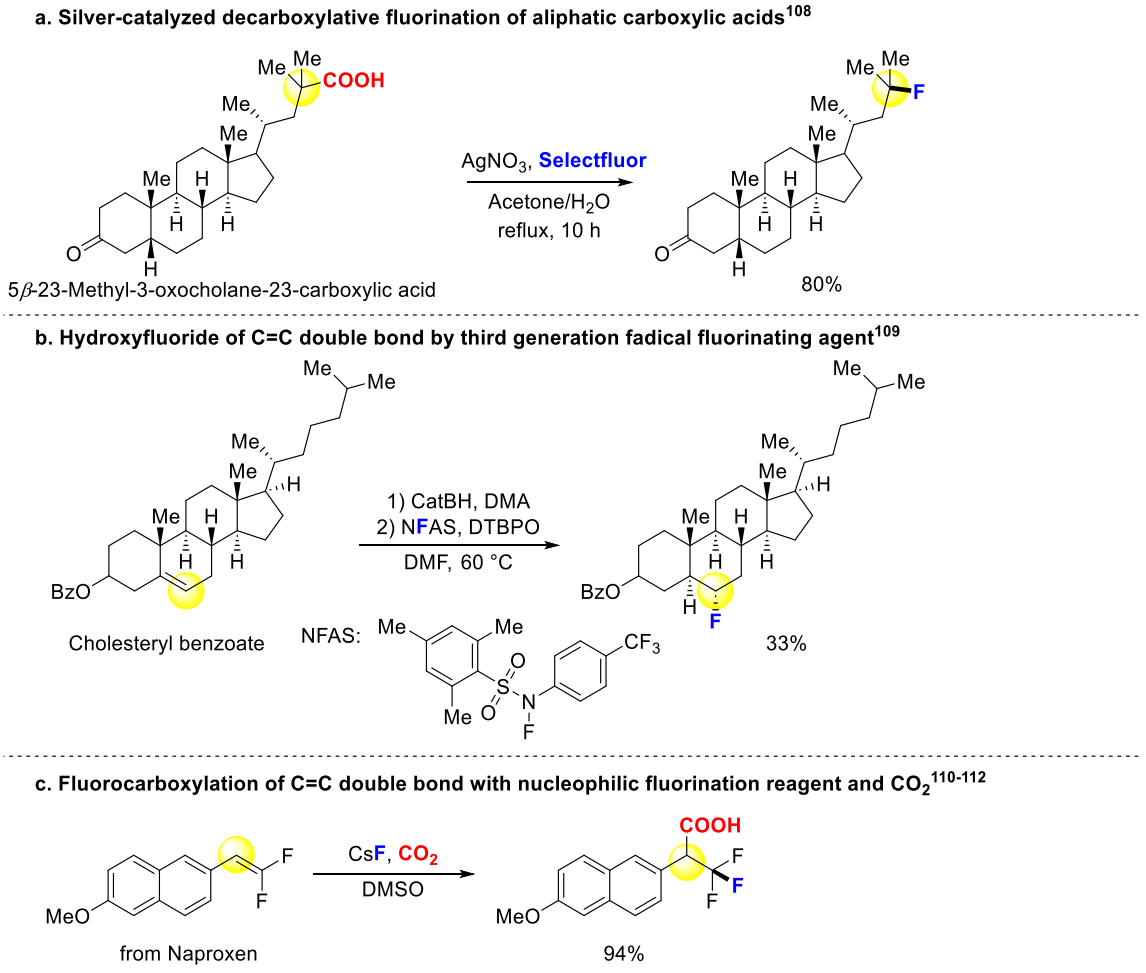
2.1.4. *Other conversions*

Besides the methods mentioned above, several other functional group transformations have been developed for late-stage fluorination of bioactive compounds. Decarboxylative fluorination has been well developed over past decades, and Li group used silver-catalyst and Selectfluor to decarboxylative fluorinate dehydrolithocholic acid derivatives (Scheme 7a)[108]. In 2018, Renaud and coworkers designed a new generation of radical fluorination agents called NFASs (Scheme 7b)[109], which have lower N−F bond dissociation energies and can be operated under milder conditions compared to the first (F_2) and second (NFSI and Selectfluor) generation agents. NFASs could hydroxyfluoride the carbon−carbon double bonds under 60 °C, and a derivative of steroids underwent well. Additionally, more reactions transfer different functional groups to fluorine through other mechanisms (Scheme 7c)[110–112]. These advancements signify a promising future for easier late-stage fluorination of bioactive compounds, as an increasing number of novel fluorinating methods continue to emerge.

Bioactive compounds labeled with ^{18}F could be used as tracers for non-invasive visualization and quantification of molecular interactions, receptor binding, metabolism, and other dynamic processes in living organisms. PET is a significate application of fluorination using ^{18}F tracers, and so many works have been reported over the past decades[113–117].

Despite the development of numerous late-stage fluorination strategies, several challenges in this field remain unresolved. One major challenge in nucleophilic fluorination is the weak nucleophilicity of fluorine anions in the presence of hydrogen bond donors, which are common pharmacophore features in bioactive molecules. Oppositely, unproductive side reactions might occur without hydrogen bond donors due to the fluorine's basicity. Electrophilic fluorination using reagents like NFSI and Select-F offers high reactivity but comes with drawbacks such as high cost and poor atom economy. Overcoming this obstacle through the development of new general transition-metal catalytic methods would greatly benefit late-stage fluorination strategies.

For medicinal chemistry, selective late-stage fluorination of bioactive molecules is essential for rational design of SAR and optimization of pharmacokinetics. However, achieving regioselectivity without directing groups presents a significant challenge that hinders these goals. The use of directing groups, on the other hand, restricts the substrate scope, posing an additional obstacle. While various fluorination methods through functional group conversion have been developed, they often require pre-functionalization and cannot accurately modify bioactive compounds. Consequently, there remains a lack of practical and widely applicable late-stage fluorination reactions for medicinal chemistry. Furthermore, the purification of C−H fluorinated products from starting materials continues to be problematic[45,118]. Addressing these challenges and advancing fluorination strategies would greatly benefit medicinal chemistry, enabling more practical and efficient late-stage modifications.



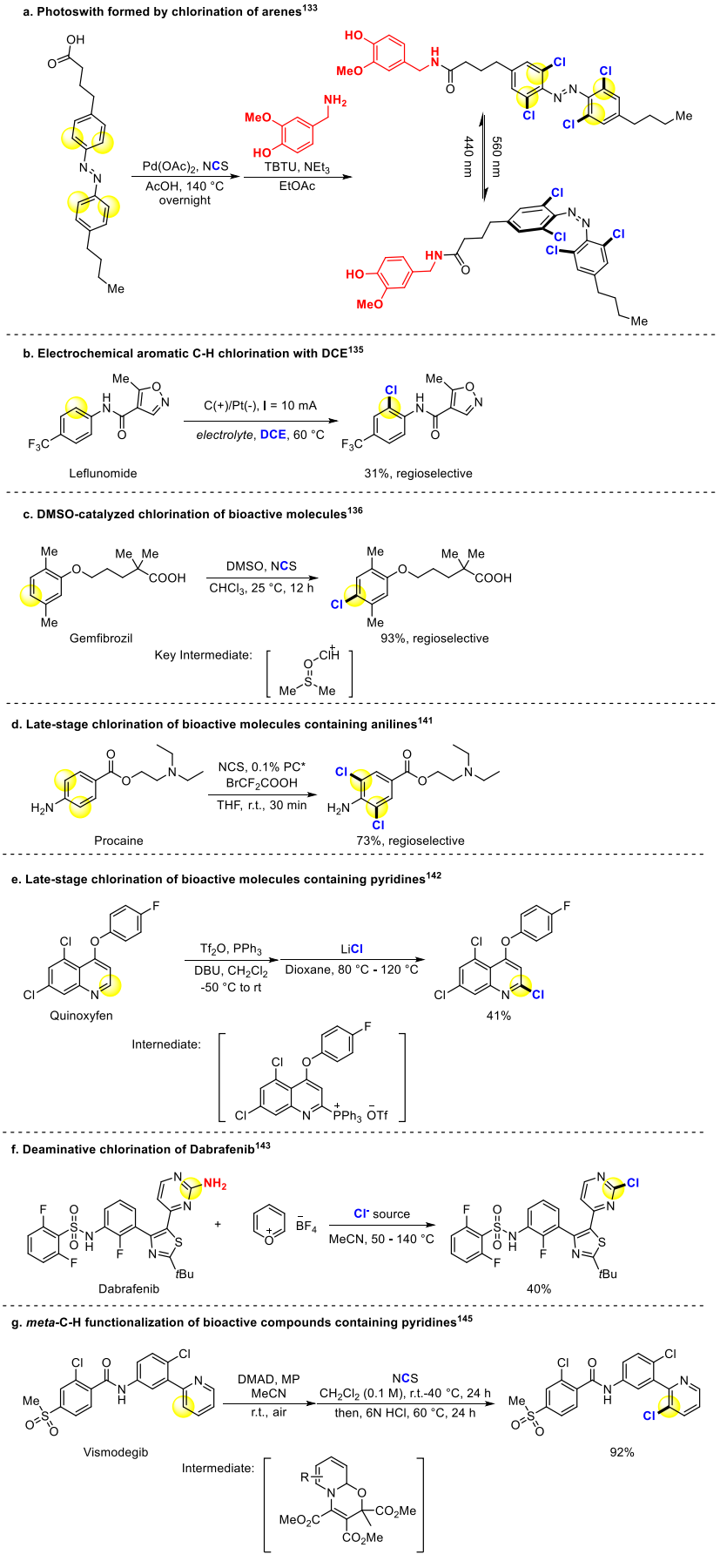
Scheme 7 Other fluorination strategies.

2.2. *Chlorination of bioactive compounds*

The introduction of chlorine atoms into bioactive compounds, as exemplified by Xarelto[119,120], Jardiance[121], and Vraylar[122], among the top 200 marketed small molecule drugs, can significantly alter their bioactivity spectrum and pharmacokinetic properties. The larger atomic radius of chlorine (atomic radius 0.79 Å) compared to hydrogen (atomic radius 0.53 Å) can result in different steric effects[49], potentially influencing the binding affinity of bioactive compounds. Furthermore, heavy halogens like chlorine, bromine, and iodine can form a unique region called the σ-hole in the positive outer region along the covalent bond[123]. This leads to the formation of halogen bonds[124], a non-covalent interaction, with nucleophilic groups such as oxygen, sp^3-hybridized nitrogen, aromatic rings, or sulfur[125–127]. These interactions can significantly improve binding affinity[128]. Additionally, the introduction of chlorine atoms can slightly increase molecular lipophilicity and membrane permeability (Table 1)[36,38,39,129,130], thus impacting the absorption and distribution of bioactive compounds. Moreover, chlorine incorporation serves as an effective method to block metabolic sites, similar to fluorine incorporation[131].

2.2.1. *Chlorination of arenes*

Chlorination strategies of arenes have been well developed and applied to late-stage modification of bioactive compounds for drug discovery. In 2014, Baran group invented a new chlorinating reagent called "Palau'chlor", which is practical and reactive with broad substrate scope and high regioselectivity. Clotrimazole could be selectively chlorinated with good yield[132]. In 2016, Trauner group used *N*-chlorosuccinimide (NCS) as the chlorine source, and $Pd(OAc)_2$ catalyzed *o*-dichlorination of azobenzene. Interestingly, the introduction of chlorine atoms prevents the switch of benzene rings, resulting in the formation of photoswitches (Scheme 8a)[133]. Regioselective chlorination of phenol derivatives was achieved in the presence of pyridine directing groups catalyzed by palladium, demonstrating the versatility of this methodology. Similar conditions were successfully applied to diflufenican and estrone derivatives[134]. In 2019, Jiao group developed an electrocatalytic strategy for arenes chlorination with 1,2-dichloroethane as a chlorine source, and bioactive compounds were chlorinated successfully (Scheme 8b)[135]. Next year, they reported DMSO-catalyzed chlorination of bioactive molecules using NCS, demonstrating the compatibility of this mild reaction condition with numerous natural products and drugs (Scheme 8c)[136]. Notably, the chlorination of gemfibrozil, a lipid-lowering drug, was shown to decrease its solubility in water[137], and potentially enhance its antiandrogen activity[138]. In 2021, they also developed alternative system in which DMSO was replaced by nitroxides appeared and expanded the substrate scope of the past work[139]. Taran also announced the selective chlorination of



Scheme 8 Chlorination of arenes.

iminosydnones for the fast release of pro-drugs under mild conditions[140].

Anilines are the common structure in pharmaceutical compounds, a general chlorinating method for different substituted anilines was revealed by Huang, Feng, Chen and coworkers using photo-organo co-catalysis with good selectivity (Scheme 8d)[141]. McNally and Paton reported that the C−H bond of aromatic bioactive compounds could be transferred to triaryl phosphorus group, and then converted to chlorine. This method enables the chlorination of pyridines and other drugs containing pyridine building blocks (Scheme 8e)[142]. Functional groups transformation was also applied in this field, Cornella group converted amino-heterocycles into heterocyclic chlorides (Scheme 8f)[143]. The anticancer drug Dabrafenib could become a proteolysis-targeting chimeras (PROTAC) binder after this transformation[144]. Recently, Studer and coworkers make a breakthrough in *meta*-functionalization of pyridines, quinolines, and isoquinolines. They proposed a mechanism that dearomatization of the substrates occurred after reacting with dimethyl acetylenedicarboxylate (DMAD) and methyl pyruvate (MP), followed by rearomatization and functionalization. Among the process, *meta*-halogenation of bioactive compounds could be completed with medium to good yields (Scheme 8g)[145].

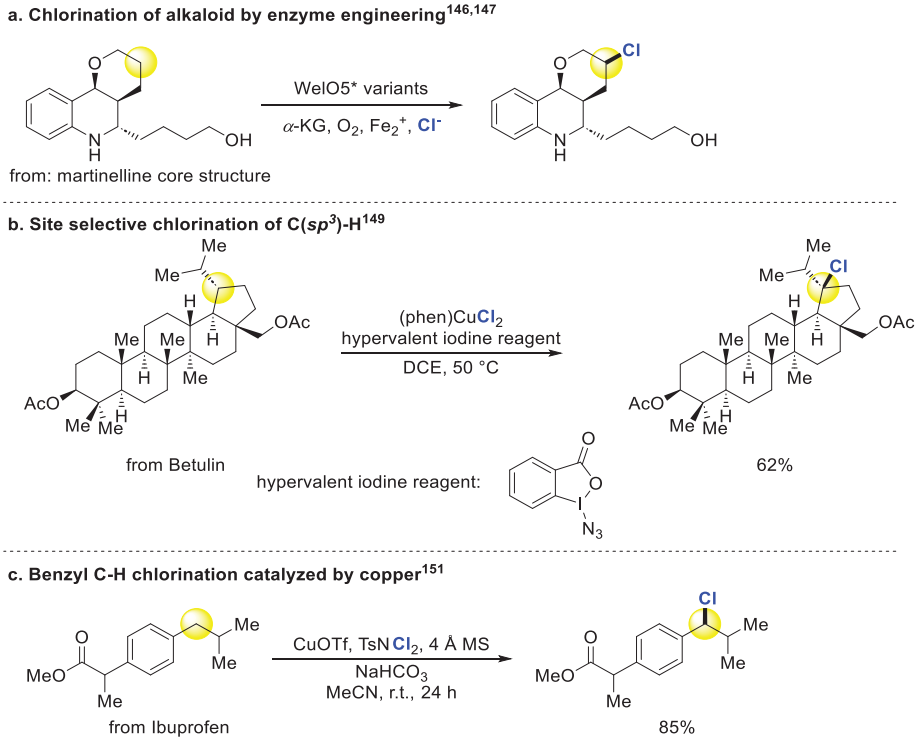
2.2.2. *C(sp^3)−H bond chlorination*

There have been some efficient works on the C(sp^3)−H chlorination in recent years. Enzyme engineering is a hot research topic for chlorination. Buller engineered a halogenase *WelO5** for chlorination of martinelline-derived fragment and soraphens selectively (Scheme 9a)[146,147]. Meanwhile, Hoebenreich engineered *Wi*-WelO15 to chlorinate a kind of alkaloid[148]. Selective chlorination of tertiary C(sp^3)−H bond was achieved using a combination of copper and hypervalent iodine reagents in mild condition. The different substrates with various types of groups could be tolerated in this system with good selectivity. And many bioactive compounds were suitably chlorinated in excellent yields (Scheme 9b)[149]. A method of photocatalytic C(sp^3)−H chlorination was put forward, and 5α-cholestane could bear the condition well[150]. A new copper catalytic strategy could be used to chlorinate benzyl, allylic and γ-carbonyl hydrogen, and several drugs and natural products were chlorinated in medium to excellent yields (Scheme 9c)[151].

