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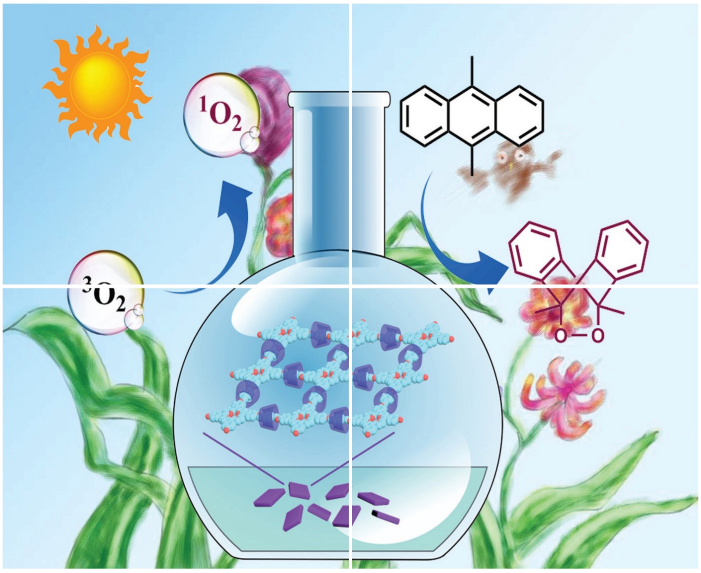

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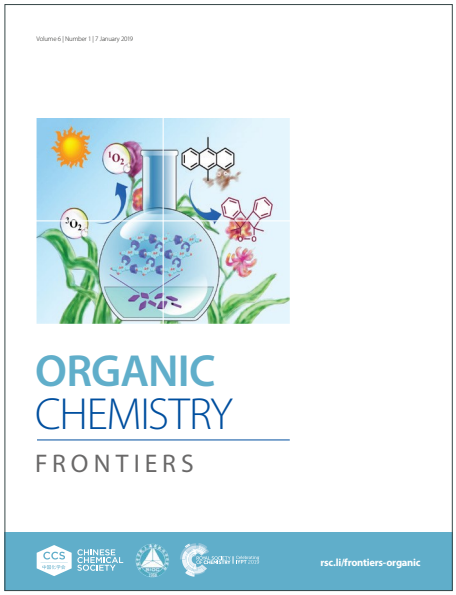

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C–H Bond Halogenation: Unlocking Regiodivergence and Enhancing Selectivity through Directing Group Strategies

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Abstract

Organohalides represent a crucial class of compounds widely used as key precursors for organometallic reagents, bioactive molecules, and nucleophilic substitution reactions. The increasing prominence of cross-coupling reactions has further elevated the importance of aryl halides, establishing them as key building blocks in organic synthesis. Recent advances in C–H functionalization have underscored the strategic role of directing groups, in which functional groups act as internal ligands to facilitate C–H activation. This method has emerged as a highly efficient approach for forming C–C and C–X bonds with exceptional regioselectivity directly from otherwise inert C–H bonds. This review highlights recent progress in applying various functional groups, including carboxylic acids, aldehydes, amides, 8-aminoquinoline, *N*-oxides, PIP, pyridine, and other heterocyclic systems, as directing groups in C–H halogenation reactions over the past five years.

Key words: C–H halogenation; Directing group; Late- stage functionalization; Heterocycles.

1. Introduction

The carbon−halogen (C–X) bond is one of the most crucial functional groups in organic chemistry. It is widely utilized in various applications, including the synthesis of natural products,[1-3] pharmaceuticals,[4-6] and agrochemicals,[7-9] as well as in materials science[10-12] and molecular recognition.[13,14] Organic halides serve as both synthetic precursors and target compounds in the synthesis of organometallic reagents and their subsequent transformations.[15]

Organohalides have become significantly more important and are now considered essential building blocks in organic synthesis, especially with the emergence of cross-coupling chemistry.[16,17] Particularly, aryl and heteroaryl halides are highly valued due to their prevalence in pharmaceutically relevant molecules and high industrial demand.[18] Previously, synthetic strategies utilized strong oxidizing agents for preparing organohalides due to the less polarised

C–H bond, which has the same electronegativity as carbon and hydrogen.[19] This approach poses significant drawbacks and challenges, including harsh reaction conditions, hazardous operations, toxic reagents, poor selectivity, formation of byproducts and over-halogenated substrates. Traditional methods, however, failed to produce highly selective halogenated products, which has been surpassed by emerging new atom-economical direct C–H activation methodology to obtain halogenated derivatives.

Over the last decade, C–H activation has emerged as a modern, cost-effective and environmentally friendly tool for organic synthesis, proved to be an effective transformation in many compounds regarding selectivity and milder reaction conditions. Various strategies, including transition-metal catalysis,[20] photocatalysis,[21,22] enzyme catalysis,[23,24] a metal-free approach[25,26] and electrochemical methods,[27,28] have been developed to create C–X bonds. Despite tremendous advancements in C–H functionalization, developing site-selective or regioselective halogenations of organic compounds remains challenging. The most common way to control site selectivity in C–H functionalization is using directing groups such as, amides,[29] quinolinamides,[30] carboxylic acids,[31] N-oxides[32] etc. The Literature review indicates that nearly all reports on C–H halogenations employ these directing groups to mediate site-selective C–H bond functionalization (Fig. 1).[33,34] Very few studies have explored methods that do not rely on a directing group for site selectivity.[35,36] Additionally, while significant progress has been made in the C–H halogenation of aromatic compounds, fewer studies focused on the synthesis of vinyl and alkyl halides.[37,38]

The carbon-halogen (C–X) bonds exhibit potency as synthetic intermediates, facilitated convenient access to various functionalizations achieved through different methodologies such as nucleophilic substitution,[39] metal-halogen exchange,[40] radical reactions,[41] and transition metal mediate transformations.[42] Therefore, valuable information regarding reactivity profiles allow one to plan synthesis where organohalide functionality can be incorporated, which remains intact throughout the entire process until it is either integrated into the target compound or modified. This highlights the importance of carbon–halogen bonds in organic chemistry. Although several specialized reviews and book chapters have focused on C–H functionalization over the past decade, a dedicated literature review on directing group-assisted C–H halogenation (including fluorination, chlorination, bromination, and iodination) has yet to be published. This review aims to fill that gap by providing a comprehensive overview of C–H halogenation reactions facilitated by a variety of directing groups. It categorizes methodologies for the synthesis of aryl, vinyl, alkyl, and heteroaryl halides, drawing from literature published between 2019 and 2024. Additionally, it highlights recent advancements

in this area and offers a comparative analysis with traditional halogenation approaches, emphasizing improvements in efficiency and selectivity.