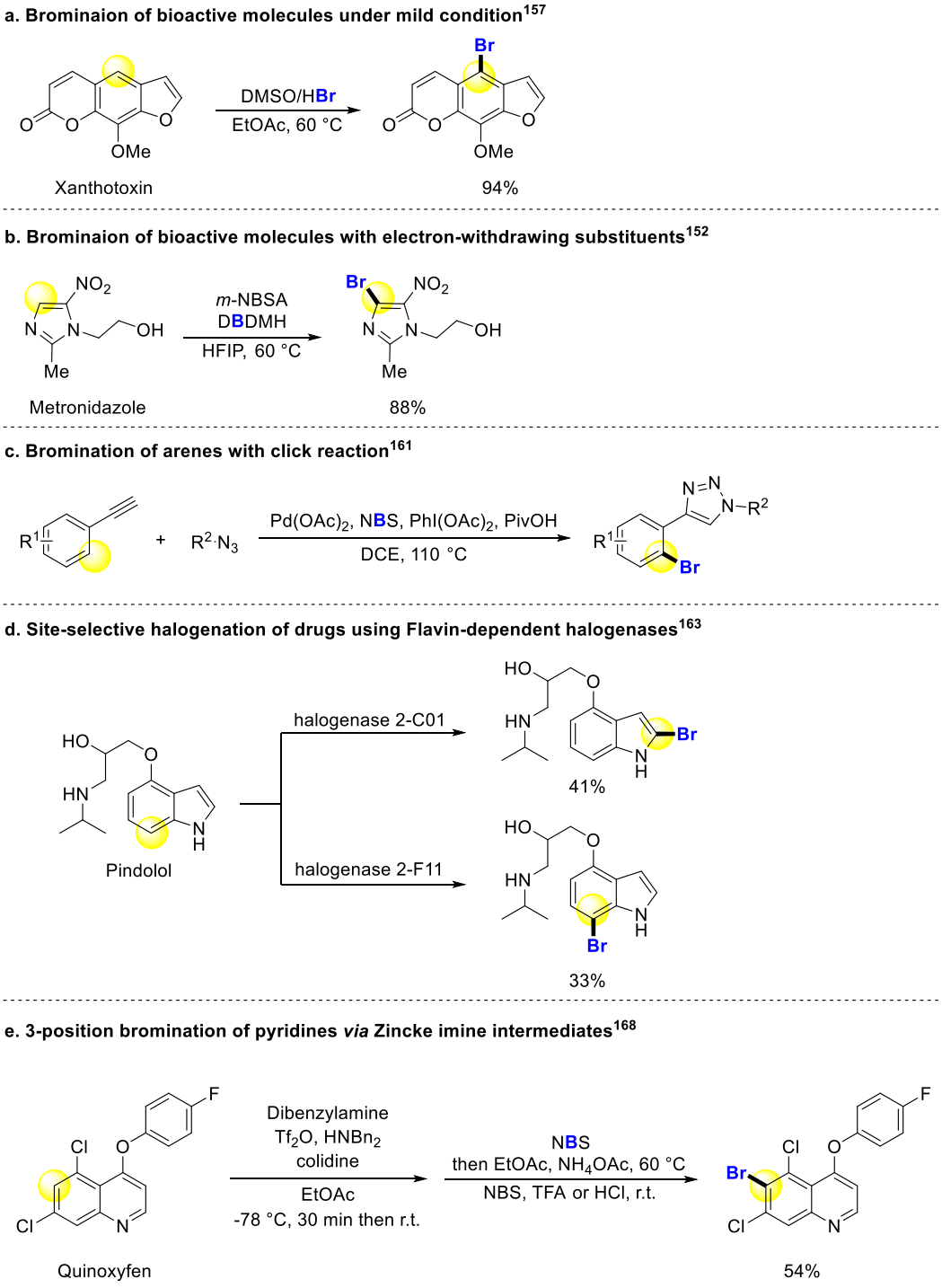
While the chlorination strategy has been well-established, the concept of late-stage modification in chlorination remains relatively unexplored. To the best of our knowledge, there are quite a few drugs containing chlorine atoms, and the positions and quantities of substituents are key determinants of their biological activity. Hence, it is imperative to develop selective chlorination methods that allow precise control over regioselectivity. Moreover, expanding the substrate scope of these strategies, particularly for chlorination of electron-deficient aromatic rings, remains an unsolved challenge[152−155]. This necessitates the exploration of new chlorination reactions that exhibit both regioselectivity and broad substrate compatibility, which can significantly contribute to the rapid advancement of medicinal chemistry and drug discovery.

2.3. *Bromination of bioactive compounds*

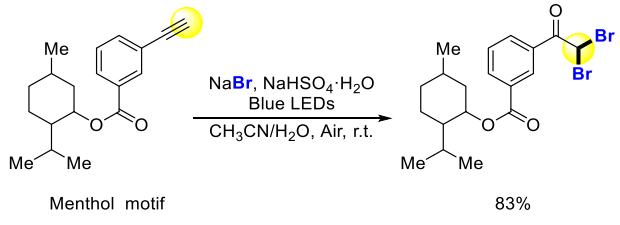
Opsumit[156], one of the top 200 small molecule drugs for pulmonary arterial hypertension, contains two bromine atoms in different aromatic rings. The introduction of bromine atoms may



Scheme 9 Chlorination of alkanes.



Scheme 10 Bromination of arenes.



Scheme 11 Other bromination reactions.

have a similar impact on bioactive compounds with the introduction of chlorine atoms to a certain extent. The larger radius of bromine atoms (0.94 Å)[49] contributes to enhanced hydrophobic effects and van der Waals interactions, potentially improving binding affinity in bioactive compounds. However, it may also introduce steric clash effects and reduce binding affinity. The strategies developed are usually suitable for chlorination, bromination, and even iodination, so we would just expound these works in a certain chapter without repetition.

2.3.1. *Bromination of arenes*

Bromination of bioactive molecules often accompanies chlorination due to the suitability of developed methods for both halogenations, and occasionally iodination. In 2015, Jiao group reported a general method for oxidative bromination and iodination of electron-rich arenes and heteroarenes, however, this strategy could not complete the bromination and iodination of electron-deficient aromatic rings. Even though, many drugs could be brominated under mild oxidation reagent DMSO and relatively low temperature (Scheme 10a)[157]. Lou group used this strategy to brominate Marchantin C, and obtained a series of analogs with anticancer activity 2−6 fold higher[158]. In 2022, Jiao and coworkers made a breakthrough in bromination of electron-deficient aromatic rings. They reported an efficient catalyst *m*-NBSA, and it could promote electrophilic halogenation of arenes with electron-withdrawing substituents. And the bromination of lots of bioactive molecules proceeded under this condition smoothly (Scheme 10b)[152]. Panda developed a DMSO promoting bromination of many arenes including bioactive compounds[159]. Furthermore, Koley brominated aminoquinolines including drug analogs without metal, oxidant or additive under a mild condition[160]. Correa created a bromination method with click reaction at *ortho*-position of phenylacetylene, potentially applicable in biological studies (Scheme 10c)[161].

Electrochemistry was also used for the bromination of drug molecules by Liu, Rivera and coworkers in 2017[162]. Lewis pioneered the directed evolution of flavin-dependent halogenases, providing a powerful tool for late-stage bromination of bioactive compounds. And different halogenases could be applied to brominate bioactive compounds selectively (Scheme 10d)[163]. Chen reported a tungstate-catalyzed biomimetic oxidative halogenation of arenes, enabling the bromination of select bioactive molecules[164]. Porphyrins and their analogs are significant for organisms in different parts. Shinokubo selectively realized the bromination of porphyrins and analogs on different aromatic rings[165]. Thibaudeau revealed a strategy for the bromination of aniline building blocks[166]. In 2021, Sharma group developed a selective para-bromination method for the N-substituted site of the aromatic ring, which has been successfully applied in drug modification[167]. Lately, McNally group developed an excellent strategy for halogenation of the 3-position of pyridines using a ring-opening and ring-closing process *via* an NTf-Zincke imine intermediate. Many bioactive molecules can undergo late-stage modifications through this reaction (Scheme 10e)[168].

2.3.2. *Other bromination*

There are a few strategies developed for alkyl bromination, offering opportunities to modify bioactive compounds. In 2019, Jiang group reported that visible-light-promoted oxidative halogenation of alkynes could get dibrominated alkanes. This method could provide several late-stage dibrominated drug derivatives (Scheme 11)[169].

The bromination methods used for bioactive compounds modification faced similar problems with chlorination, including regioselectivity and substrate scope. While bromine is a superior halogen bond donor compared to chlorine, its introduction can affect the effectiveness of ligands. Nevertheless, a significant drawback of introducing bromine atoms is the reduction in solubility for molecules (Table 1), which may prevent bioactive compounds from becoming drug candidates.

3. Oxygenation of bioactive compounds

The introduction of oxygen functionality into bioactive compounds can lead to various changes in their properties. For physicochemical properties, incorporation of different groups containing oxygen atoms generally decreases the compound's log*P* and improves its solubility, except for the carbonyl group (Table 2). Moreover, the binding affinity between the compound and its target may increase due to the formation of new interactions, such as hydrogen bonds and salt bridges. In some drugs, the removal of oxygen-containing groups may lead to the loss of their biological activities[170−172]. Furthermore, introduction of oxygen atoms may alter the pharmacokinetic properties of bioactive compounds, for example, introduction of a hydroxyl group may accelerate the metabolic rate of the drug[173].

Indeed, oxygenation reactions have been extensively developed, encompassing various transformations such as C−H bond oxygenation[176−178], oxygen insertion[179], conversion of functional groups to hydroxyls[180−185], hydroperoxidation[186−188] and oxygenation through C−C/C=C bond cleavage[189−191], some of which are applied to late-stage modification of bioactive molecules.

3.1. *Hydroxylation of bioactive compounds*

Hydroxyl groups frequently appear in marketed drugs, and they play crucial roles in the pharmacodynamic and pharmacokinetic properties of drugs[192]. These groups not only contribute to the formation of hydrogen bonds, which can increase the biological activity of drugs[193,194], but they can also enhance the metabolism of bioactive compounds by serving as prodrugs[195,196]. Moreover,

Table 2 Selected properties of substrate and product in oxygenation.

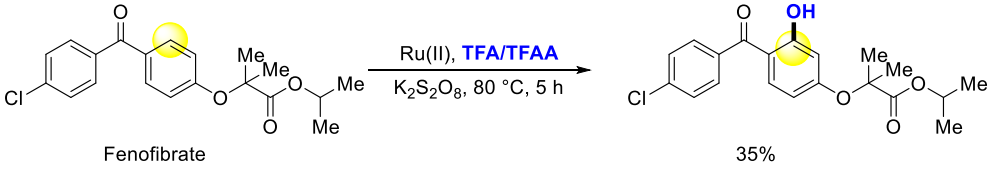
Substrate	Product	Substrate/Product	
		Log*P*[a]	S_w (mg/L)[a]
		2.13/1.64	1789/76,500
		2.52/1.02	517/38,000
		2.52/5	517/410
		2.52/1.45[c]	517/19,000[b]
		2.95/1.59	300/2000[b]
		4.69[c]/2.49[c]	2.9[b]/810[b]

[a]Data from references[38,39,174,175]; log*P*: octan-1-ol/H_2O partition coefficient; S_w: aqueous solubility at 25 °C, mg/L.

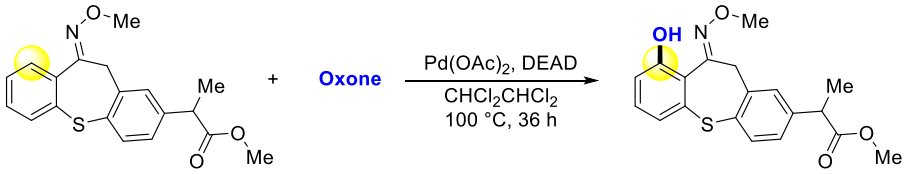
[b]Predicted S_w at pH 7, 25 °C by Scifinder (https://origin-scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf).

[c]Predicted log*P* at 25 °C by Scifinder (https://origin-scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf).

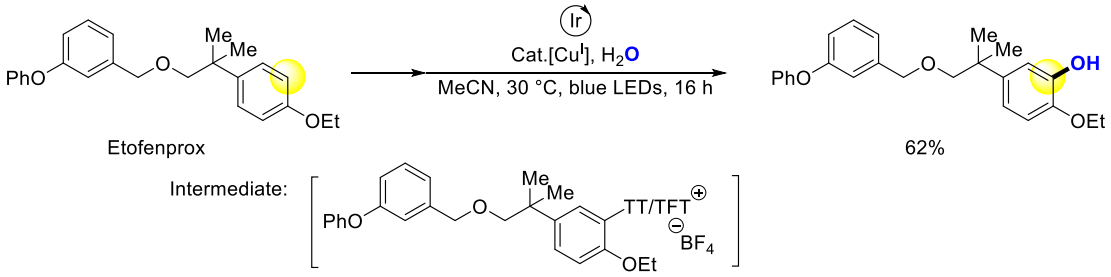
a. Late-stage hydroxylation of Fenofibrate catalyzed by Ru(II)[200]



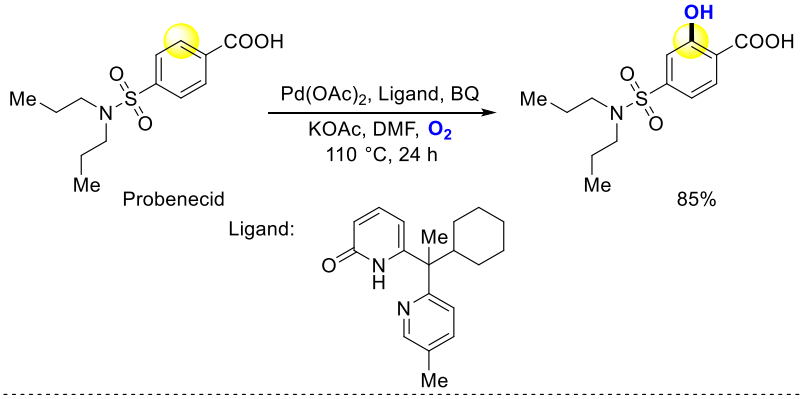
b. Late-stage hydroxylation of Zaltoprofen directed by oxime ether[202]



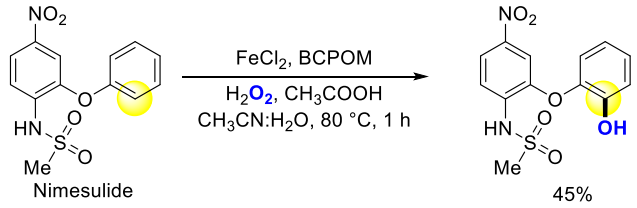
c. Selective hydroxylation of arenes *via* photoreox catalysis[204]



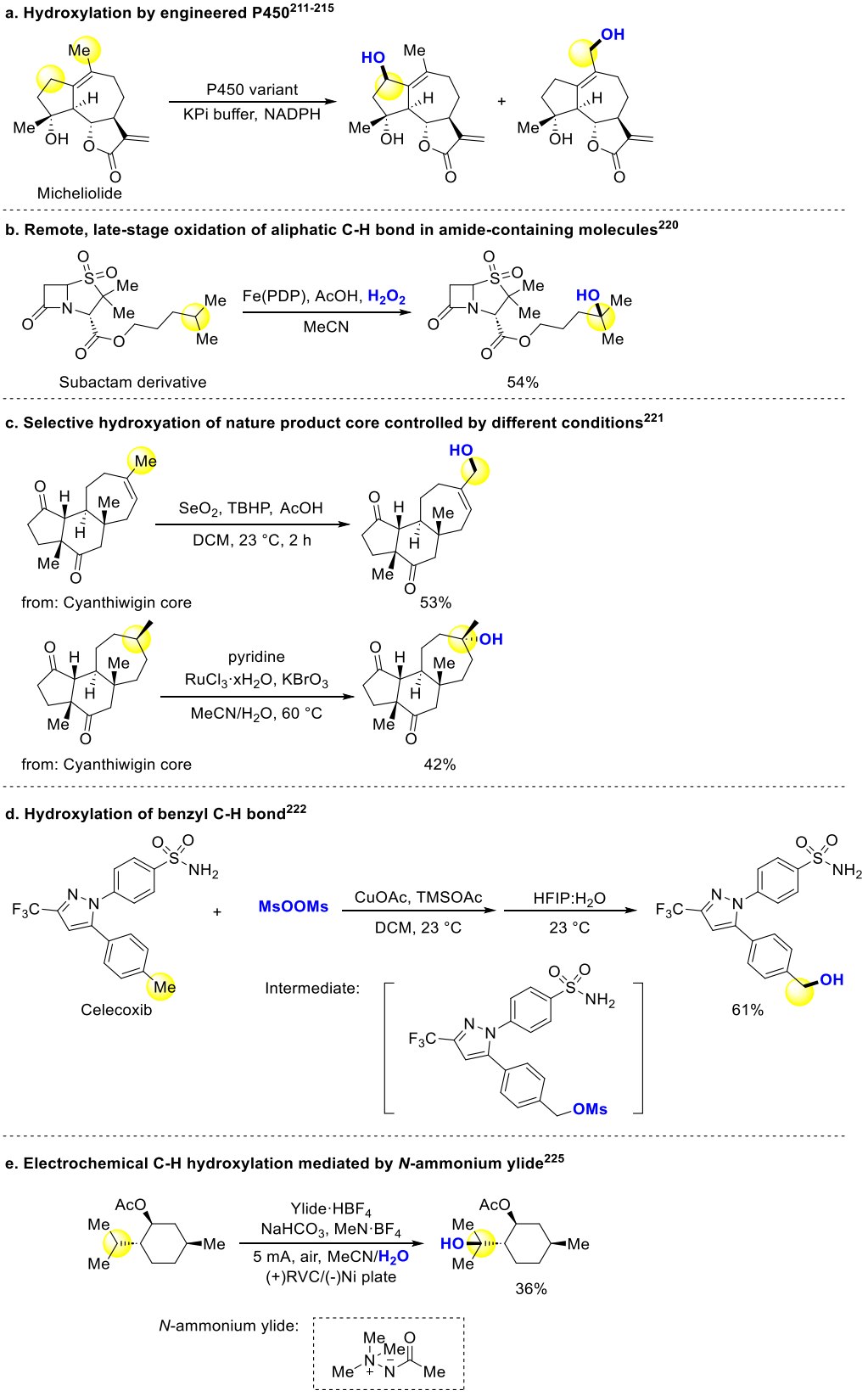
d. Ligand enabled hydroxylation of drugs with O_2[206]



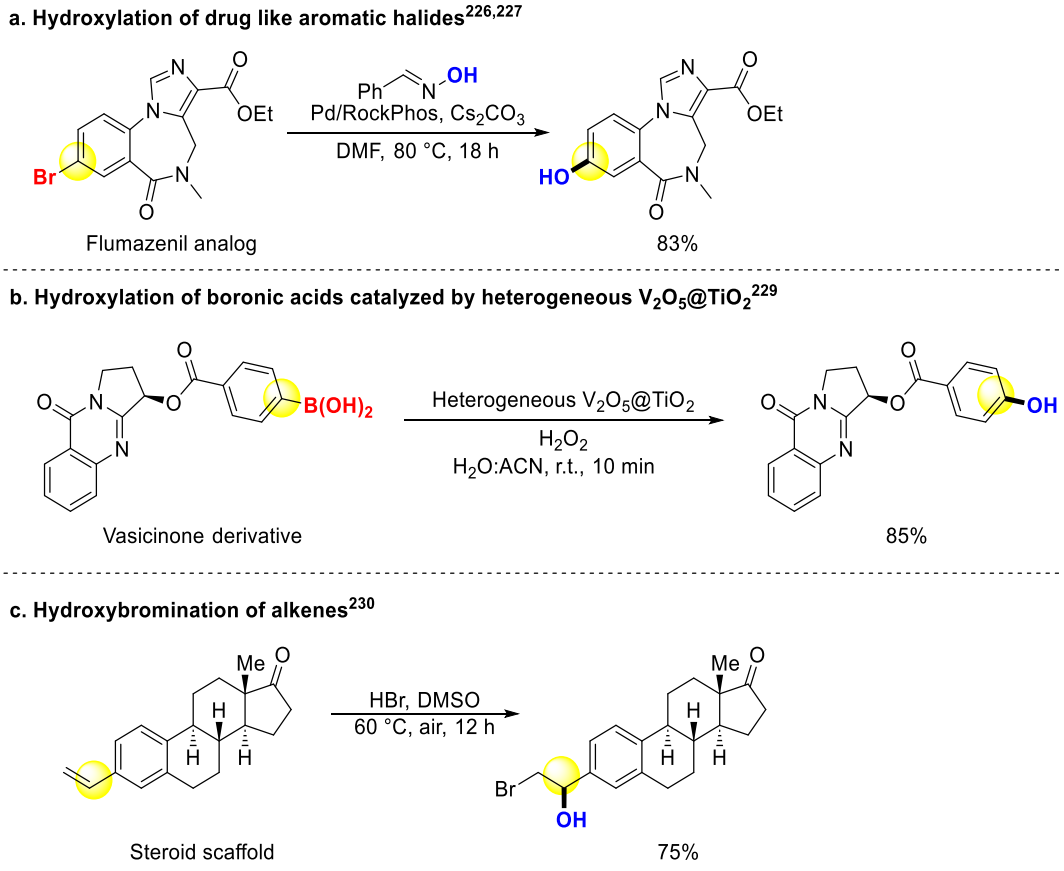
e. Hydroxylation of arenes catalyzed by iron[207]



Scheme 12 Hydroxylation of arenes.