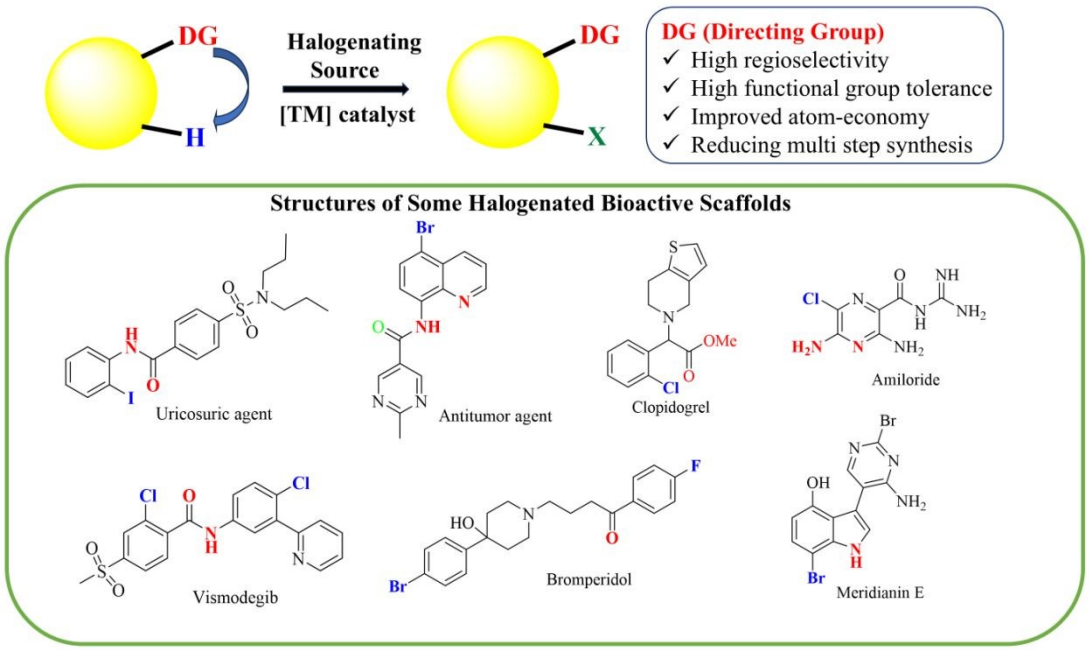

Fig. 1. Directing group strategy for C−H halogenation.

2. Classification of directing groups

In recent years, the use of Lewis-basic directing groups for regioselective C–H halogenation has emerged as a modern and versatile strategy for constructing C–X bonds. These directing groups are typically classified based on their functional nature and coordination strength—ranging from strongly to weakly coordinating, and including removable, non-removable, traceless, or transient types. This approach has become one of the most powerful tools for achieving site-selectivity in C–H halogenation reactions. These transformations proceed through diverse mechanistic pathways, including transition-metal catalysis, visible-light-induced processes, photocatalysis, and electrochemical methods, offering enhanced efficiency and adaptability across a wide range of synthetic applications.

2.1. 8-Aminoquinoline as directing group

The quinoline framework has attracted significant interest from researchers due to its widespread presence in biomedical and organic synthesis. Quinolines serve as essential structural components in numerous pharmaceuticals and biologically active natural products.[43] Traditional halogenation methods, such as electrophilic substitution using halogenating reagents, have been surpassed by direct C–H bond functionalization approach, which provides

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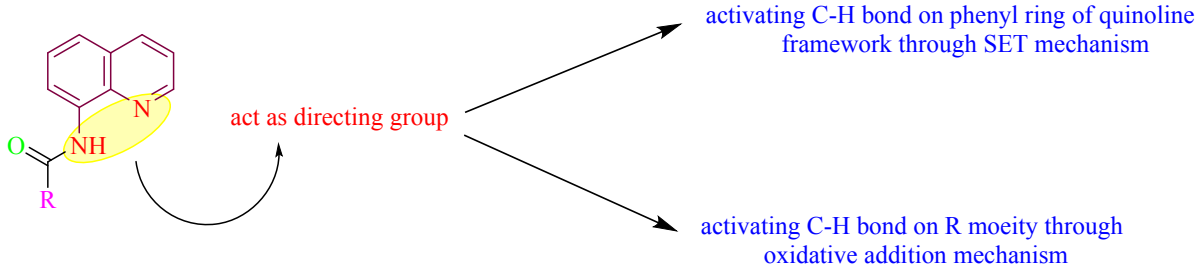
greater efficiency and selectivity. A pivotal advancement in utilizing the quinoline framework came in 2005 when Daugulis introduced a bidentate directing group, 8-aminoquinoline.[44] This innovation has drawn considerable attention in recent years, as it enabled highly selective and efficient C–H bond functionalization in a variety of aromatic, heteroaromatic, and aliphatic compounds.[45] By facilitating chelation-assisted coordination with transition metals, 8-aminoquinoline, as a bidentate directing group has proven instrumental in advancing remote and site-selective C–H bond functionalization. The use of bidentate directing groups continues to be a powerful and versatile strategy for activating C–H bonds, making them a cornerstone of modern synthetic protocols.



In 2019, Long *et al.* developed an efficient method for synthesizing specific halogenated derivatives of 8-amidoquinoline. The optimal results were achieved using an inexpensive iron (III) catalyst (5 mol%), NXS or X_2 (X = Br, I) (0.6 mmol) as the halogenating agent, $CH_3(CH_2)_5COOH$ (0.3 mmol) and $NaHCO_3$ (0.3 mmol) as additives, in water as a benign solvent at room temperature for 24 h, using air as the oxidant (**Scheme 1**). A significant yield improvement of approximately 90% was observed with the addition of $CH_3(CH_2)_5COOAg$, highlighting the beneficial role of a long-chain carboxylic acid as potential phase transfer reagent. To extend the utility of the protocol, *N*-(5-bromoquinolin-8-yl)pivalamide underwent a simple Suzuki coupling reaction with boronic acids, yielding products in moderate to good amounts. Mechanistic investigations revealed that the catalytic cycle proceeded *via* a radical pathway. Key steps include chelate formation, deprotonation, bromine radical attack *via* an SET (single-electron transfer) mechanism, oxidation, and metal dissociation from the intermediate *via* a proton transfer (PT) process, leading to the final product.[46]