Scheme 13 Hydroxylation of alkanes.



Scheme 14 Other hydroxylation reactions.

hydroxyl groups can also be a synthetic handle for the rapid synthesis of new analogs[197], as well as a link position for PROTAC, among others.

3.1.1. *C−H bond hydroxylation of arenes*

Phenols are significant building blocks in drugs, and introducing hydroxyl in bioactive molecules is a convenient way to seek a molecule with better activity[176]. As the well-sold drug Advair[198], which treats asthma, contains phenolic hydroxyl groups.

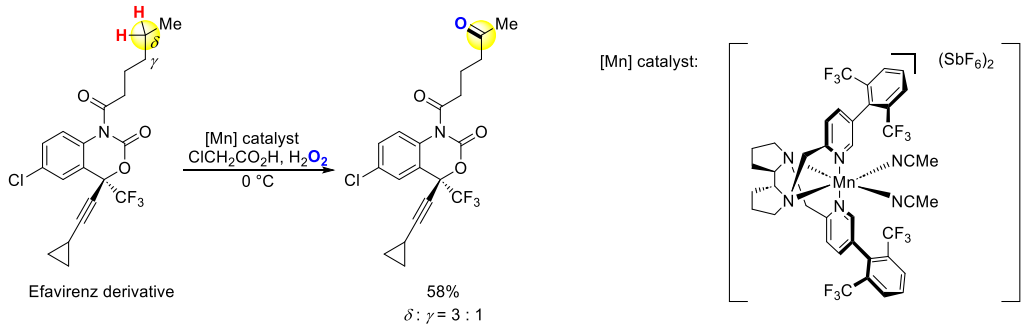
In 2012, Rao and coworkers announced that Pd-catalyzed carbonyl directed *o*-hydroxylation of arenes, demonstrating good selectivity and moderate yields in the hydroxylation of Ibuprofen ethyl ester[199]. They later replaced the Pd catalyst with Ru or Rh catalysts in a similar system, successfully hydroxylating Fenofibrate under this condition (Scheme 12a)[200]. Siegel developed a metal-free C−H bond oxidation strategy for the preparation of tocopherol and its derivatives, as well as late-stage functionalization of natural product clovanemagnolol precursor[201]. Moreover, Jiao group reported oxime ether directed C−H bond hydroxylation of arenes, and a nonsteroidal anti-inflammatory drug Zaltoprofen could be modified under this condition (Scheme 12b)[202]. Ritter group reported a mild method whereby bioactive compounds could be converted to corresponding phenols *via* methanesulfonate intermediates[203]. Ritter and coworkers revealed another strategy for hydroxylation of arenes through aryl sulfonium salts intermediates, and the substrates were hydroxylated at electron-rich positions. Many drugs could be late-stage hydroxylated well in mild condition (Scheme 12c)[204]. Through the same aryl sulfonium salts intermediates, Patureau uses UV-light and TEMPO to hydroxylate arenes[205].

In addition, Yu and coworkers developed a palladium-catalyzed hydroxylation method with molecular oxygen as an oxygen source. This method enabled the smooth modification of drugs and peptides with excellent site-selectivity (Scheme 12d)[206]. Han group reported an arene C−H hydroxylation method using an iron catalyst. This transformation from arenes to phenols exhibited remarkable selectivity even in the absence of directing groups (Scheme 12e)[207]. Recently, Correa revealed a Ru-catalyzed method by which many Tyr-containing peptides could be hydroxylated[208]. This innovative approach provides a means to introduce hydroxyl groups selectively into peptide structures.

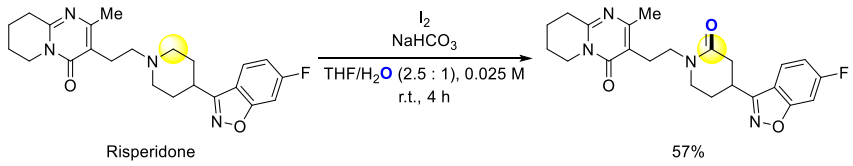
3.1.2. *C(sp^3)−H bond hydroxylation*

There were a number of strategies for late-stage C(sp^3)−H hydroxylation of molecules. In 2009, Sherman group engineered P450 mono-oxygenase with an amino-sugar-derived anchoring group to achieve the hydroxylation of many complex molecules[209]. In 2012, Fasan and coworkers achieved the selective hydroxylation of artemisinin *via* modified P450 catalysis[210]. These P450 engineering techniques have been applied to develop methods for the late-stage hydroxylation of bioactive compounds (Scheme 13a)[211−215]. Furthermore, Lei developed a site-selective and metal-free aliphatic C−H hydroxylation method of cholesterol in total synthesis[216]. In 2007, White group reported an iron-catalysis method for hydroxylation of aliphatic C−H bond in which bioactive molecules could be

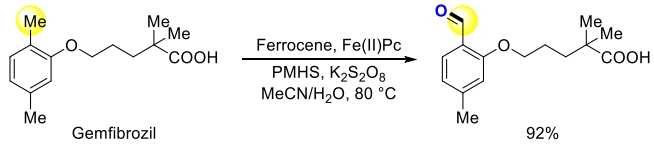
a. Regioselective oxygenation of methylenes catalyzed by Mn[237]



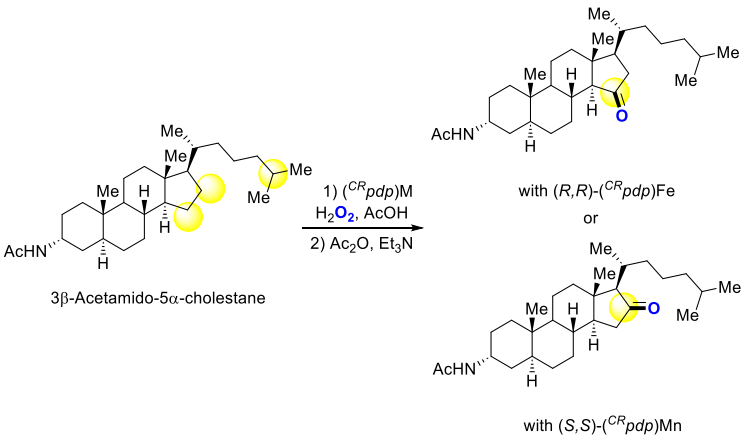
b. Metal-free oxidation of methylenes mediated by iodine[241]



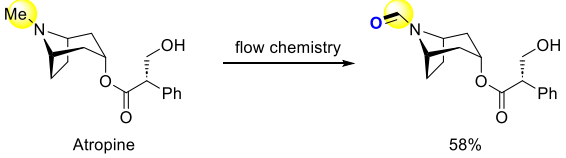
c. Selective oxidation of methyls to aldehydes[244]



d. Predictable selectivity in remote C-H oxidation of steroids[246]



e. Selective organophotocatalytic oxidation of *N*-Me utilizing flow chemistry[247]



Scheme 15 C(sp^3)−H bonds oxidation of bioactive compounds.

hydroxylated[217,218]. They also developed a series of oxidative diversification methods for amino acids and peptides catalyzed by iron, including hydroxylation[219]. In 2019, they achieved chemoselective tertiary C−H hydroxylation using Mn(PDP)/chloroacetic acid catalyst for late-stage functionalization (Scheme 13b)[220]. Stoltz disclosed functionalization of natural product core cyanthiwigin, with hydroxylation occurring at positions C12 and C15 under different conditions respectively (Scheme 13c)[221]. Ritter group reported a selective benzyl hydroxylation method similar to their previous work for arenes, tolerating different groups and complex molecules (Scheme 13d)[222]. Notably, hydroxylation of celecoxib led to the formation of its metabolite with lower activity[223,224]. Baran revealed an electrochemical C−H oxidation strategy, the selectivity of this method could be controlled by using different condition. And hydroxylation of some bioactive compounds could bear this condition (Scheme 13e)[225].

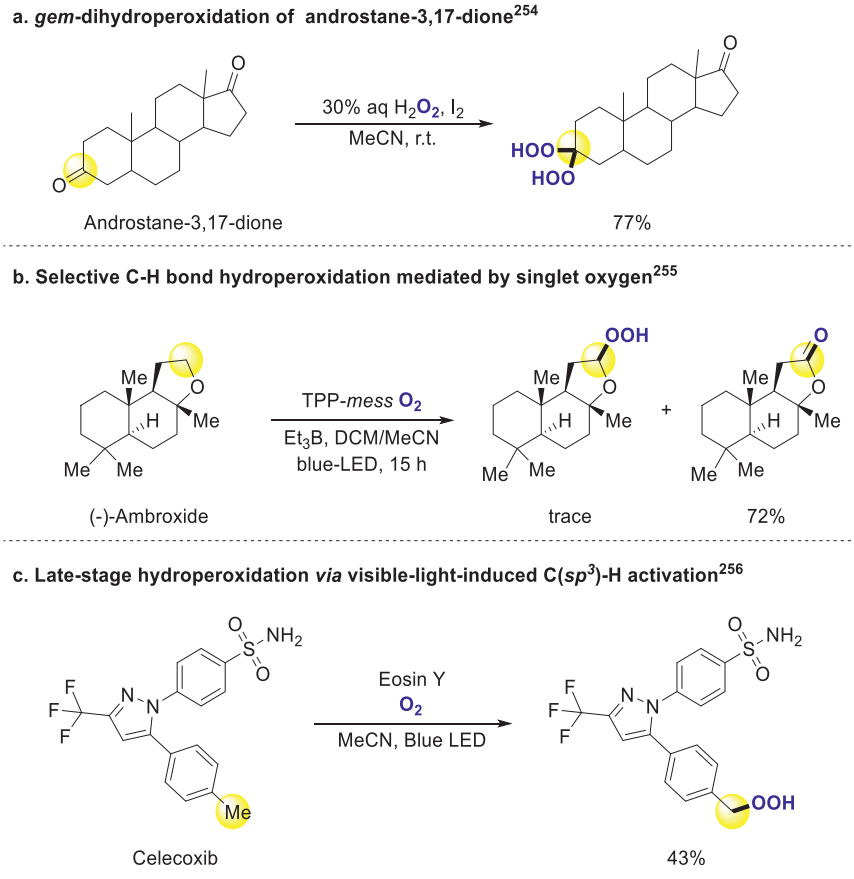
3.1.3. *Other hydroxylation reactions*

There were some late-stage hydroxylation strategies of bioactive compounds through functional group transformation. Maloney, Fier and coworkers reported two approaches that converted aromatic halides to phenols under mild condition (Scheme 14a)[226,227]. Shi group transferred aryl borides to phenols with trichloroacetonitrile as an activator under blue LED, and steride derivatives underwent this condition[228]. Another work of converting aryl borides to phenols was reported by Maurya, and many bioactive molecules could be late-stage hydroxylated (Scheme 14b)[229]. Jiao and coworkers used DMSO as an oxygen source to transfer simple organobromides or olefins to bromohydrins, and the hydroxybromination of (+)-δ-tocopherol derivative underwent to produce the corresponding product (Scheme 14c)[230]. They also reported another DMSO involving a unique transformation introducing hydroxyl into cyclohexanones with aromatization. A cholesterol analog was smoothly converted to the corresponding catechol[231].

The precise introduction of hydroxyl groups into bioactive compounds remains a formidable challenge due to the structural similarity between methylene C−H and methyl C−H[232]. However, the position of hydroxyl groups is critical for investigating the SAR and druggability of bioactive compounds in medicinal chemistry and drug discovery. Therefore, the accurate prediction of hydroxylation sites in bioactive molecules holds significant significance. The achievement of selectivity in late-stage hydroxylation reactions would mark a breakthrough, especially in the context of bioactive compounds containing aryl rings or aliphatic chains.

3.2. *Carbonylation of bioactive compounds*

Aldehyde groups are well-known structural alerts in pharmaceutical science due to their high reactivity and rapid metabolism. However, it is noteworthy that certain marketed drugs, including Streptomycin and Spiramycin[233,234], contain aldehyde groups,

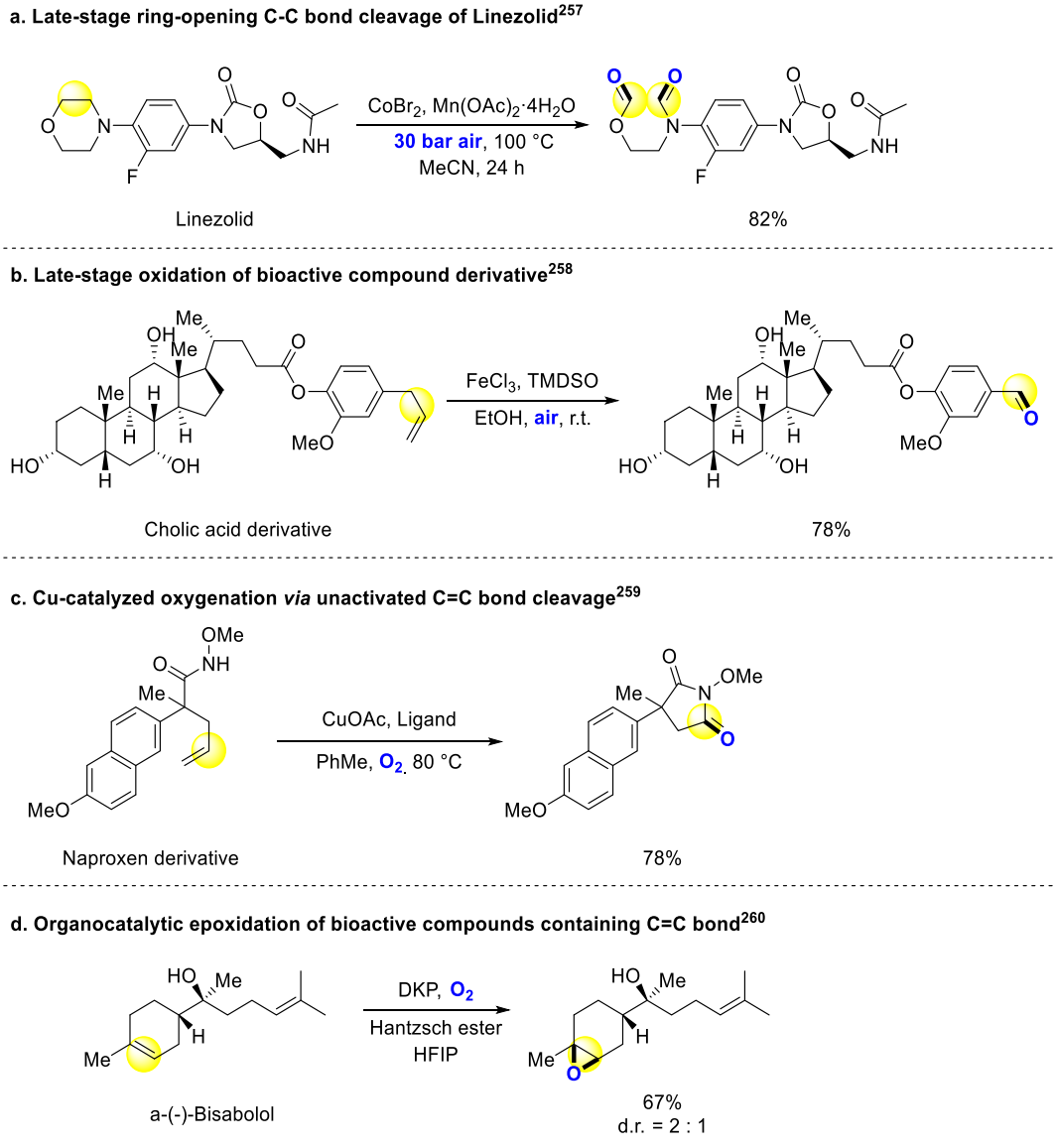


Scheme 16 Peroxidation of bioactive compounds.

suggesting that their presence can be safely designed into bioactive compounds[235]. Other carbonyl groups, such as ketones, esters, and amides, predominantly appear as linkers or skeletons within bioactive molecules.