Iodination and bromination

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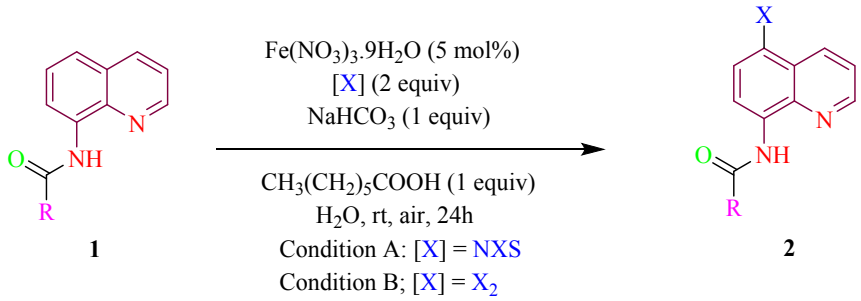
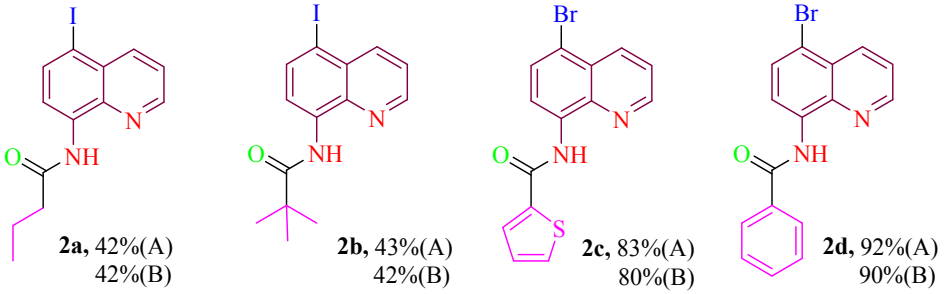
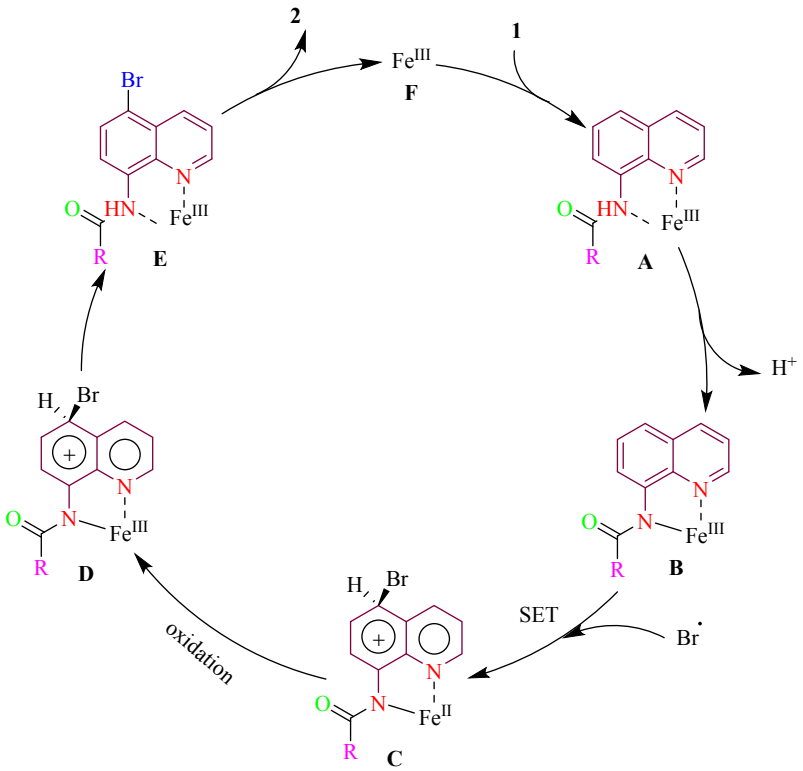


Representative examples



Proposed mechanism



Scheme 1. Fe(III)-catalyzed C-5 halogenation of 8-aminoquinoline amide

Sanford and her team successfully developed a copper-mediated method for regioselective radiofluorination of *N*-protected 8-aminoquinoline. The approach utilized either K^{18}F or Ag^{18}F as the fluorinating agent, with Ag^{18}F serving as both a nucleophile and base. This dual role enabled fluoride substitution and proton sequestration by activating the C–H

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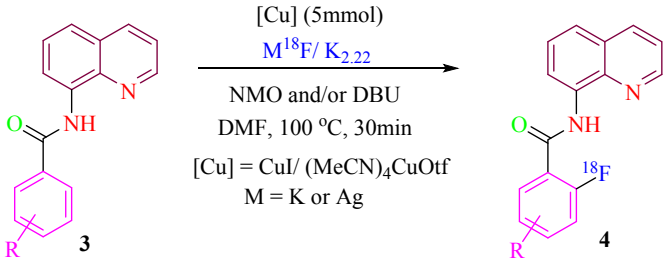
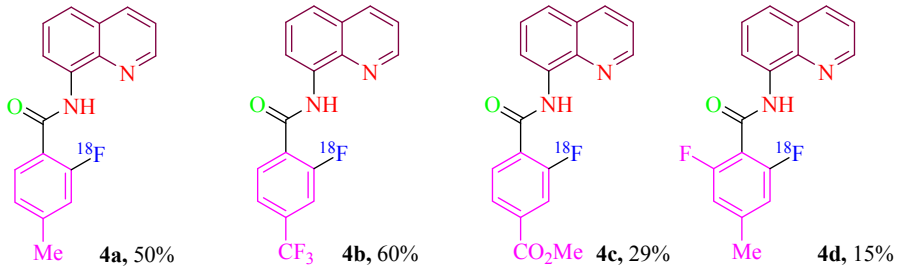
bond. The reaction employed *N*-methylmorpholine N-oxide (NMO) as an oxidant, DBU as a base, and copper catalyst in DMF at 100 °C for 30 min (**Scheme 2**). Substituting CuI with the more soluble $(MeCN)_4CuOTf$ significantly improved the reaction outcomes. The method demonstrated a broad substrate compatibility, effectively fluorinating *N*-protected 8-aminoquinolines with diverse substituents. It was employed in automated synthesis of high-specific-activity doses of the RARβ_2 agonist [^{18}F]AC261066, validating its utility in radiopharmaceutical development.[47]

Radiofluorination



Representative examples



Scheme 2. Copper mediated radiofluorination of *N*-protected 8-aminoquinoline

Chen et *al*., in 2020, developed a new approach for direct chlorination of acrylamides at room temperature using palladium catalyst and *N*-chlorosuccinamide (NCS) as halogenating reagent. This method resulted in single *Z*-stereoisomer in excellent yield, formed from a variety of functionalized acrylamides **(Scheme 3)**. The approach proved effective for both *α*-substituted and *α,β*-disubstituted acrylamide substrates. Mechanistic studies revealed that the formation of a reversible palladacycle through coordination with a bidentate directing group serves as the rate-determining step. This is followed by oxidative addition and subsequent reductive elimination, ultimately furnishing the desired product.[48]

Chlorinated acrylamides

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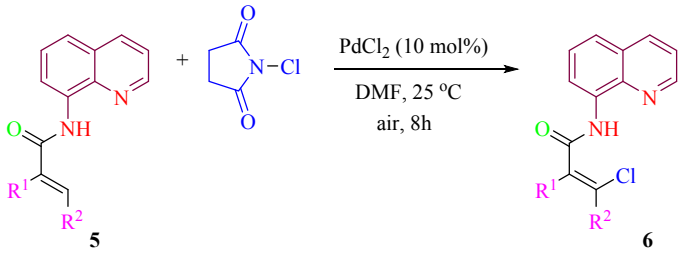
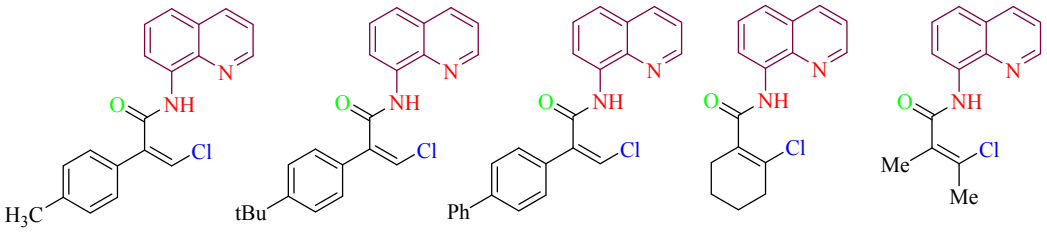
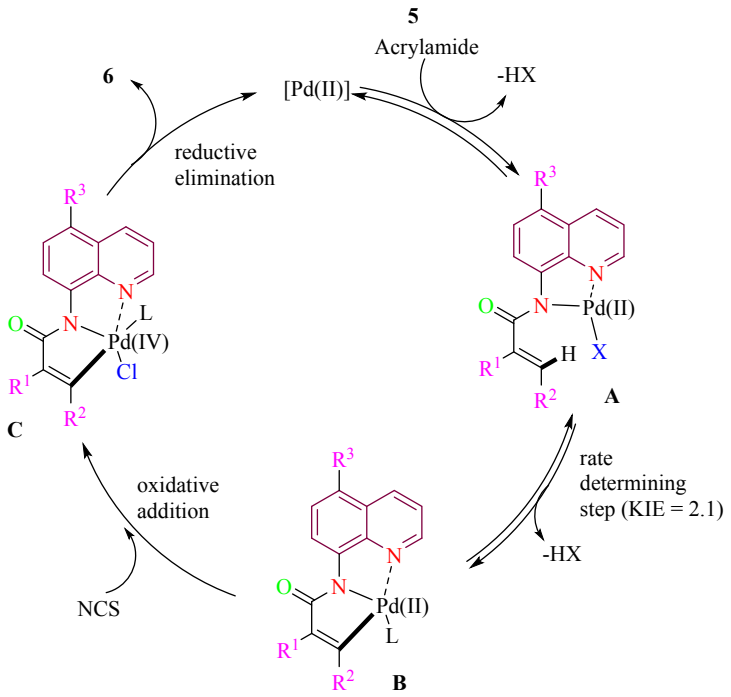


Representative examples



Proposed mechanism

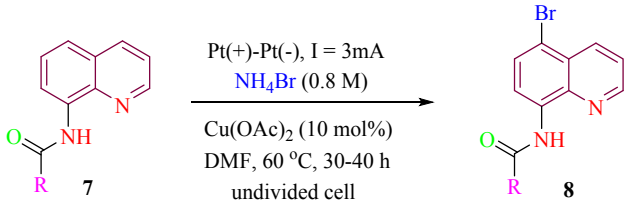


Scheme 3. Stereoselective chlorination of acrylamides

In 2020, Fang group reported C5 bromination of 8-aminoquinoline amide under green electrochemical conditions. The method utilized inexpensive, non-toxic $Cu(OAc)_2$ as catalyst and NH_4Br as both brominating reagent and electrolyte, achieving high yield of desired products (**Scheme 4**). Cyclic voltammetry experiments revealed that NH_4Br generated Br_2 or Br_3^- species during electrolysis while Cu^{2+} formed a complex with 8-aminoquinoline directing group. The proposed mechanistic pathway involves a typical catalytic cycle, beginning with the coordination of 8-aminoquinoline to the metal center. This is followed by the attack of a

bromine radical *via* a single-electron transfer (SET) process, a subsequent proton transfer (PT) step, and finally, metal dissociation to furnish the target product.[49]

C5 bromination



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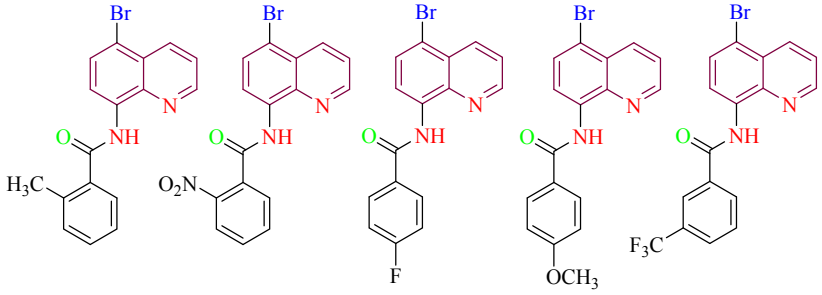
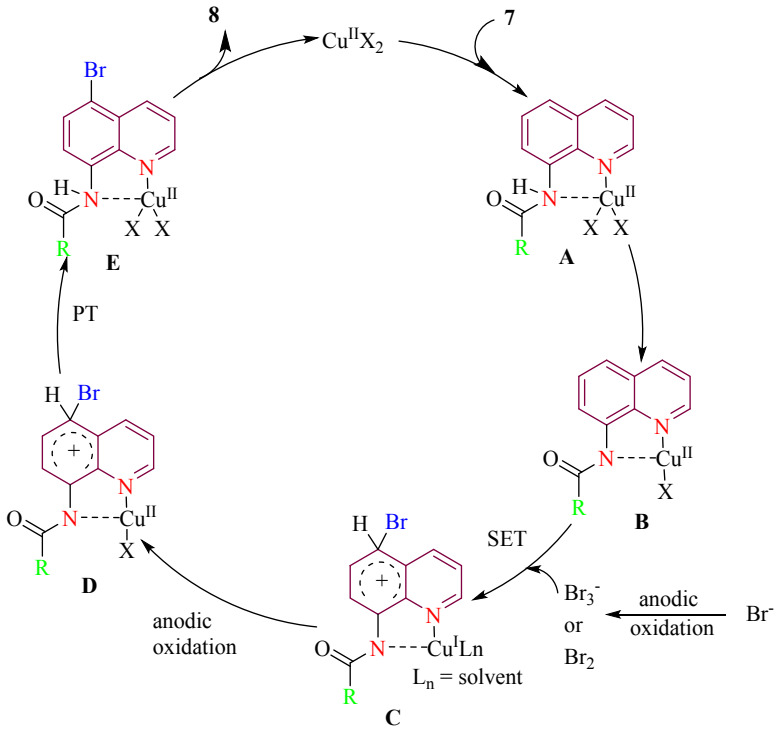


Proposed mechanism



Scheme 4. Electrochemical oxidative C5 bromination of 8-aminoquinoline amide

Subsequently, Guo and colleagues reported that organic halides could serve as source of halogens during electrocatalytic oxidation. They developed an efficiently and conveniently system for halogenating the C5-H position of 8-aminoquinolines at room temperature by