3.2.1. $C(sp^3)-H$ bond oxygenation

$C(sp^3)-H$ bond oxygenation is another way to introduce oxygen element into bioactive compounds. Although achieving selective C−H bond oxidation remains a challenge, significant progress has been made in recent years. In 2013, White group developed an electrophilic, bulky catalyst Fe(*S,S*)-PDP, and used it to promote oxidation of methylenes selectively[236]. Then, they revealed another oxidation method for methylenes catalyzed by manganese which is coordinated by similar ligands previously used with moderate to good chemo-selectivity (Scheme 15a)[237]. Bryliakov and colleagues applied this catalyst in the C−H oxidation of (−)-ambroxide[238]. Recently, Li group utilized this type of manganese catalyst to complete highly selective benzyl oxidation with a wide substrate scope[239]. In 2016, Maes developed an aerobic oxidation method using iron or copper catalysts for the oxidation of (aryl) (heteroaryl)methanes, and the natural product Papaverine could be modified to corresponding ketone under this condition[240]. Talbot and Burley developed a metal-free method that used iodine as oxidant agent to transfer methylenes near nitrogen atoms to carbonyl groups, and several industrially relevant drug scaffolds could be selectively oxidized (Scheme 15b)[241]. Zhao reported an oxidation reaction of tertiary amines at two positions with PIDA/I_2 system, and Obscurine worked well under this condition[242]. In 2019, a graphitic carbon nitride based heterogeneous photocatalyst was used to facilitate methylenes oxidizing, and Corydaline, Indoprofen, and Indobufen could be generated using this method[243]. In the same year, Han and coworkers developed a significant protocol, in which the toluene motif could be selectively converted to benzaldehyde, and many bioactive compounds containing toluene structure were oxidized to corresponding oxygenation products smoothly (Scheme 15c)[244]. Then in 2020, Chand and coworkers revealed another strategy to selectively oxidize $C(sp^3)-H$ bonds to carbonyls by molybdenum



Scheme 17 Oxygenation through carbon−carbon/carbon = carbon bonds cleavage.

catalysis[245]. Costas, Stefano, Olivo and coworkers developed a strategy for predicting reaction sites and late-stage oxidizing bioactive molecules (Scheme 15d)[246]. Barham applied flow chemistry to accomplish the oxidation of N−CH_3 commonly found in various bioactive compounds, expanding the synthetic possibilities for these molecules (Scheme 15e)[247]. Similar to hydroxylation, there is still a lack of universal regioselective strategies for conversion of C(sp^3)−H to carbonyl groups.

3.3. *Peroxidation of bioactive compounds*

Peroxidation represents an alternative approach for incorporating oxygen elements into small molecules. While its utilization in the modification of bioactive compounds remains limited, it bears significance in certain cases. Notably, Artemisinin, a renowned drug employed in malaria treatment, features a peroxide group as its key pharmacophore. The breakdown of the peroxide bridge and the production of hydroperoxides may be one of the explanations for its antimalarial activity[248−250]. Meanwhile, many works have been focused on the development of antimalarial drugs containing peroxide groups[251−253].

In 2006, Iskra group converted ketones to *gem*-dihydroperoxides under catalysis of iodine, and androstane-3,17-dione could be transferred to corresponding product with good yield (Scheme 16a)[254]. Su and coworkers revealed a singlet oxygen-mediated strategy for selective C(sp^3)−H hydroperoxidation (Scheme 16b)[255]. In 2020, Xing and coworkers employed photocatalysis for the hydroperoxidation of benzylic C(sp^3)−H bonds. This method was applied to the late-stage modification of celecoxib, an anti-inflammatory drug, resulting in the desired product (Scheme 16c)[256].

The significance of the peroxide group in antimalarial drugs has been well-established, and its application will continue to expand to other diseases with the development of synthetic chemistry and pharmaceutical science. However, the construction of peroxide bridges in late-stage modifications remains a challenge for chemists.

3.4. *Oxygenation with C−C/C=C bond cleavage*

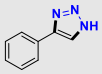
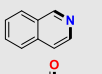
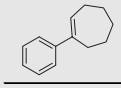
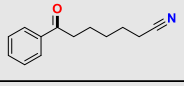
Carbon−carbon bonds cleavage is a suitable procedure to introduce oxygen atoms. Beller and coworkers realized a manganese and cobalt co-catalyzed the C(sp^3)−C(sp^3) bond oxygenation under high pressure. Linezolid, a kind of prescription antibiotic, was successfully converted into open-ring oxidative product (Scheme 17a)[257]. Han group presented an iron-catalyzed oxidative C−C bond cleavage strategy for converting allylarenes to aryl aldehydes. This method enabled the smooth modification of various bioactive compounds containing the corresponding structures (Scheme 17b)[258]. Jiao group broke C=C double bonds to introduce oxygen into small molecules to form cyclic imides. This method could be applied to synthesize succinimide-containing medicines and drug analogs (Scheme 17c)[259]. In 2021, Zografos revealed a work about epoxidation of alkenes by introducing molecular oxygen. And a number of bioactive molecules could be late-stage modified to epoxides with medium to excellent yields (Scheme 17d)[260].

An aliphatic ring containing one or two oxygen atoms is common in marketed drugs, such as Lexapro[261] and Cialis[262,263]. Changing the carbon atom to oxygen atom selectively in late-stage will be more convenient than *de novo* synthesis using the substrate containing the moiety. While there have been remarkable advancements in oxygenation methods involving C−C/C=C bond cleavage, certain deficiencies still exist, especially regarding regioselective C−C/C=C bond cleavage in complex bioactive molecules. In this context, skeleton editing has emerged as a valuable approach for C−C/C=C bond cleavage and is expected to become a practical tool in this field.

4. Nitrogenation of bioactive compounds

Of the versatile role of nitrogen elements among drugs, 182 drugs contain at least one nitrogen atom among the top 200 small molecule drugs by retail sales in 2021[264]. Nitrogen can appear in various forms, including primary amines, amides, *N*-heterocycles, and so on, which are common pharmacophore groups in bioactive compounds. Late-stage nitrogenation offers a means to modify the structure and physicochemical properties of bioactive compounds, which in turn can have a substantial impact on their pharmacodynamics and pharmacokinetics. For example, the introduction of amino groups into the benzene ring reduces log*P* and improves water solubility, while construction triazole in phenylacetylene does the opposite (Table 3). These structural and physicochemical changes are of great importance in medicinal derivatization. Leonori and coworkers applied their late-stage C−H amination method in microscale parallel reactor, and efficiently enriched derivative library of natural products and peptides[265]. Inspired by adequate combination of virtual screening and large-scale convergent synthesis[266], it can be speculated that tighter collaboration between chemists and pharmacists will stimulate the potential of late-stage modification into hit/lead exploration. Late-stage nitrogenation serves not only in the investigation of SAR and structural modification but also in optimizing druggability, as well as the development of novel molecular probes/antibody conjugated drugs (ADC)/drug-delivery conjugates/PROTACs. Some potential applications for *in situ* proteome profiling have been proposed before[267]. Hence, installing such nitrogen-bearing functional moieties to bioactive compounds in a minimally

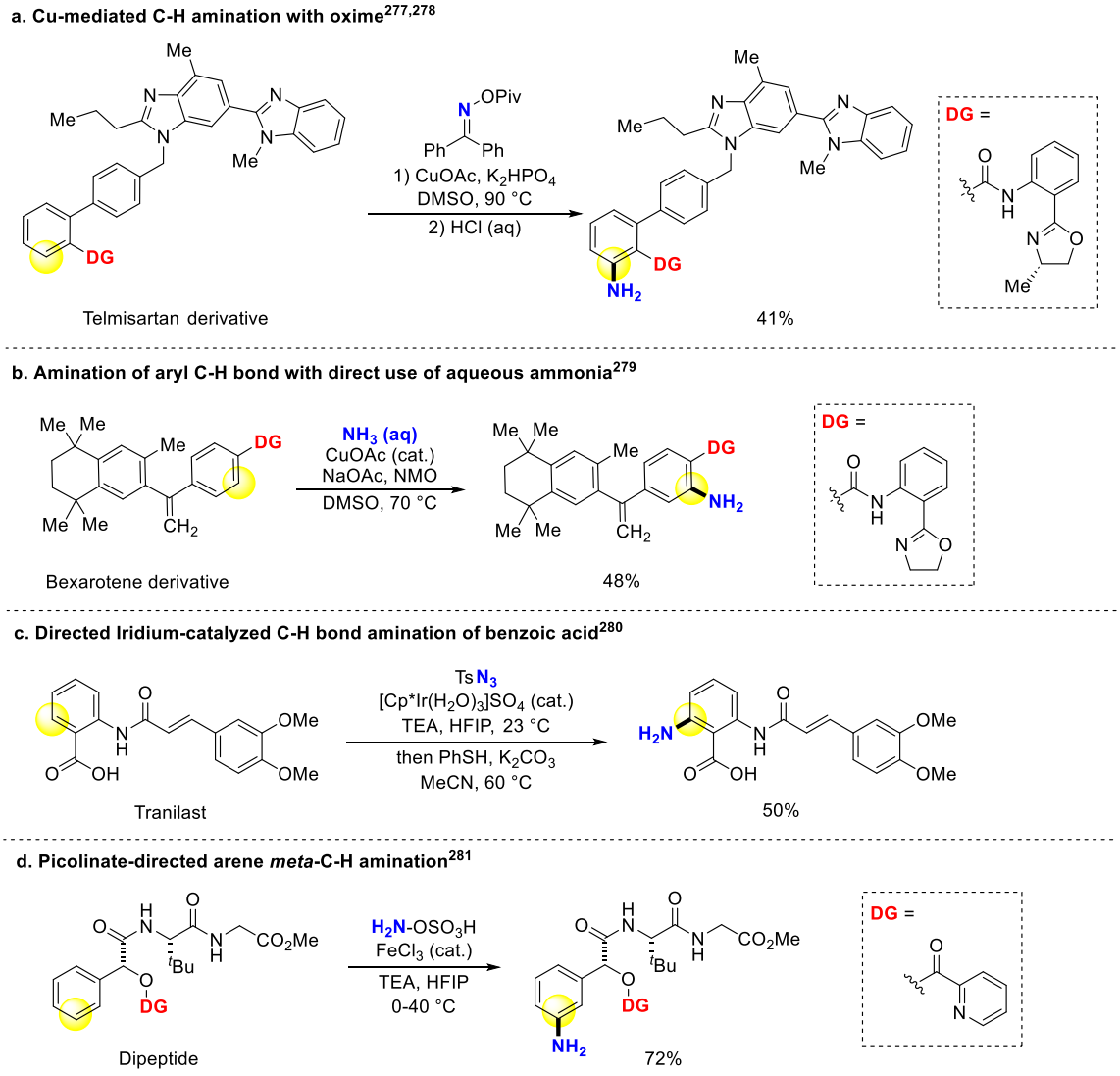
Table 3 Selected properties of substrate and product in nitrogenation.

Substrate	Product	Substrate/Product	
		Log*P*[a]	S_w (mg/L)[a]
		2.13/0.90	1789/34,100
		1.58/1.00	5500/4900[b]
		2.70[c]/2.90[c]	430[b]/200[b]
		3.04[c]/2.08	280[b]/8100[b]
		4.85[c]/2.16[c]	1.6[b]/180[b]

[a]Data from references[36,268−273]; log*P*: octan-1-ol/H_2O partition coefficient; S_w: aqueous solubility at 25 °C, mg/L.

[b]Predicted S_w at pH 7, 25 °C by Scifinder (https://origin-scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf).

[c]Predicted log*P* at 25 °C by Scifinder (https://origin-scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf).



Scheme 18 Transition-metal-catalyzed arenes C−H bond activation.

impacted way is of great importance. Considering the numerous synthetic approaches in these filed, the latest advances focusing on late-stage nitrogenation of bioactive compounds, related skeleton-editing methodologies and specific *N*,*O*-difunctionalization approaches are discussed below.

4.1. Primary amination of bioactive compounds

Despite the common increase of hydrogen bond donors, introduction of primary amines brings about different properties changes counting on substrate types[274]. Compared with parent arenes, primary amination will augment electronic density of conjugated ligands, and enhance their $\pi-\pi$/cation$-\pi$ interaction with electron-deficient target pockets[275]. As for alkyl substrates, primary amination provides a potential positive electronic center[276], which will benefit receptor-ligand electrostatic interactions as well as compound dissolution.

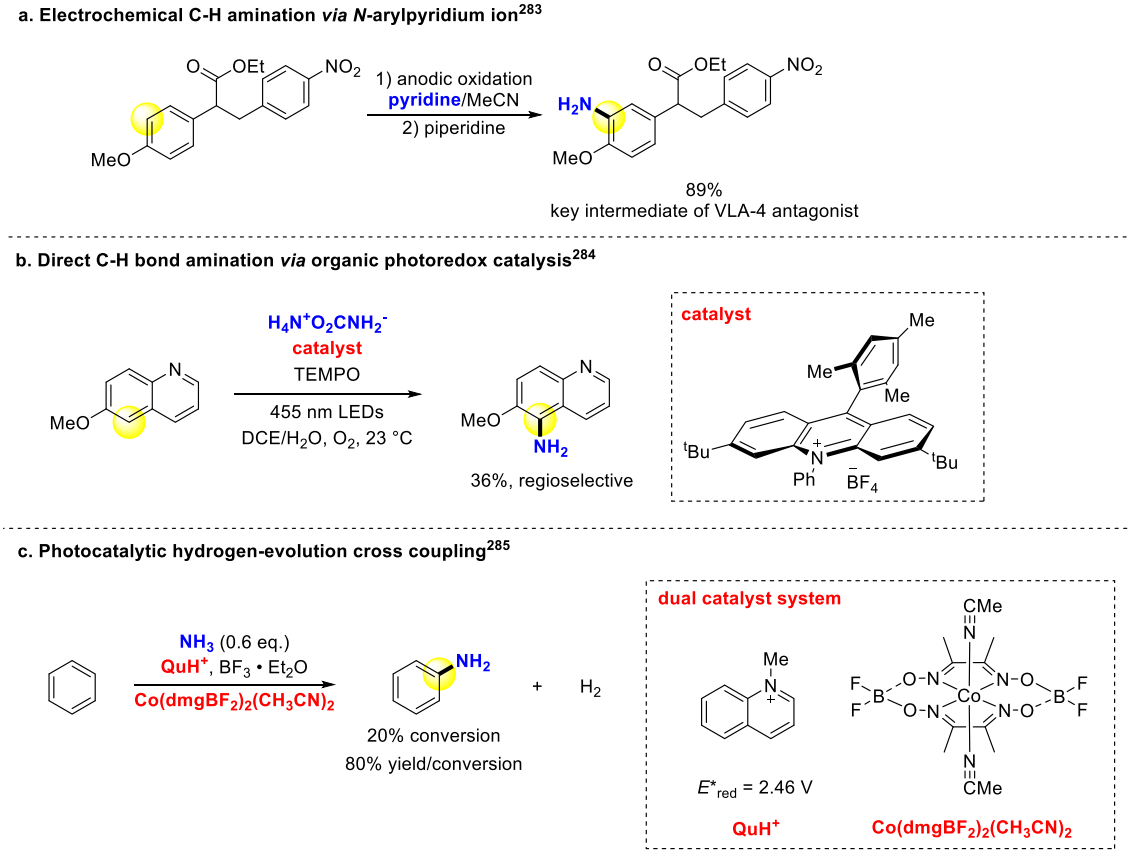
As the ubiquity of primary amines across bioactive compounds, their synthesis method counts a great deal. As for anilines, electrophilic aromatic substitution (S_EAr) is one of the most practical, atom-economic reactions in functionalizing arenes. The traditional S_EAr approach in aniline synthesis involves the nitration of arenes followed by reduction. But that seems unsuitable for late-stage application due to its poor functional group tolerance, bad reliance on protective group manipulations, and highly acidic reaction conditions.