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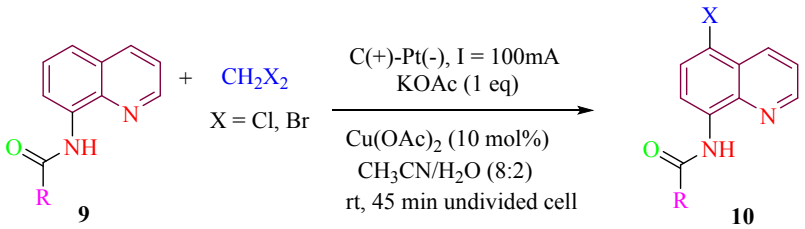
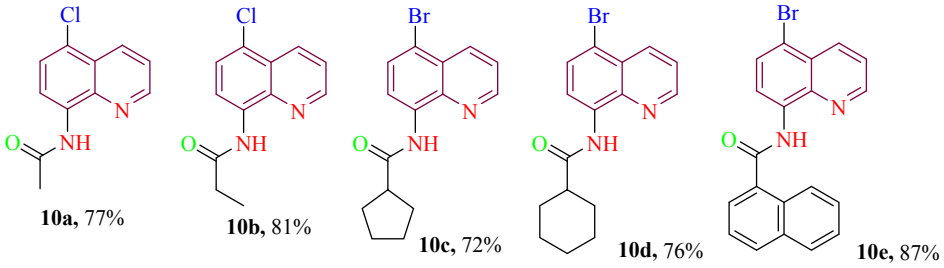
combining electrocatalysis and continuous flow reactions. This system utilized common solvents such as dichloromethane (DCM) and dibromomethane (DBM) as sources of chlorine and bromine, respectively, eliminating the need for additional oxidizing agents (**Scheme 5**). By applying a constant current of 100 mA to the reaction mixture in continuous flow, the desired products were obtained rapidly with high yields. The method is easily scalable to gram quantities due to the use of a continuous flow device. Notably, the reaction followed the SET mechanistic pathway to achieve the desired product.[50]

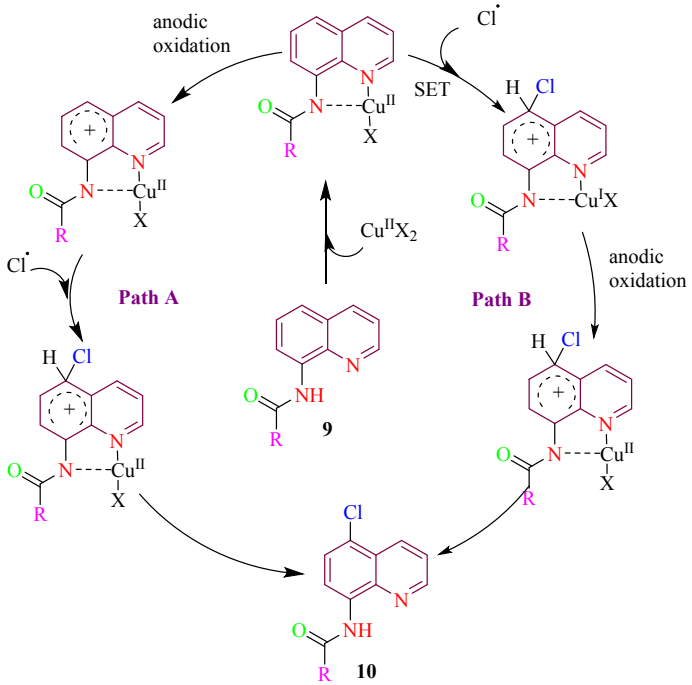
C5-chlorination and bromination



Representative examples



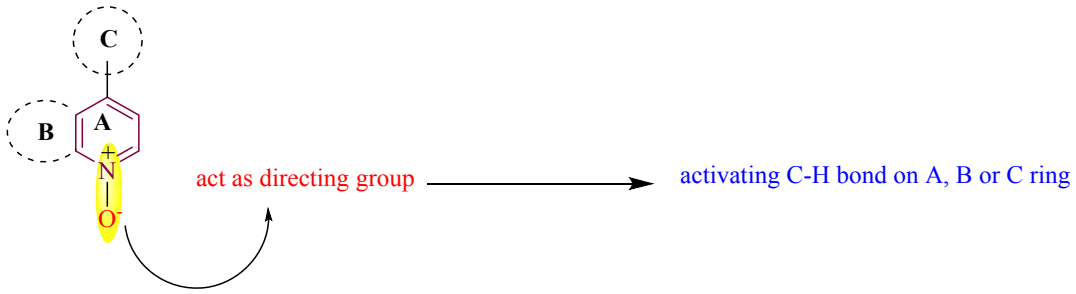
Proposed mechanism



Scheme 5. Copper catalyzed electrochemical oxidative C-5 halogenation of 8-aminoquinoline amide

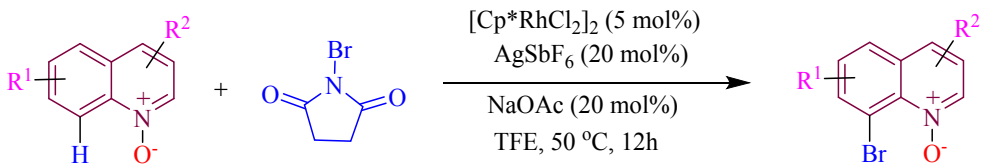
2.2. *N*-oxide as directing group

Substrates containing weakly coordinating *N*-oxides have emerged as valuable synthons for exploring alternative directing groups in C−H functionalization. The use of *N*-oxide directing groups offers a versatile platform for developing synthetic methods to access diverse heterocyclic compounds. These approaches, however, face challenges related to the effective coordination of the *N*-oxide with metal catalysts. Regioselectivity in such transformations are typically achieved through the formation of *N*-oxide-chelated metallacycle, which plays a critical role in guiding the functionalization to the desired position.[51]



Dhiman *et al.* developed a method for bromination at C8 position of *N*-oxide quinoline, mediated by $[RhCp^*Cl_2]_2$ catalyst. The optimized mild reaction conditions yielded the desired products efficiently, with broad substrate scope, tolerating diverse functional groups at other positions of the model substrate (**Scheme 6**). Mechanistic studies highlighted the active role of Rh(III) catalyst in the catalytic cycle, with the formation of a key rhodacycle intermediate (**A**), suggesting that C−H activation is the rate-limiting step. This was confirmed through controlled experiments, deuterium labelling studies, and kinetic isotope effect (KIE) analysis. The desired product **12** was formed from intermediate **C**, derived from **B**, through one of two pathways: nucleophilic addition or oxidative addition/reductive elimination.[52]