Transition-metal-catalyzed arenes C−H bond activation is an important approach for direct amination. Yu and Dai initially explored an oxazoline-based directing group within copper-mediated late-stage heterocyclic functionalization, and then combined it with oximes in primary amination of telmisartan (Scheme 18a)[277,278]. Furthermore, Chang and Baik reported the usage of aqueous ammonia as a nitrogen source in copper-catalyzed aryl C−H bonds amination through a disproportionation pathway[279]. After simple transformation of the oxazoline-derived directing group, Bexarotene and Probenecid ortho-amination derivatives can be easily constructed (Scheme 18b). Applying the innate carboxyl in benzoic acid as directing group, Matute and Johansson got rapid access to various drug amination derivatives *via* iridium-catalyzed arenes C−H bond activation under room temperature (Scheme 18c)[280]. Besides, Falck and colleagues uncovered a meta-selective arene amination approach

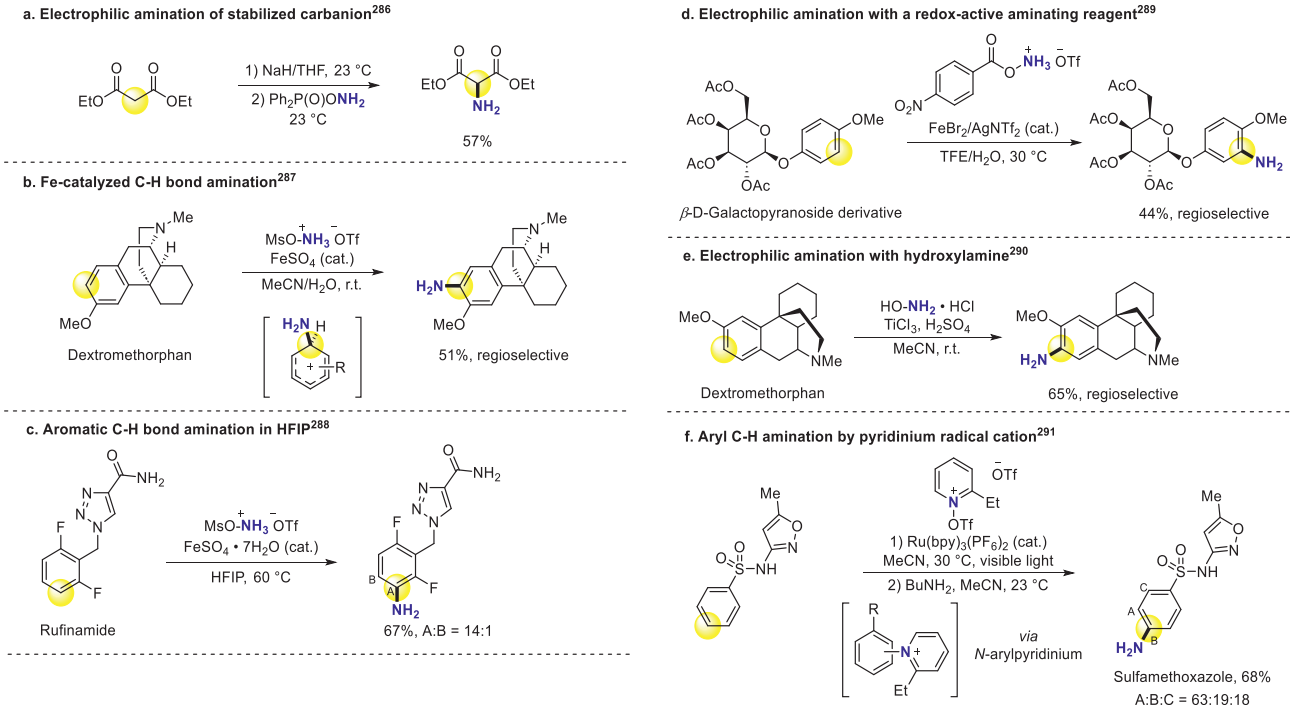
through a Fe=N participated S_EAr mechanism and utilized it to late-stage modification (Scheme 18d)[281].

Over the past decade, direct C−H bond electrophilic amination has emerged as an efficient method, including newly developed electrophilic aminating reagents utilization, such as hydroxylamine-*O*-sulfonic acid (HOSA)[282], novel integration with electrochemistry or photochemistry, and so on. For instance, Yoshida group coupled anodic oxidation with nucleophilic pyridine attack, among which the first-step one-electron oxidation lays foundation for aromatic C−H functionalization (Scheme 19a)[283]. The amino group is introduced at site with the largest coefficient of the LUMO in cation intermediate. Unlike that, Nicewicz[284], Tung and Wu[285] utilized photocatalytic approach to activate arenes substrates. Nicewicz converted diverse protected phenols, haloarenes and nitrogen heteroaromatics to corresponding anilines through an organic photooxidant and nitroxyl radical catalyst system (Scheme 19b)[284]. Except for monosubstituted arenes, other various substrates such as protected phenols, haloarenes, and nitrogen heteroaromatics were also applicable to this method. Tung and Wu developed hydrogen-evolution cross-coupling strategy for amination and hydroxylation of arenes. Their exquisite dual catalyst system, comprising photocatalysis and cobalt catalysis, accomplished atom-economic amination of arenes with no need of any oxidant (Scheme 19c)[285].

Elevating reactivity of electrophilic aminating reagents through attaching more electron-deficient leaving groups could achieve direct amination under mild conditions. Vedejs group applied *O*-di(*p*-methoxyphenyl)phosphinylhydroxylamine as NH_2^+ equivalent for direct amination of stabilized sodium and potassium enolates (Scheme 20a)[286]. Falck presented dirhodium-catalyzed C−H arene amination with hydroxylamines as nitrogen sources[282]. Morandi and coworkers developed the Minisci protocol with $MsONH_3OTf$ as aminating reagent[287]. The protonated state increases reagent electrophilicity and the deactivating ammonium substituent prevents over-amination. This method directly constructed primary anilines in Flurbiprofen, 17β-estradiol-3-methyl ether, and dextromethorphan with good selectivity on the more electron-rich aromatic site (Scheme 20b). As they descried in substrate table, this method was compatible with unprotected amines and hydroxyl groups, and its application in more complex bioactive substrates is expected. Ritter and coworkers realized hexafluoroisopropanol (HFIP)-aided radical aromatic C−H bond amination that provided free anilines in a single step[288]. The solvent HFIP, known for strong polarity and hydrogen bond-donating ability but weak nucleophilicity, expanded substrate scope across more electron-poor arenes, such as nitrobenzene, by lowering the lowest unoccupied molecular orbital (LUMO) of $MsONH_3OTf$ to increase overall electrophilicity. The late-stage functionalization of Moclobemide and Rufinamide revealed its potential for drug modification (Scheme 20c). Jiao group developed various RCO_2NH_3OTf as new redox-active aminating reagents and introduced primary amines to β-D-galactopyranoside, 18-crown-6 derivatives affording single regioisomers (Scheme 20d)[289]. Some unprotected hydroxyl-substituted substrates also worked well. Moreover, a Ti-mediated electrophilic amination method was disclosed by Sanford with hydroxylamine as a nitrogen source (Scheme 20e)[290]. Several heteroaromatic substrates like thiophene could also be transformed with modest regioselectivity. Additionally, a one-pot pyridination-aminolysis approach



Scheme 19 Direct C−H bond amination *via* electrochemistry and photochemistry strategies.



Scheme 20 Direct C−H amination by electrophilic aminating reagents.

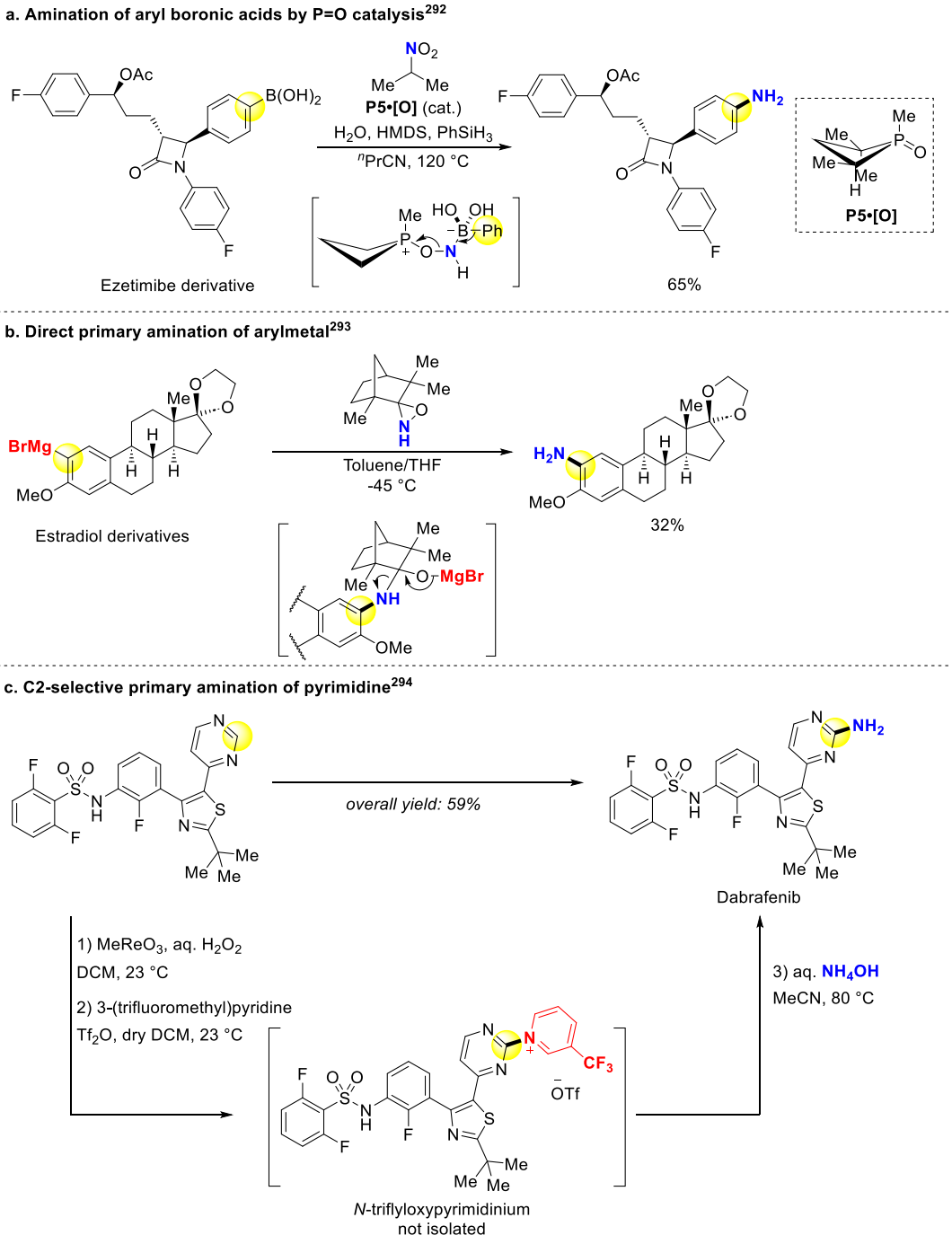
has been discovered by Ritter group[291]. With aid of visible light, the pyridinium radical cation generated *in situ* from *N*-OTf 2-ethlpyridine effectively aminated bioactive arenes, which enabled quick access to the broad-spectrum antimicrobial Sulfamethoxazole (Scheme 20f). There was high compatibility with heterocyclic arenes like pyrrole and isoxazole in this method, which implies great potential in late-stage pharmacophores derivatization.

Radosevich group disclosed the primary amination of aryl boronic acids through capturing newly-generated intermediate oxazaphosphirane[292]. They coupled Nef decomposition with $P^{III}/P^{V}=O$ redox cycling to sustainably produce active intermediates (Scheme 21a). Besides improving the electrophilicity of N sources, enhancing nucleophilicity of aromatic arenes has also been investigated. Kürti and Ess combined aryl Grignard reagents with N−H oxaziridine for direct primary amination of pharmaceutically relevant estradiol, terpenoid, and carbohydrate derivatives (Scheme 21b)[293]. Chang group came up with C2-selective pyrimidines amination in an enthalpy-driven manner, during which the C2/C4 selectivity was accomplished through nucleophilic substitution of hydrogen (S_NH) process, and applied it to fast synthesis of the anticancer drug Dabrafenib (Scheme 21c)[294].

The site-selectivity of late-stage amination methods is highly desired, as the position of amino groups significantly impacts the activity and metabolic feature of bioactive compounds. While there have been advancements in reactant activation methods, achieving precise site-selectivity in amination reactions remains challenging, particularly for heteroaromatic substrates.

Transition-metal-catalyzed cross-coupling of amines and aryl halides is a classical method to construct primary (hetero)arylamine. Ma and coworkers developed Ullmann-type cross-coupling of (hetero)aryl halides to afford various amination products, which has been widely used in industrial and academic pharmaceutical synthesis[295−298]. For instance, their CuI/BPMPO system[295-298c] and Cu_2O/MNBO system[295-298d] enable versatile primary amines construction from (hetero)aryl chlorides and bromides, respectively (Scheme 22a). And Chen simplified the synthesis of retinoic acid receptor α/β (RARα/β) agonist Tamibarotene with a non-pressurized Ullmann-type L-proline/DMSO system (Scheme 22b)[299]. Besides, Buchwald−Hartwig amination is also universal across drug discovery[300]. As selected example, Pyke group applied sequential Buchwald−Hartwig amination to synthesize ligands of Tec Src homology 3 (SH3) domain, which could be useful in cancer and osteoporosis drug development. In the second Buchwald−Hartwig reaction, they utilized lithium bis(-trimethylsilyl)amide (LiHMDS, or LHMDS) as an ammonia equivalent for primary aniline formation (Scheme 22c)[301].

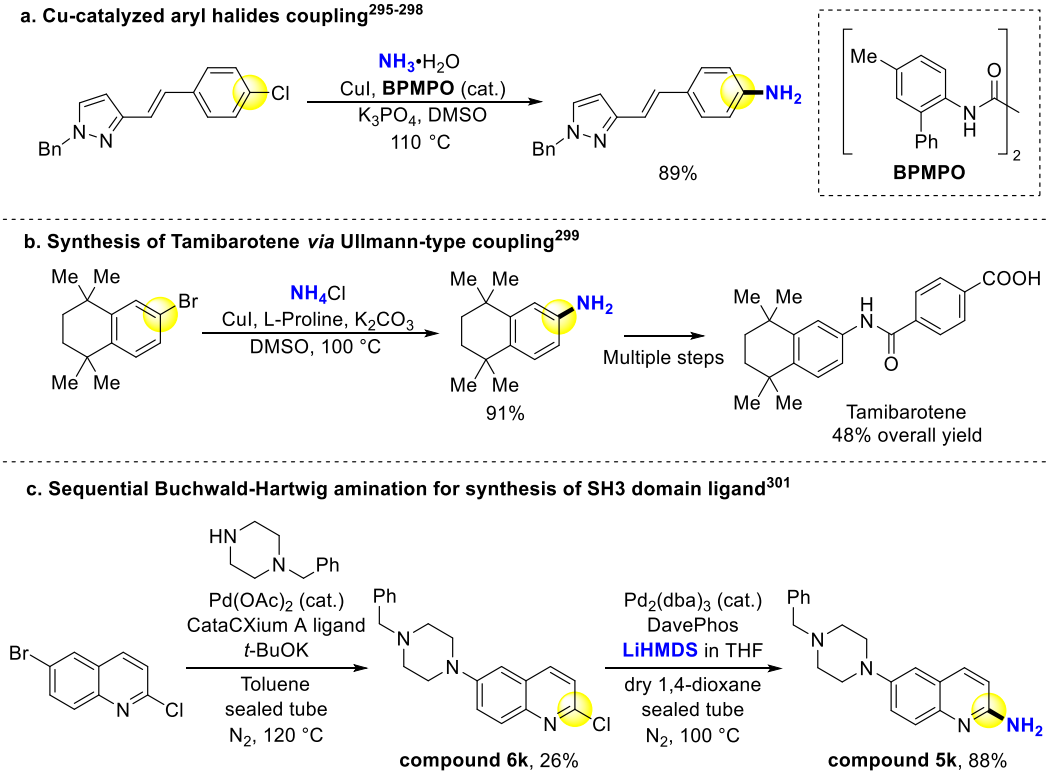
Since reductive amination of unsaturated bonds is highly atom-economic in primary amination, Jagadeesh and Beller discovered $Ni(OTf)_2$-Triphos catalyzed hydrogenative coupling of nitriles with ^{15}N-isotope labeling ammonia/NH_4OAc, accessing to ^{15}N-labeled drug-derived primary amines which could be useful for specific metabolites identification (Scheme 23a)[302]. They also developed a cobalt-based homogeneous catalyst and disclosed its application in reducing carbonyl compounds with gaseous ammonia and hydrogen (Scheme 23b)[303]. Notably, Leonori reported a tandem method for non-canonical aniline synthesis, consisting of condensation between amines and carbonyls before progressively dehydroaromatization of newly formed cyclohexene[304]. This protocol successfully modified commercial medicines and natural products with aniline substructure (Scheme 23c). Li group converted various naturally bioactive phenols into corresponding anilines by use of hydrazine as nitrogen source. According to their proposed mechanism, *in situ* generated palladium hydride reduces phenol to cyclohexanone intermediate, which subsequently undergoes hydrazine condensation, dehydrogenative



Scheme 21 Primary amination of prepared aryl reagents.

rearomatization, and finally reductive N−N bond cleavage (Scheme 23d)[305]. As a common bioactive motif, amino acid bearing chiral α-primary amine carboxylic acid, thus the prevention of undesired self-coupling is always achieved by passively introducing protecting groups. However, these extra protecting-deprotecting procedures inevitably lead to efficiency loss. Struggling with this dilemma, Zhou's work realized direct asymmetric amino acids synthesis from diazoesters and ammonia with only catalytic copper[306]. They solved both the metal poison problem and enantioselective carbene insertion problem with Tp*Cu−HBD complex (Scheme 23e).

Additionally, late-stage dealkylating C−C bond amination is an effective route for actualizing reversal of hydrophobic to hydrophilic properties (Table 3). Site-direct C−C bond primary amination is an emerging strategy for substituted anilines synthesis. In this field, Jiao and coworkers developed dealkylating C−C bond amination *via* C(sp^2) −C(sp^3) bond[307] and C(sp^2) −C(sp^2) bond[308] cleavage from alkylarenes and styrenes respectively, involving newly generated benzyl azide intermediate followed by rearrangement under acidic conditions (Scheme 24a). Furthermore, the easy preparation of phenylalanine derivatives might help to accelerate the development of chemokine receptor



Scheme 22 Cross-coupling of aryl halides for primary anilines formation.

CCR3 antagonists[309]. And aza-Hock rearrangement C−C bond amination, starting from benzyl alcohols *via* hydroxylamine intermediates, has been realized by Hashmi and coworkers (Scheme 24b)[310].