C8 bromination



11 **12**

Representative examples

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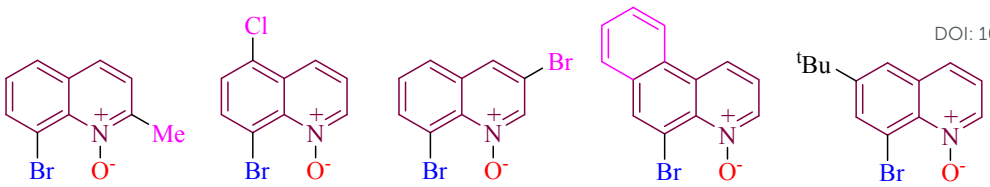
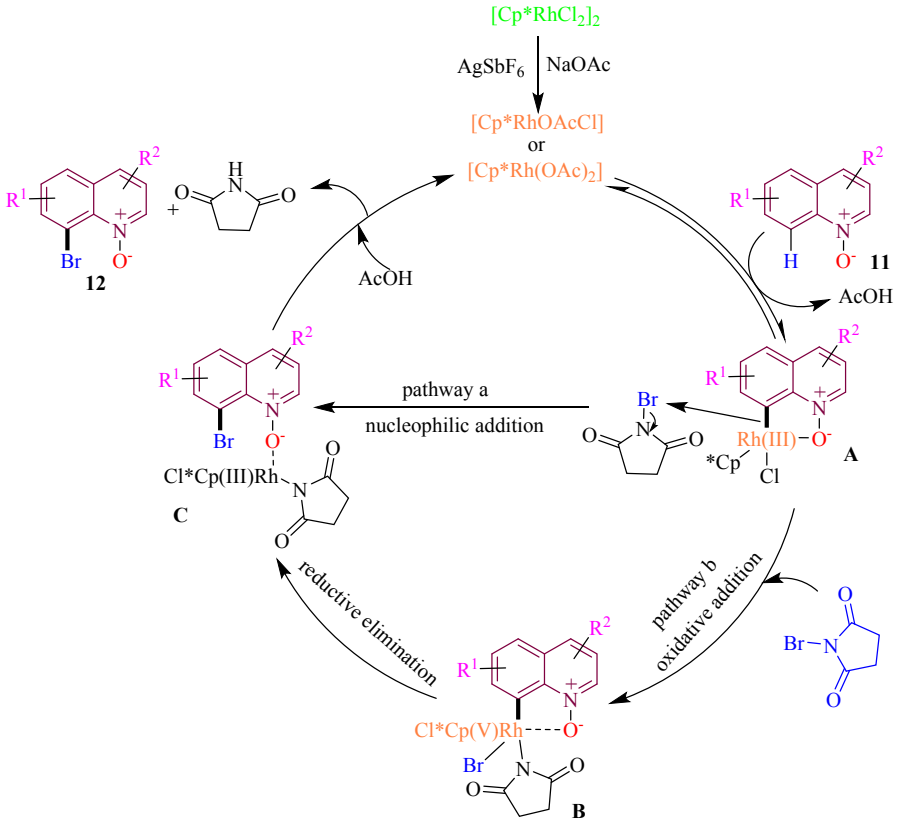


12a, 52% **12b,** 64% **12c,** 41% **12d,** 84% **12e,** 74%

Proposed mechanism



Scheme 6. Rh(III) mediated highly regioselective C-Br formation of quinoline *N*-oxide through C(8)-H activation.

Next, in 2024, Zhou *et al*. reported that C–H iodination of 1-aryl pyridine *N*-oxides, facilitated by $Pd(OAc)_2$, occurred under electrochemical oxidation conditions using I_2 as the iodine source (**Scheme 7**). The reaction involved isoquinoline *N*-oxides with *para* or *meta*-substituted aryl groups at 1-position yielded the corresponding iodinated products. Electron-donating groups on the aryl ring enhanced the reaction, producing relatively high product yields. The reaction is considered to proceed through the mechanistic pathway where the palladium catalyst cleaved the *ortho*-C−H bond at 1- or 3-position to form a palladacycle, which then reacted electrochemically generated I^+ and produced the final products.[53]

C–H iodination

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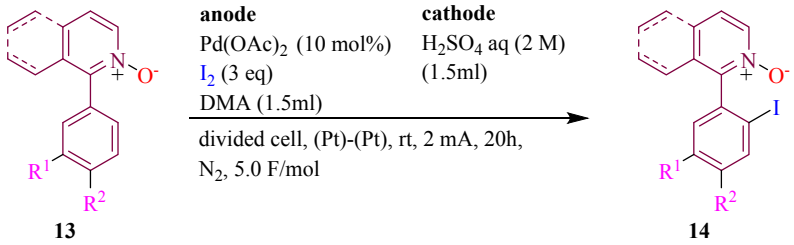
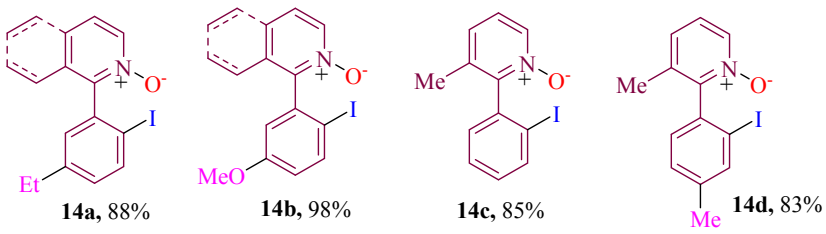
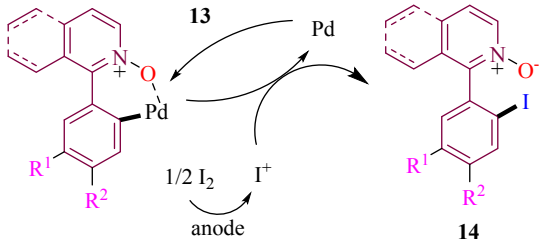


Representative examples



Proposed mechanism



Scheme 7. Palladium assisted electrochemical iodination of 1-arylpyridine *N*-oxides

2.3. Amide and Weinreb amide as directing group

Amides are essential functional groups in numerous natural products, polymers, agrochemicals, drug molecules, and synthetic intermediates.[54] Due to their planar geometry and the high degree of delocalization of the nitrogen lone pair, amide bonds exhibit notable stability compared to other functional groups. The use of substituted or unsubstituted amide-based directing groups in C–H functionalization was first introduced by Li *et al.* in 2012. This approach gained momentum because the simple directing group operates through a monodentate binding mode and effectively controlling reactivity, stereoselectivity, and regioselectivity.[55,56] The activity of the amide group is attributed to the carbonyl moiety, which facilitates C–H bond activation by forming an intermediate cyclometallated complex that enables the synthesis of the desired products. Secondary and tertiary amide functionalities have been extensively employed as directing groups for site-selective functionalization of target molecules' C–H bonds. As a result, amide functional groups are regarded as highly significant and frequently used weak-coordinating directing groups in C–H functionalization chemistry.

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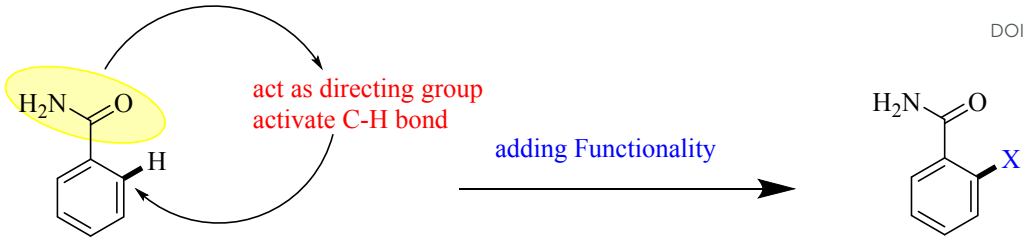
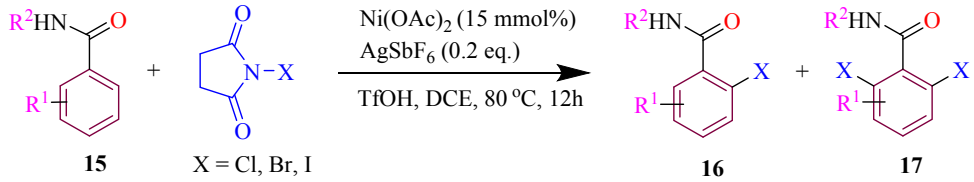


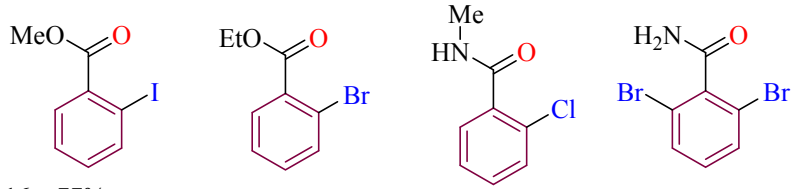
In 2019, Li *et al.* employed this strategy for C–H bond activation to synthesize various regioselective halogenated derivatives of electron-deficient arenes including benzamides, benzoic esters, and sulphonamides. Under optimized reaction conditions, where $Ni(OAc)_2$ was used as a catalyst, NXS (X = Cl, Br, I) served as the halogenating agent and TfOH acted as an acid additive which afforded satisfactory yields (**Scheme 8**). Encouraged by these results, the synthesis was extended to other di-halogenated derivatives of electron-deficient arenes that also achieving moderate to good yields. The amide directing group activated the C–H bond by forming a chelate complex with nickel catalyst, which further underwent oxidative addition with *N*-halosuccinimide followed by reductive elimination to afford the desired products.[57]

Regioselective halogenation



15 X = Cl, Br, I **16** **17**

Representative examples



16a, 77% **16b,** 70% **16c,** 71% **17,** 75%

Proposed mechanism

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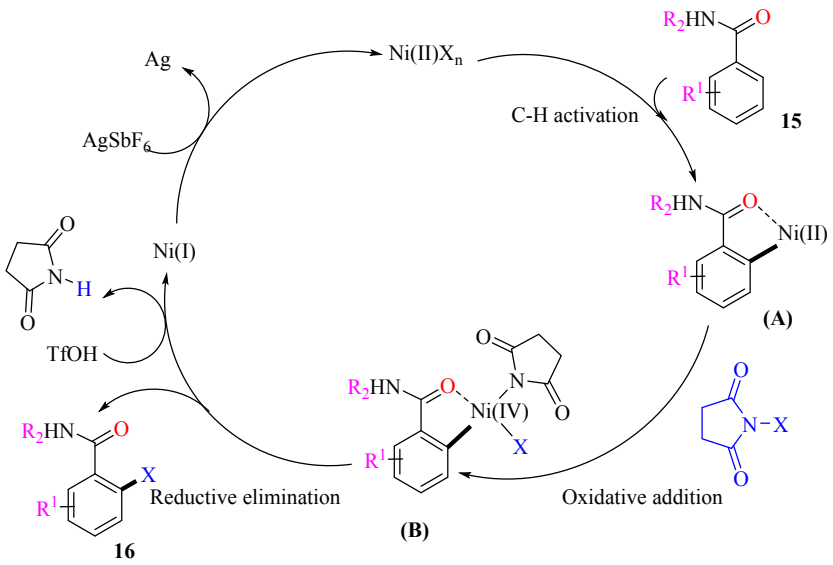
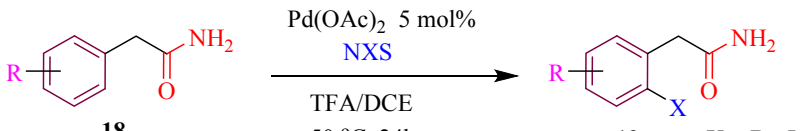


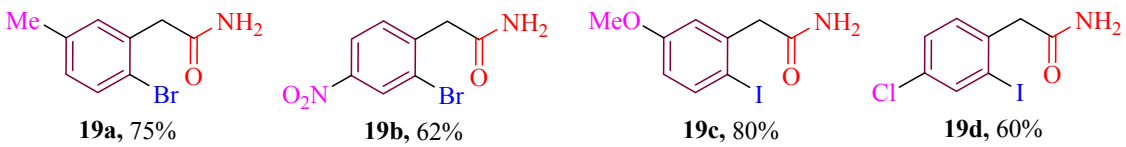
Scheme 8. Ni(II)-catalyzed halogenation of benzamide

Addition to this, Jaiswal *et al*. reported a regioselective *ortho* C–H bromination and iodination methods for challenging aliphatic arylacetamide derivatives, utilizing *N*-halosuccinimides as halogenating agents. This protocol represented the first example of direct bromination and iodination of arenes with primary amide group, achieved using palladium(II) salts without the need for bulky auxiliaries (**Scheme 9**). Various mechanistic studies indicated that the reaction proceeded through *in situ* generation of imidic acid from primary amides under Brønsted acidic conditions. This process likely facilitated the formation of six-membered metallacycles, where the nitrogen atom coordinated with palladium(II), aiding in forming C–X bonds. The critical role of trifluoroacetic acid (TFA) was also identified where it acted as an activator for *N*-halosuccinimides through protonation and assisted in amide's tautomerization process to imidic acid.[58]

***ortho*-halogenation**



Representative examples



Proposed mechanism

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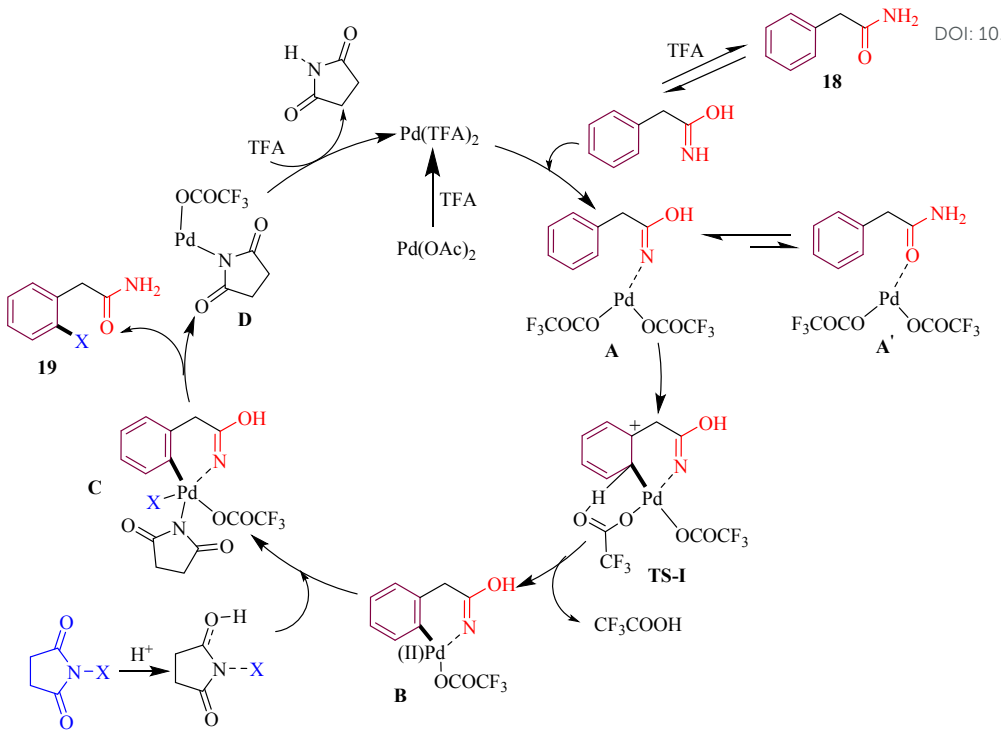
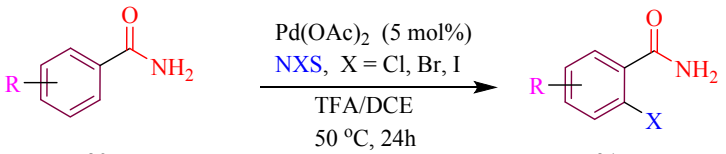