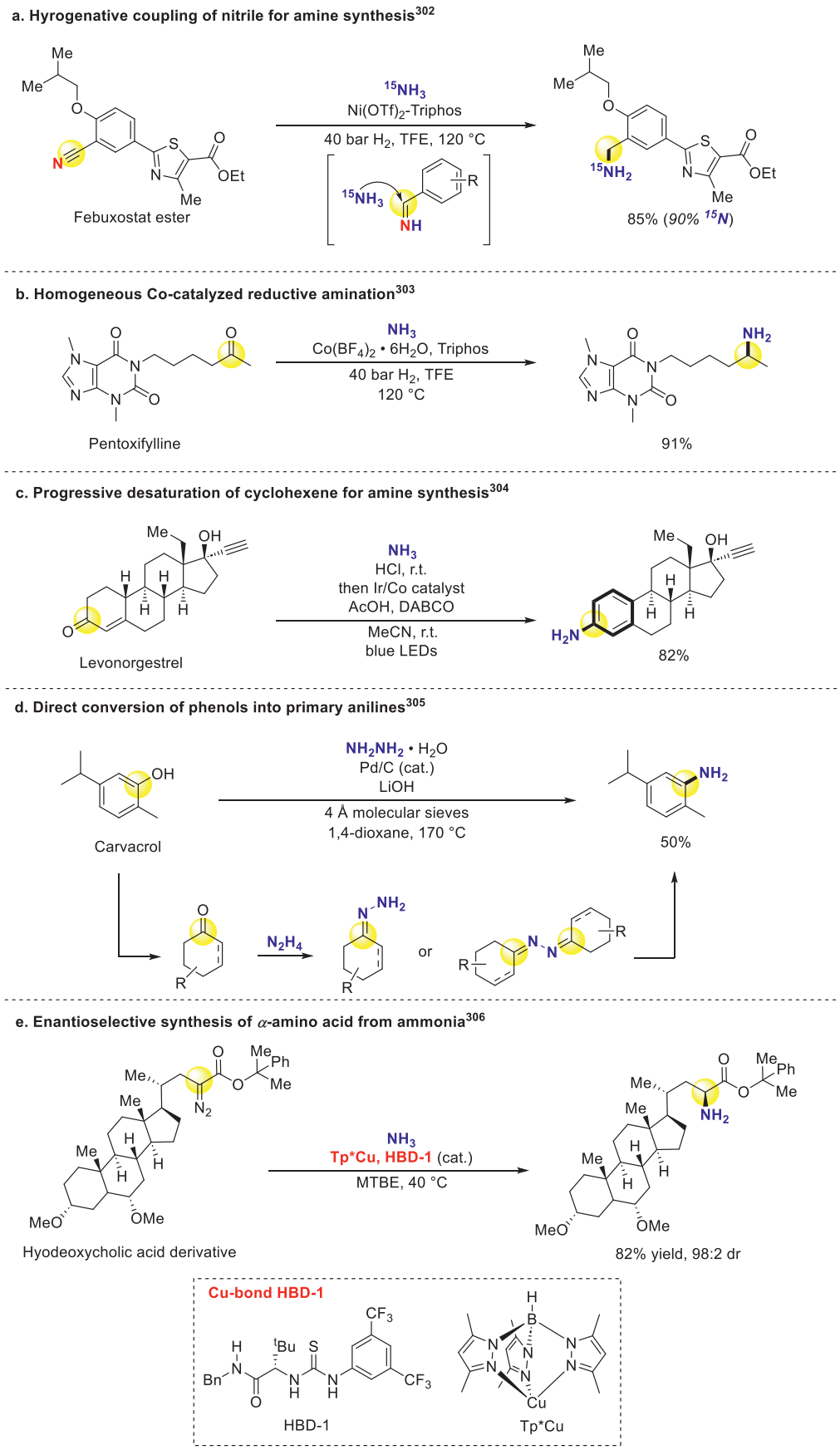
While there are diverse methods for primary amine synthesis, it is still underdeveloped in direct nitrogenation to construct α-fully substituted primary amines. Since sterically hindered primary amines are popular among pharmaceutical agents[311−314], developing such late-stage approach would help to introduce extra hydrogen bond attachment and potential positively charged site.

4.2. *Amidation of bioactive compounds*

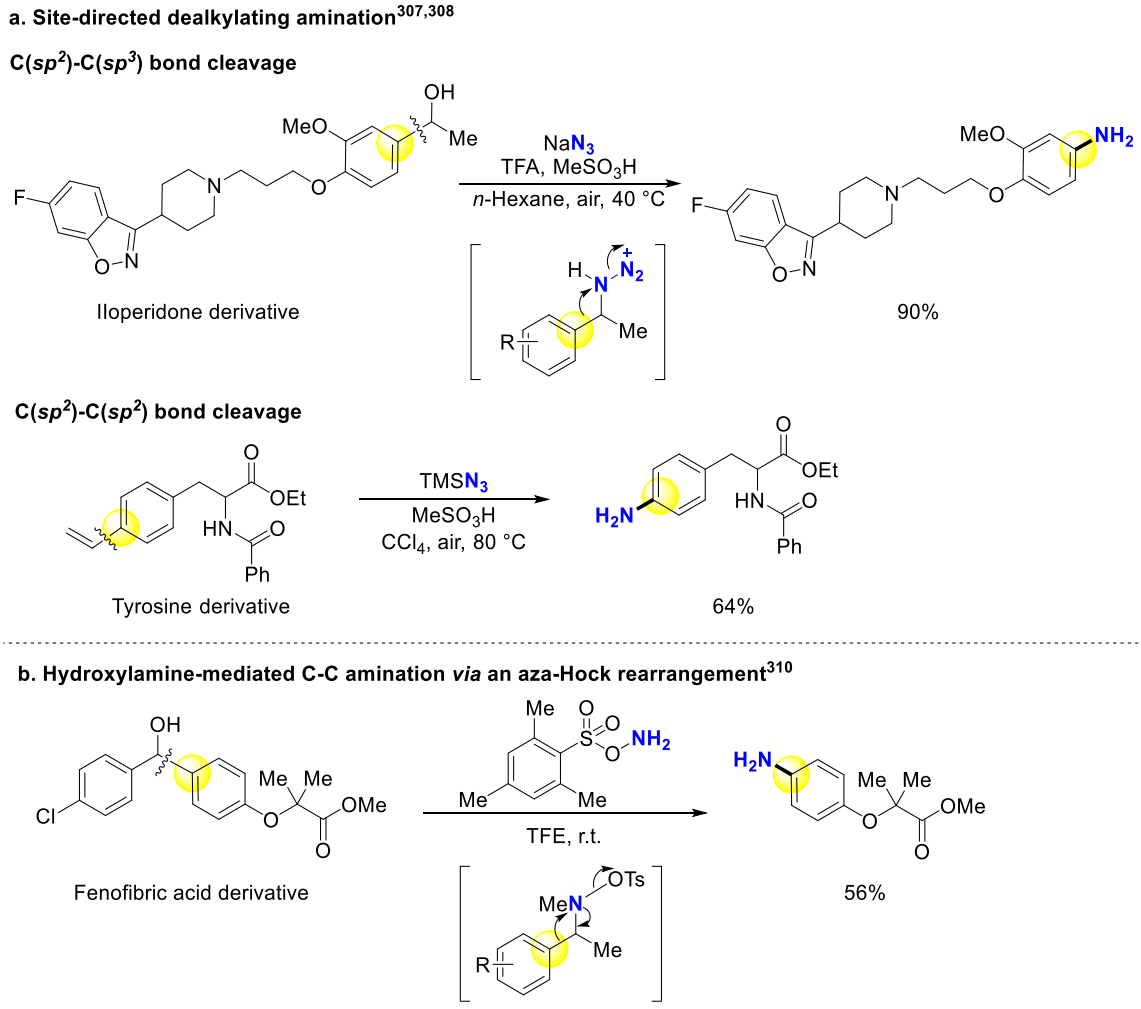
Since amide is an important building block among peptides, chemical probes, drugs, and natural products, it plays an increasingly prominent role in drug design and development. Among the top 200 small molecule drug retail sales in 2021, 120 drugs contain at least one amide[264]. Compared with parent carbonyl compounds, newly-generated amides provide extra hydrogen bond acceptors and donors, and one-atom linker extension implies more flexible molecular conformations.

Chang and Baik developed two-step carboxylic acid amination to afford γ-lactams through intramolecular C−H insertion[315,316]. 1,4,2-dioxazol-5-ones prepared from carboxylic acids, proceeded decarboxylation after coordinating with Ir catalyst, and the desired γ-lactams were generated through enantioselective C−H insertion of metal nitrenes (Scheme 25a). Furthermore, Hong and Chang elaborated on a stepwise lactone-to-NH lactam replacement approach for easy bio-isosteres conversion[317]. Lactone is a common biological interaction motif but well-known for its metabolic instability, and this defect might be ameliorated by lactone/lactam transformation while retaining bioactive hydrogen bond interaction. They advanced the previous method[315,316] by combining reductive C−O bond cleavage of lactones (Scheme 25b). The late-stage conversion of steroid bromodomain inhibitor to its lactam derivatives implied that favorable binding mode of products might emerge from the newly-introduced free NH. Chen and Ma reported an amine-boranes involved photoredox amidation reaction, in which photocatalyst *fac*-Ir(ppy)$_3$ assisted acyl radical intermediate formation and the radical subsequently generated amide−borane complex before its conversion to desired amide (Scheme 25c)[318].

Apart from carboxylic acid, other carbonyl compounds can also be used for late-stage amide construction. Beckmann rearrangement of newly synthesized oximes is a common stepwise method to construct amides from ketones and aldehydes (Scheme 26)[319−321]. For attaining late-stage application of Beckmann rearrangement, many researchers modified the traditional harsh conditions by employing various promoters[322,323]. The groups Lambert[324] and Guo[325] developed geminal dihalides-activated Beckmann rearrangement, and applied it to late-stage modification of steroids. Lambert and coworkers proposed a self-propagating mechanism, in which a formerly generated nitrilium ion might alkylate the latter oxime to proceed rearrangement (Scheme 26a)[324]. Guo and colleagues similarly applied dichloroimidazolidineddiones (DCIDs) in similar fashion for Pregnenolone derivation (Scheme 26b)[325]. Hall group developed a boronic acid/perfluoropinacol system for mildly converting Pregnenolone oxime to corresponding amide, without protecting alcohol (Scheme 26c)[326]. McLaughlin and Brennan disclosed calcium-catalyzed Beckmann rearrangement, in which the transient [HO^- Ca^{2+} PF_6^-]



Scheme 23 Late-stage nucleophilic primary amination.



Scheme 24 Late-stage dealkylating C−C bond amination.

attacked the nitrilium to accelerate following rearrangement (Scheme 26d)[323]. These achieved Prasterone/Pregnenolone-derived amides could also be used as cytotoxic agents on different cancer cell lines[327,328].

In addition, late-stage Beckmann rearrangement of cyclic nature products will provide unnatural skeletal types for activity screening in the early stage of drug discovery. Hyodo group actualized direct NH insertion to ketones *via* transoximation/Beckmann rearrangement, and replaced explosive O-protected hydroxylamines with O-protected oximed (Scheme 27a)[329]. Osborn applied Beckmann rearrangement to afford glycoside-derived lactams from oxime precursors (Scheme 27b)[330]. Zhang accessed poly-heterocyclic skeletal types from β-caryophyllene (Scheme 27c)[331].

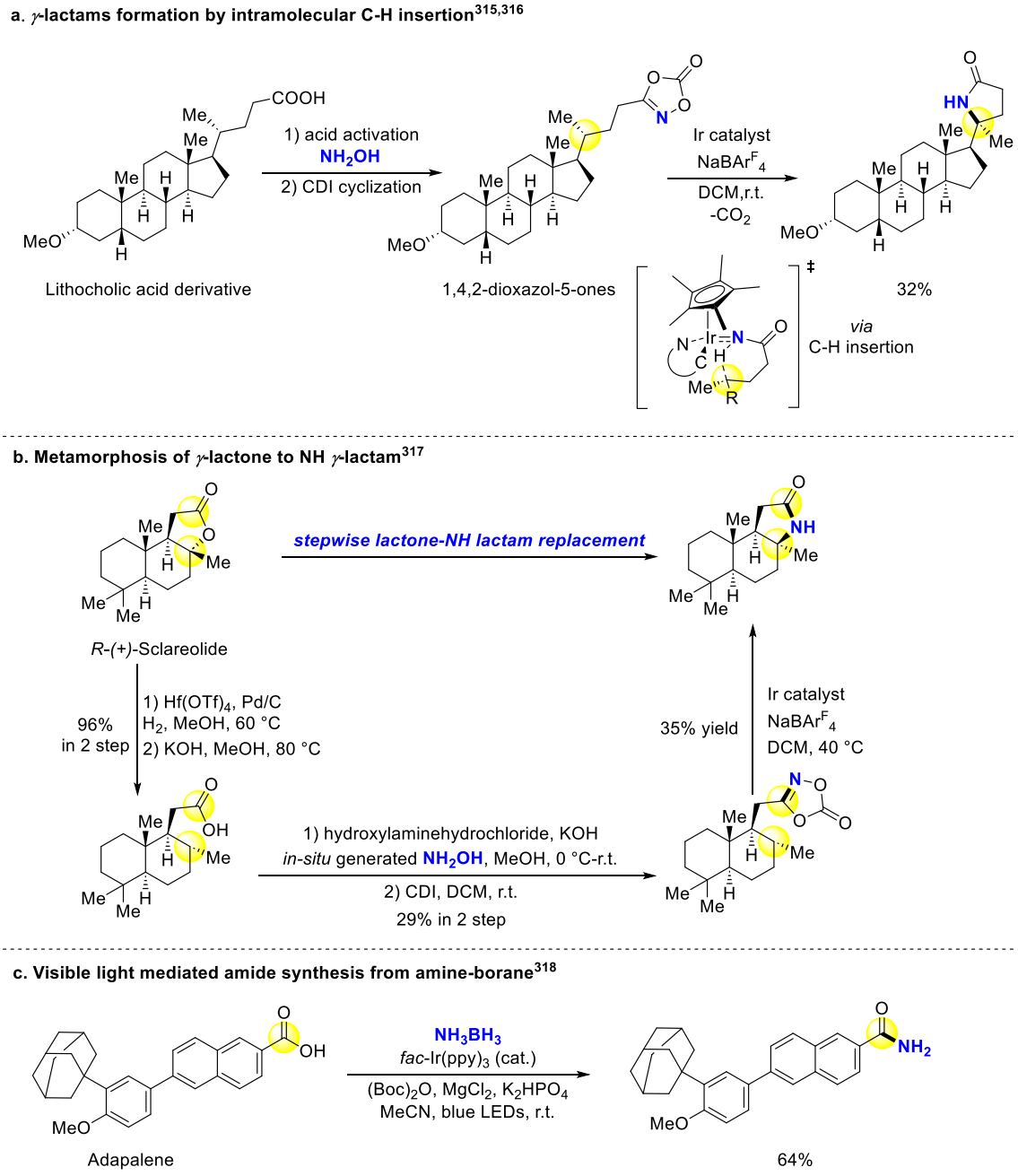
In the field of Schmidt-type transformation[332], Aubé and Tantillo synthesized a series of fused lactams and bridged lactams in a regioselective way by utilizing stabilized cation−π/cation−n interaction (Scheme 28a)[333−337]. Jiao group described a copper-catalyzed aerobic oxidative system for converting ketones to primary amides[338]. Looking for more benign nitrogen sources, they further developed cascade activation of nitromethane for preparing amides and nitriles. In this approach, the active N-donor species are generated through successive activation by triflic anhydride/formic acid/acetic acids (Scheme 28b)[339].

In the field of amide synthesis, since α-substituted aliphatic chiral amides are common substructures across bioactive compounds like Aliskiren[340−343] and Cebulactam A[344−346], efficient α-enantiopure amides synthesis methods and late-stage application require further development.

4.3. *Late-stage introduction of triazole and tetrazole*

As representative products of "click chemistry", triazole and tetrazole are widely used across every stage in drug discovery, such as labeling biomacromolecules with fluorescent probes for target identification[347] and mechanism of action study[348], and rapid preparation of ADC drugs (Scheme 29a)[31].

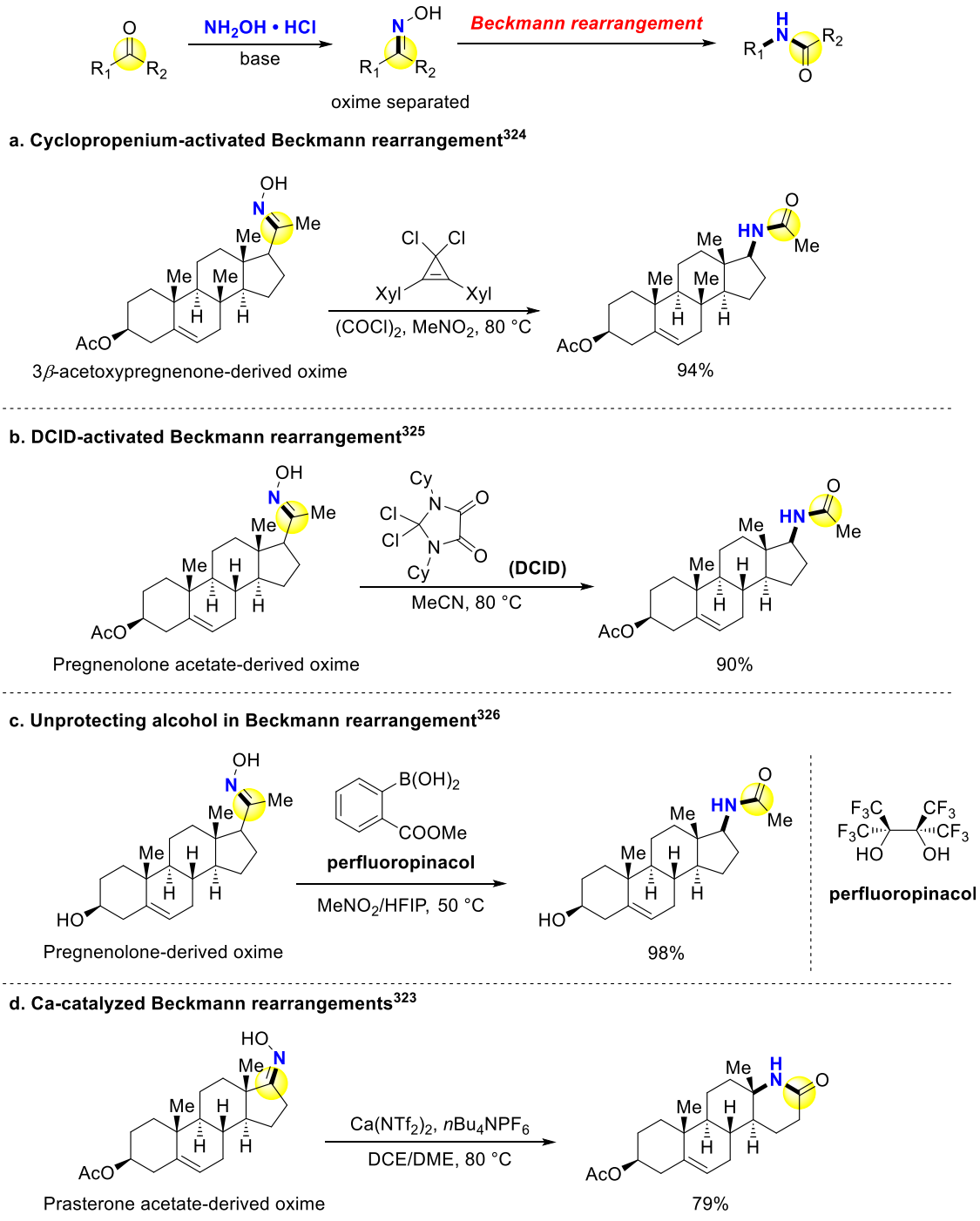
Triazole and tetrazole are more than connection units in bioconjugation, and they can also serve as critical pharmacophores and bio-isosteres in place of carboxylic acids, aromatic rings, and double bonds[349−352]. Besides that, according to their specific steric properties, they could be applied as effective amide surrogates but have fixed configurations and increased metabolic stability[353]. Moody group applied late-stage Chan-Lam amination to effective construction of diverse triazole-contained integrin inhibitors with various substituents for idiopathic pulmonary fibrosis (IPF) drug SAR study (Scheme 29b)[354]. Recently Glorius and



Scheme 25 Late-stage amide formation from carboxylic acids.

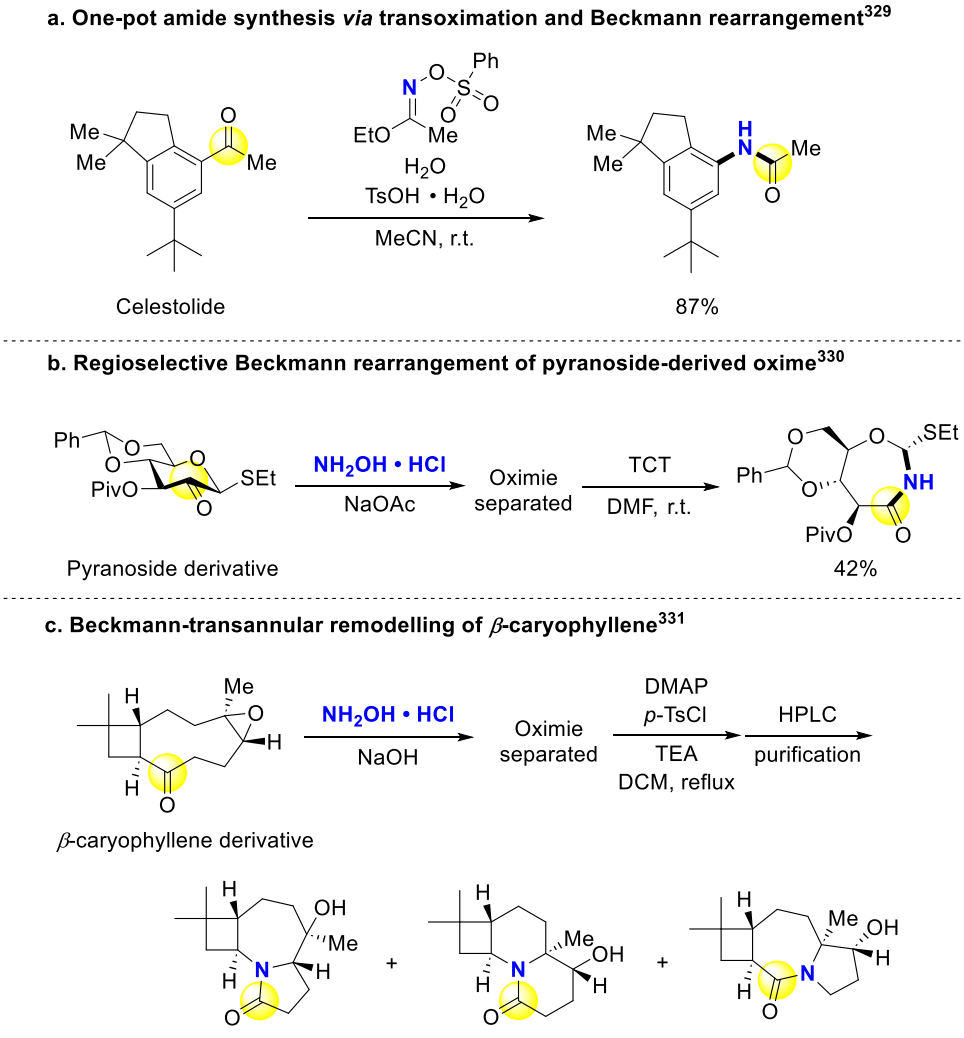
Fridman developed steroid-based and ergosterol-based triazole cationic amphiphiles for antifungal bioactive compounds optimization (Scheme 29c)[355]. Furthermore, Moss and Wang found that the reduction of amyloid-β protein (Aβ) plateau significantly increased about 2-fold when introduced tetrazole into the cyano position of the parent compound, which implied the newly introduced tetrazole structure might occupy an essential binding site (Scheme 29d)[356]. Maurya and coworkers conjugated Ciprofloxacin with various bioactive molecules in CuI-nanoparticle-catalyzed click reaction. And they evaluated the antibacterial activity of these pharmaceutical conjugates, further broadened the chemical space of lead discovery (Scheme 29e)[357]. Besides, NH-triazole is also a useful handle for further structural modification and biological optimization.

Since azide is one of the prototypical triazole precursors, in-situ azide generation will simplify triazole introduction. Abell and Sirinivasan successfully converted arenes to *N*-aryl-1,2,3-triazoles through a one-pot tandem reaction, which was initiated from C−H bond borylation, followed by copper-catalyzed azidation and azide−alkyne click reaction at the end[358]. This approach was applied to equip (±)-α-tocopherol nicotinate, nicotine, and resveratrol with triazole (Scheme 30a). Metzger group synthesized various tetrazole analogs of natural fatty acids from corresponding fatty nitriles, and provided potential homoprostanoids due to structure similarity (Scheme 30b)[359]. The group of Seo afforded triazole- and tetrazole-decorated-side chain peptoids *via* nucleophilic substitution and subsequent [3 + 2]-cycloaddition on solid support (Scheme 30c)[360]. Jiao and

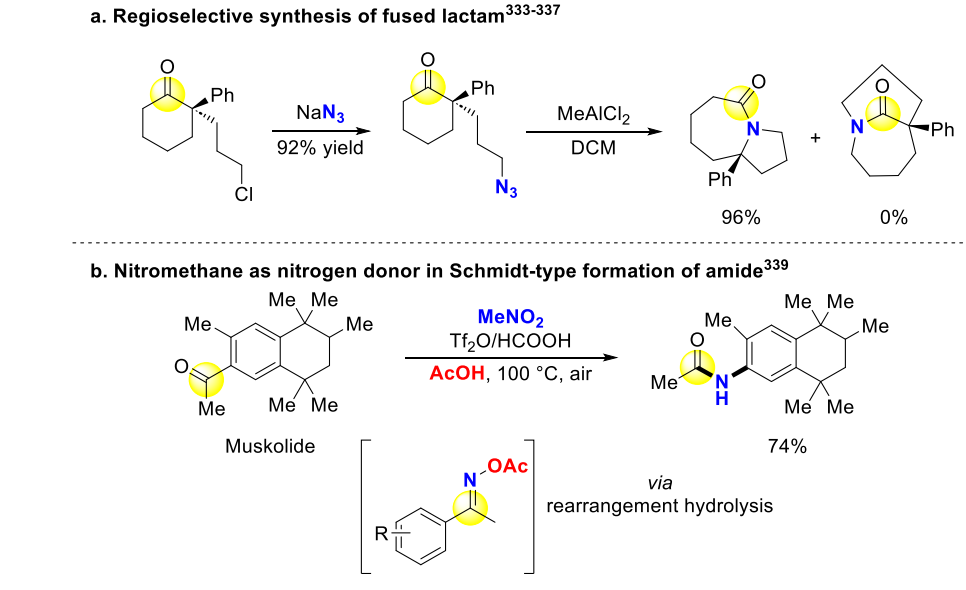


Scheme 26 Late-stage stepwise amide synthesis by Beckmann rearrangement.

coworkers accessed triazole equipped Estradiol derivatives through copper-catalyzed nitrogenation of alkynes. In this approach, the key intermediated is generated *in situ* by Pummerer-type rearrangement between the N donor DPPA and the solvent DMSO (Scheme 30d)[361]. While in Gazvoda's work, they obtained 4-substituted-1*H*-1,2,3-triazoles derivatives through terminal alkyne coupling with newly formed hydrazoic acids (Scheme 30e)[362]. They avoided direct usage of hazardous hydrazoic acid by *in situ* generations from sodium azide under formic acid conditions. In addition, the formic acid also served as a reductant for regeneration of Cu(I) species. Except for classical [3 + 2] cycloaddition, other innovative late-stage triazole synthesis methods have also been reported. Bi group used primary amines as substrate, developed revised [4 + 1] annulation with perfluoroalkyl *N*-mesylhydrazones (PFHZ-Ms)[363] or difluoroacetaldehyde *N*-tosylhydrazones (DFHZ-Tfs)[364] accessing to regioselective preparation of substituted 1,2,3-triazole products (Scheme 30f). The reported mechanism involved twice HF elimination and *N*,*N*-diisopropylethylamine aided sulfonic acid release before intramolecular cyclization.

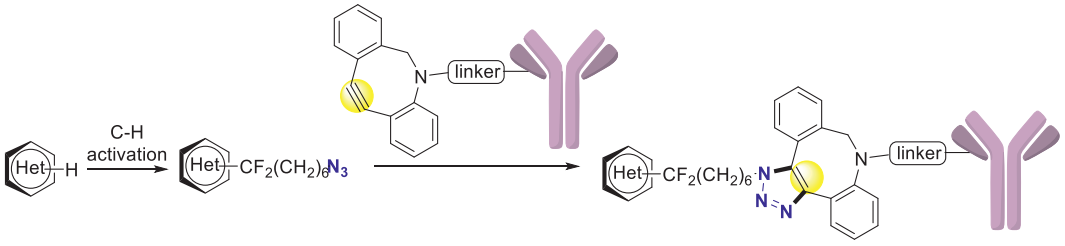


Scheme 27 One-pot amide synthesis and Beckmann rearrangement in natural product derivatization.

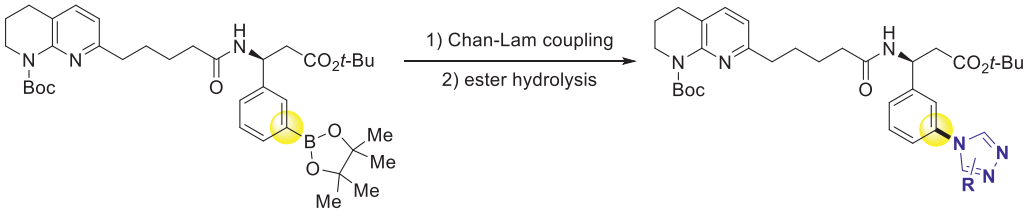


Scheme 28 Schmidt-type amide synthesis.

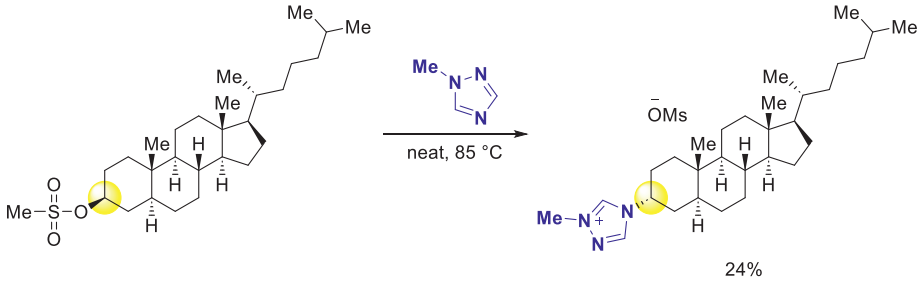
a. Bioconjugation through C-H bond functionalization[31]



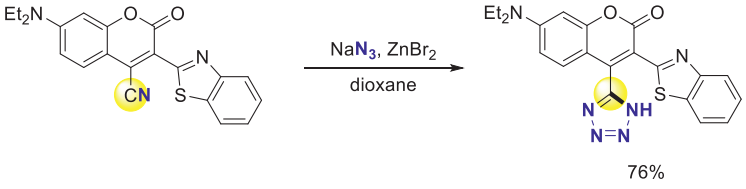
b. Late-stage Chan-Lam amination for integrin inhibitoes SAR study[354]



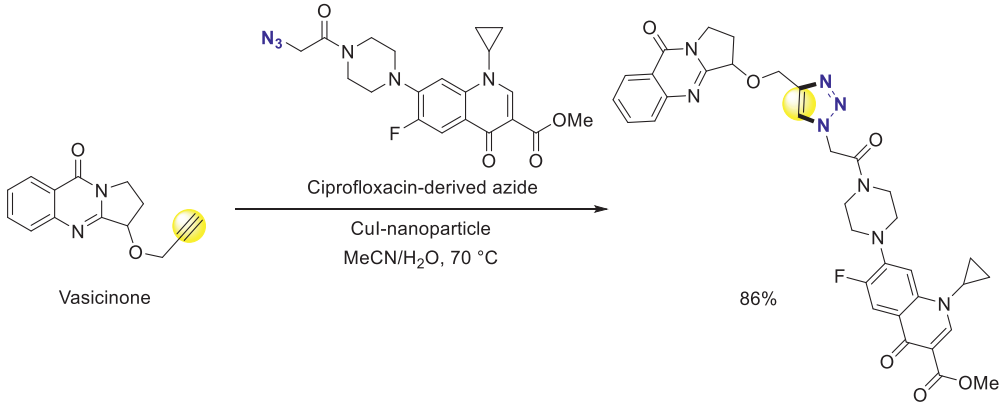
c. Late-stage triazole equipment for antimicrobial compounds discovery[355]



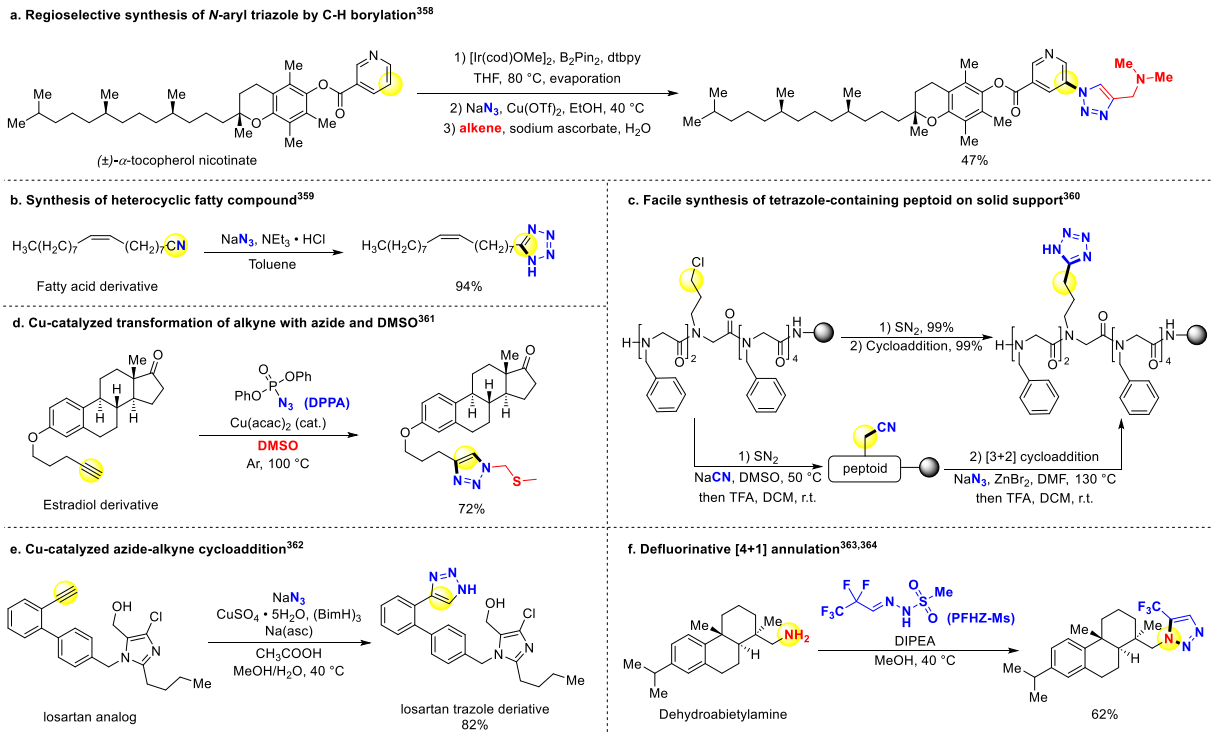
d. Enhancement of Aβ aggregation inhibition by late-stage tetrazole introduction[356]



e. Synthesis of bioactive molecule-Ciprofloxacin conjugate for antibacterial investigation[357]



Scheme 29 Late-stage introduction of triazole and tetrazole in drug discovery.



Scheme 30 Late-stage introduction of triazole and tetrazole.

Due to their special conformation, atropisomeric 1,2,3-triazoles are useful pharmacophores in medicinal chemistry[365–367], but the late-stage introduction is rarely studied. Direct cycloaddition reaction might be stuck by decreased reactivity of sterically substituted internal alkynes, therefore novel stereo-controlled synthetic protocols are highly required.

4.4. *Late-stage skeletal editing with nitrogenation*

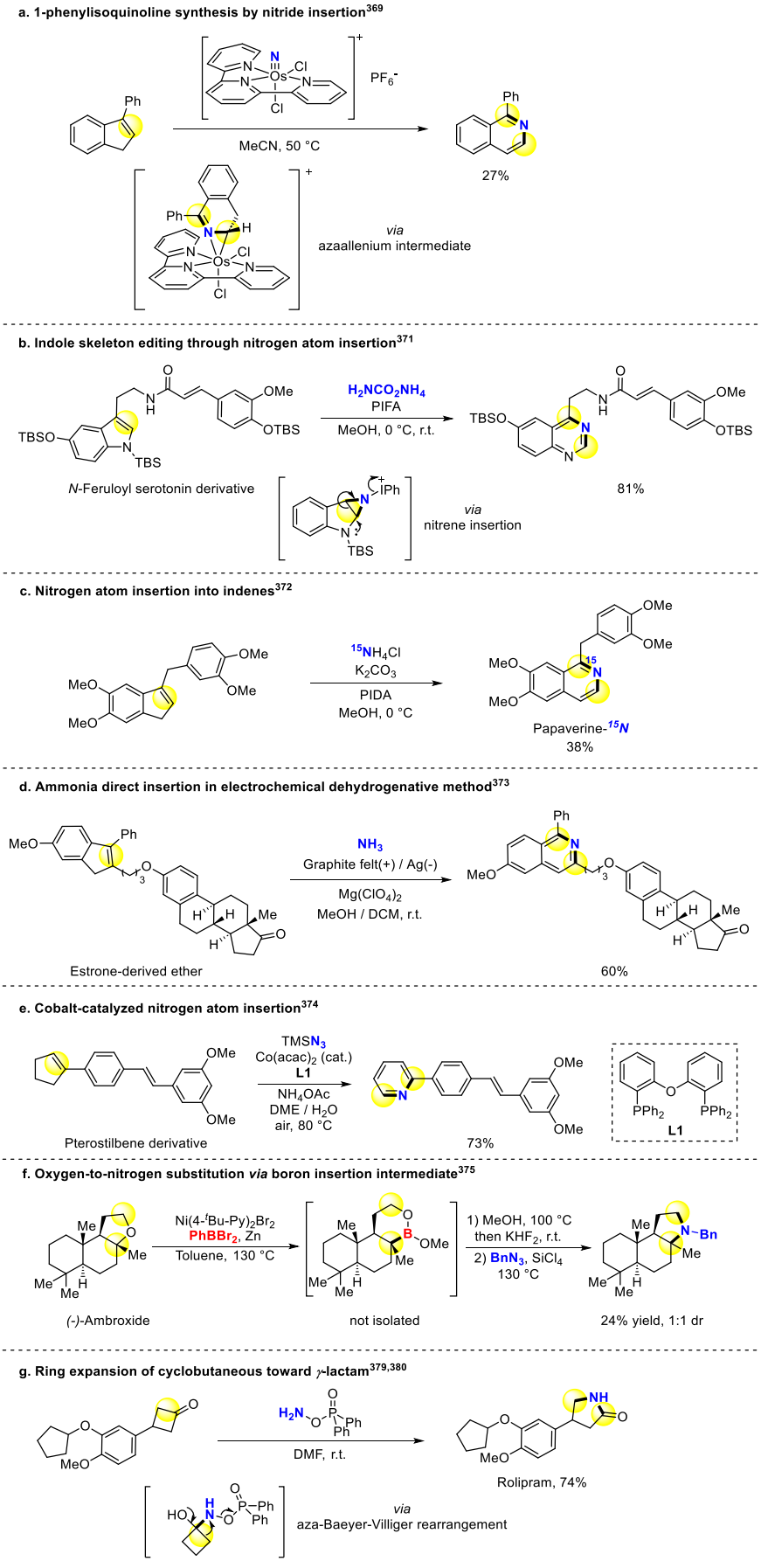
Compared to branches modification, direct skeletal editing will completely reverse physicochemical and pharmaceutical properties, further expanding drug chemical space for phenotypic and target screening in the early stage of drug discovery[368]. We herein introduce researches focusing on late-stage skeletal editing with Nitrogenation. Levin and colleagues developed osmium nitrides as N-reagents and applied them to construct isoquinolines from indenes (Scheme 31a)[369], which could simplify the synthetic routes of isoquinoline scaffold and facilitate its application in antifungal studies[370]. Morandi group disclosed the skeletal editing reaction of indoles to access corresponding aromatic ring nitrogen incorporation products *via* nitrene insertion (Scheme 31b)[371]. Diverse indole-contained sterically constrained substrates like five- or six-membered fused indole rings were evaluated with this method, affording corresponding quinazoline and quinoxaline scaffolds with good yield. Besides, they also accomplished nitrogen atom insertion into indenes in a similar way and successfully achieved the ^{15}N-labled Papaverine probe (Scheme 31c)[372]. Cheng group developed electrochemical method for direct ammonia insertion, accessing diverse substituted quinolines and pyridines (Scheme 31d)[373]. Wei and colleagues directly converted arylcycloalkenes into corresponding *N*-heterocycles through Cobalt-catalyzed nitrogen atom insertion, through which the aziridine intermediate underwent oxidative ring-opening and dehydrogenation process before performing product (Scheme 31e)[374].

Dong and Liu realized oxygen-to-nitrogen editing through zinc/nickel tandem catalyzed boron insertion of C−O bond in strained cyclic ethers (Scheme 31f)[375]. According to the proposed cleavage-then-rebound pathway, the Ni-catalyzed C−Br/B−Br coupling is the rate-determining step in boron intermediate production[375]. Other annular skeletons like lactams can be achieved through insertion and substitution strategy either. Since Schmidt reaction and Beckmann rearrangement are classical ring expansion methods for cyclic ketones accessing lactams[339,376–378], Wahl group explored skeletal editing reaction of cyclobutanones toward γ-lactams *via* Aza-Beayer-Villiger mechanism and applied it to late-stage skeleton editing (Scheme 31g)[379,380]. They took use of the inherent ring strain of hemiaminal intermediate to promote leaving group mediated rearrangement under room temperature, which enabled convenient synthesis of phosphordiesterase-4 (PDE-4) inhibitor Rolipram.

Since scaffold hopping is an effective approach to discovering new skeleton compounds, skeletal editing may become a novel method for this field without *de novo* synthesis. As seen the skeleton nitrogenation is fairly terse and efficient, but its late-stage application is rarely reported, which partly attribute to limited functional group compatibility and uncontrollable reaction selectivity. As more catalysts are discovered and more skeletal editing methods are used for LSF, skeletal editing will hopefully improve the pace and quality of bioactive compounds modification and synthesis in medicinal chemistry.

4.5. *Late-stage N,O-incorporation via C−C bond cleavage*

In light of the importance of oxygenation and nitrogenation in bioactive derivatization, specific combination methodologies of the N,O-incorporation, which provide a shortcut to equip versatile pharmacophores and biological handles, will be discussed below.

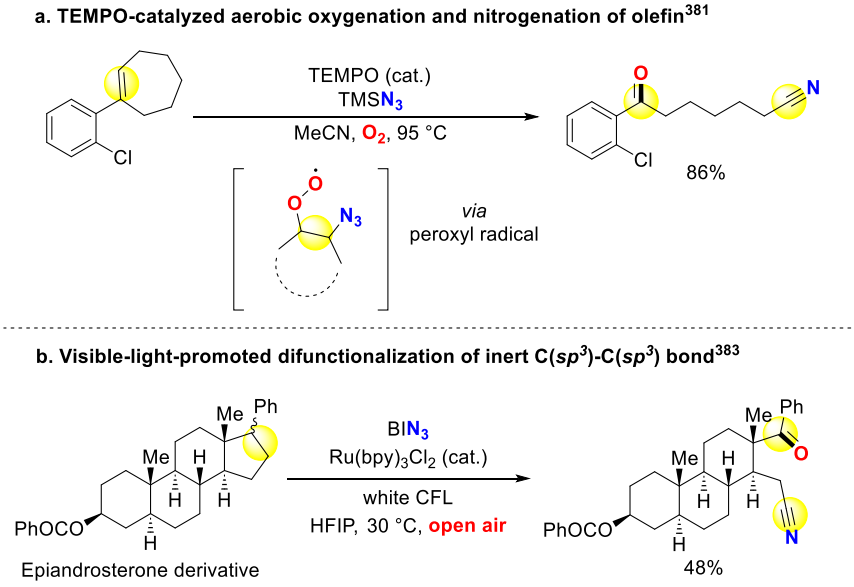


Scheme 31 Late-stage skeleton N atom introduction.

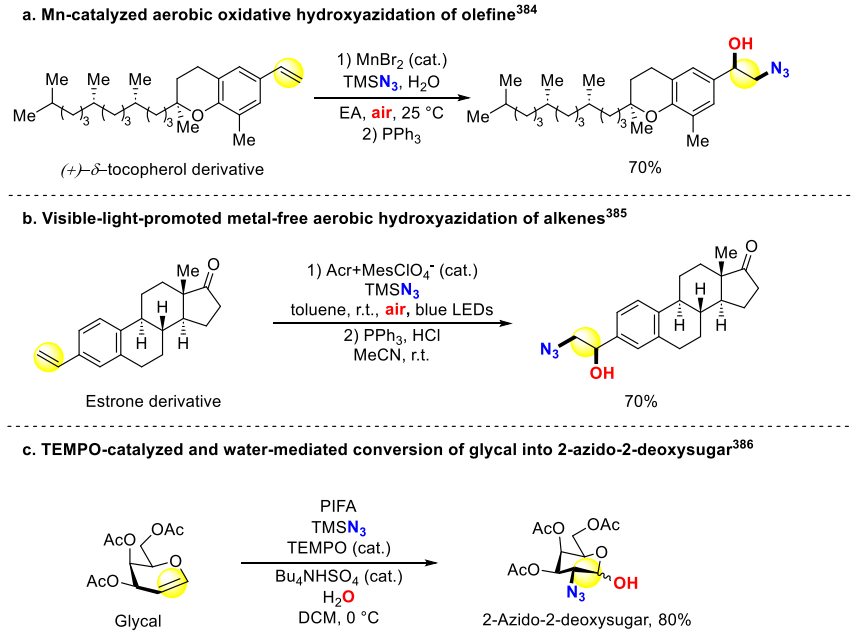
In the field of oxo nitriles synthesis, Jiao group discovered TEMPO-catalyzed aerobic oxygenation and nitrogenation system, through which they simultaneously introduced carbonyl and cyano groups *via* C=C double-bond cleavage. In this process, TEMPO-induced azido free radical attacks substrate alkene before terminating with molecular oxygen to form peroxide radical intermediate (Scheme 32a)[381]. Besides, Shi and Jiao also developed a photoinduced C(sp^2)−C(sp^3) bond cleavage approach to building cyano-containing ketones with DMSO as an oxidant[382]. Liu and coworkers disclosed visible-light-promoted selective cleavage of arene vicinal C(sp^3)-C(sp^3) bond, and the subsequent deconstructive nitrogenation successfully remodel bioactive steroid skeleton (Scheme 32b)[383].

Concerning direct synthesis of *β*-azido alcohols, Jiao and colleagues reported Mn-catalyzed hydroxyazidation of olefins, with air as oxygen source and azidotrimethylsilane ($TMSN_3$) as nitrogen source (Scheme 33a)[384]. Furthermore, with promotion of visible light, Lu group developed a metal-free aerobic hydroxyazidation of alkenes (Scheme 33b)[385]. Vankar and coworkers disclosed a TEMPO-PIFA-$TMSN_3$ system, through which they obtained 1-azido-2-deoxysugars from glycals with water as oxygen source (Scheme 33c)[386].

Besides above nitrogentation approaches, Baran, Zhu, and other scientists developed diverse methods for equipping nitrogen-bearing drug-like fragments such as imides[387,388], and morpholines[389−391], which could effectively diversify bioactive



Scheme 32 Direct synthesis of oxo nitriles *via* *N*,*O*-incorporation.



Scheme 33 Direct synthesis of *β*-azido alcohols *via* *N*,*O*-incorporation.

molecules with broad substrate scope and good regioselectivity. Chiral chromanols especially chiral 3-amino-4-chromanols are fairly important structural units in bioactive compounds and drugs[392−394], and useful synthons for the synthesis of therapeutic compounds[395]. Direct enantioselective construction of chiral 3-amino-4-chromanols is still in high demand.

5. Conclusions

Since late-stage modification has become a convenient and efficient strategy for the derivatization of bioactive compounds and natural products, it plays an increasingly important role in drug discovery. However, the disconnection of reported methodologies with their applications to modify bioactive compounds is a loss for pharmaceutical research and medicinal chemistry. Here we highlighted the latest progress on late-stage halogenation, oxygenation and nitrogenation methods, which enrich the toolbox for bioactive compounds and natural products modification. Despite the rapid evolution of synthetic methodology in every aspect, there are still some common difficulties and challenges to be solved before its widespread late-stage application. From a pharmaceutical science perspective, due to the particularity of bioactive compounds, desired approaches aimed at late-stage derivatization should meet the following requirements: multifunctional group toleration, predictable site/enantio-selectivity, broad substrate scope, and transformation effectiveness.

Firstly, LSM should demonstrate tolerance towards multifunctional groups commonly found in bioactive compounds, such as hydroxyl, carbonyl, carboxyl, nitro, cyano, amino, amide, heterocycles, α,β-unsaturated ketones, and more[13]. Recent advancements in catalysts and new reactions have contributed to addressing these challenges under mild conditions. For instance, naturally occurring bioactive peptides[396,397] often contain a variety of above functional groups, and modifying these peptides with unnatural peptides can enhance their druggability and therapeutic potential[398−400]. In recent years, significant advancements have been made in LSM of short peptides, with numerous chemical[137,401−403], enzymatic[307,400], or photocatalytic[404] approaches. Some strategies have successfully achieved the C−F, C−Cl, C−O, and C−N bond formations in amino acids and short peptides using C−H activation approaches[143,402,404]. However, challenges remain in achieving late-stage halogenation, oxygenation, and nitrogenation of naturally occurring bioactive peptides, especially those with unprotected carboxyl, hydroxyl, and amino groups, thus milder and more compatible conditions are needed. Additionally, providing details on chemoselectivity attempts and incompatible functional groups can assist medicinal chemists in adopting newly discovered methods.

Secondly, predictable chemo-, regio-, and enantio-selectivity are crucial factors during the transition from hit to lead compounds. Pharmaceutical chemists often perform SAR studies by introducing various substituents at specific positions of hit compounds using convergent synthetic routes. For instance, naturally occurring bioactive saccharides[405] and peptides[406] play vital roles in living cells and have potential therapeutic applications with subtle modification[407,408]. Chemists have made significant progress in selectively functionalizing the β-, γ-, and δ-positions of amino acids and short peptides using directing group strategies. However, these approaches are seldom utilized in bioactive peptides LSM due to limitations in suitable directing groups or amino acids[137,402]. Similarly, chemists have devised various methods, such as transition-metal catalysis, enzyme catalysis, organocatalysis, and photoredox catalysis for the selective modification of mono- and oligosaccharides[409,410]. Yet, achieving selective LSM of bioactive saccharides remains a challenge. Enzymatic catalysis, such as glycosidic bond formation, shows promise as it holds the potential for directional evolutionary advancements to address this issue. Further exploration of enzymatic approaches may lead to breakthroughs in achieving selective LSM of bioactive saccharides. While some reactions can generate multiple isomers and derivatives quickly[291], efforts are required to identify the specific bioactive structure. Biocatalytic transformations are well-known for their high selectivity compared to other catalysts, but few enzymatic late-stage methods have been disclosed mainly because of the innately narrow substrate scope[411]. Ongoing efforts like molecular biology, bioinformatics, protein engineering[412] and (meta-)genome mining[413] hold promise for expanding the scope of enzymatic late-stage methods.

Thirdly, broad substrate scope is essential due to the diversity of targets and binding pockets for bioactive molecules. These molecules encompass various scaffolds, including benzene rings, steroids, *N*-heterocycles[414], *O*-heterocycles[415], and other heterocycles[416]. For example, the functionalization of *N*-heterocycles and heteroaromatics remains facing huge challenges in synthetic chemistry[7,9]. In our opinion, while it is difficult for a single reaction to be compatible with multiple scaffolds, achieving multiple substrate compatibility while ensuring site-selectivity is feasible and necessary for LSM in pharmaceutical science.

Fourthly, transformation efficiency is crucial as bioactive compounds are valuable and hard-earned resources, whether obtained through chemical synthesis or natural extraction. It is essential to avoid introducing additional auxiliary groups, such as directing groups and protecting groups, to simplify the reaction process and achieve atom economy.

In addition to the method itself, the new molecules generated through LSM are also a valuable resource for drug screening based on target and phenotype. However, there exists a disconnect between the development of synthetic methods and the evaluation of product bioactivity, making it difficult for drug development researchers to recognize the practical significance of specific transformations. Therefore, cooperation between chemists and pharmacists, along with the establishment of compound resource-sharing platforms, can facilitate the rapid discovery of the potential applications of these generated molecules.

While it may be challenging to satisfy all the aforementioned requirements simultaneously, controlling functional group toleration and site/enantio-selectivity to a large extent will enable wide applicability of LSM methods, even within a limited range of substrates and transformation effectiveness. Meanwhile, the progressive integration of multiple technologies can expedite the development process. For instance, the rapid development of computational chemistry and artificial intelligence in reaction designing and synthesis planning have rescued chemists from verbose route exploring[417,418]. While multi-parameter optimization is the specialty of automation technology, high-throughput screening of reaction systems based on existing methods in biologically friendly environments might accelerate target reaction disclosure[419,420]. Ultimately, the combination of various technology-assisted synthetic chemistry approaches will gradually

overcome the outlined challenges, and the late-stage modification will greatly facilitate the discovery and development of the next generation of medicines.

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Author contributions

Ning Jiao conceived the project and directed the research. Tongyu Huo, Xinyi Zhao, Xiaodong Dou, and Ning Jiao wrote the paper. Zengrui Cheng, Jialiang Wei, and Minghui Zhu discussed the text the citation.

Conflicts of interest

The authors declare no conflicts of interest.

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