Scheme 9. Palladium-catalyzed *ortho* C−H bromination/iodination of aliphatic amides.

Kumar's group developed a method for regioselective halogenation (Br, Cl, and I) of aromatic ring of benzamide derivatives, using a Bronsted acid-promoted palladium(II) catalyst (**Scheme 10**). This methodology was effectively carried out with the primary amides, demonstrating compatibility with various benzamides under the established conditions, leading to the formation of halogenated products without the need for an external auxiliary. Based on a series of control experiments, the proposed mechanistic pathway has been followed which involved the coordination of imidic nitrogen atom where base-assisted internal electrophilic substitution (BIES) led to regioselective C–H activation, resulting in formation of thermodynamically favoured five-membered palladacycle. In this protocol, TFA played three critical roles; (1) facilitating the tautomerization of the amide to imidic acid, (2) activating *N*-halosuccinimide through protonation, and (3) regenerating the palladium salt.[59]

Regioselective halogenation



Representative examples

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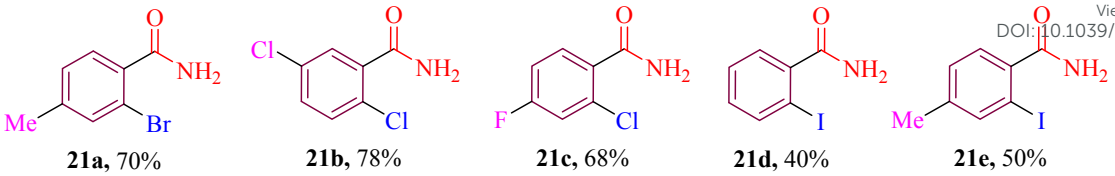
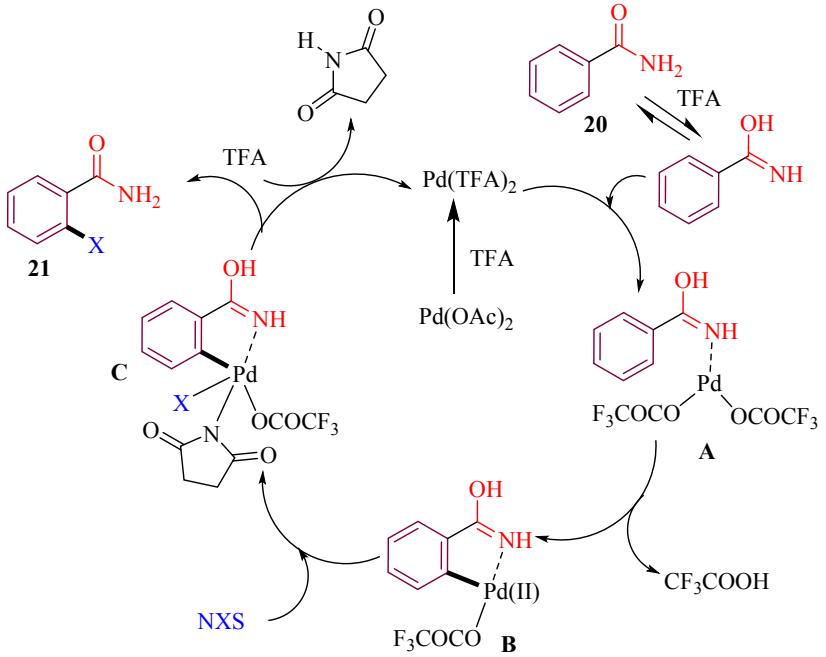


Proposed mechanism



Scheme 10. Bronsted acid promoted palladium-catalyzed *ortho* C−H halogenation of benzamides

In 2020, Ison group explored catalytic C–X bond formation and synthesized *ortho*-halogenated derivatives of tertiary benzamides, especially, *N,N*-diisopropylbenzamide. Under optimized reaction conditions involving $[Cp^*IrCl_2]_2$, AgOTf and AcOH, in 1,2-dichloroethane at 60 °C for 1 h, various iodinated derivatives were developed with good tolerance for both electron-donating and electron-withdrawing groups at the *para*-position (**Scheme 11**). Substrates with electron-donating groups yielded better results than those with electron-withdrawing groups. Brominated derivatives of the same substrates were synthesized by increasing the catalyst loading to 6 mol% and extending the reaction time to 4 h. Two possible mechanisms were proposed for the halogenation step, differing in the halogen source. The first mechanism involved direct functionalization with *N*-halosuccinimide (NXS), while the second suggested functionalization *via* acetyl hypohalite, generated *in situ* through an off-cycle equilibrium between acetic acid and halosuccinimide. Coordination of the acetyl hypohalite to the iridium center facilitated product formation *via* reductive elimination. This different approach of reaction pathway is quite interesting to be considered for further development of halogenated aromatic compounds.[60]

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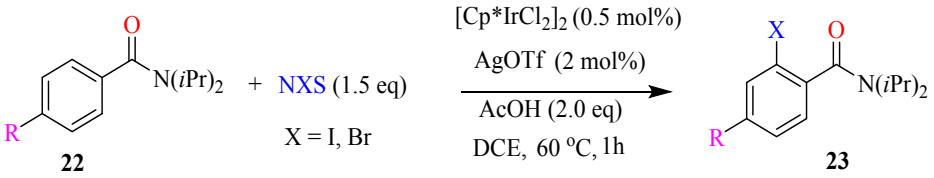
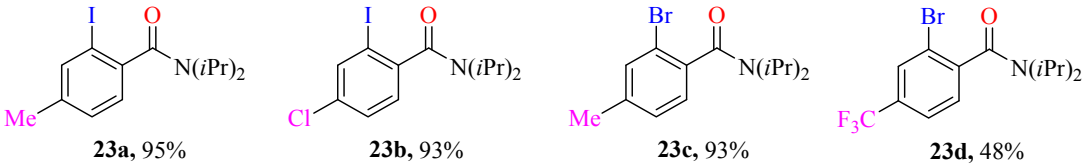
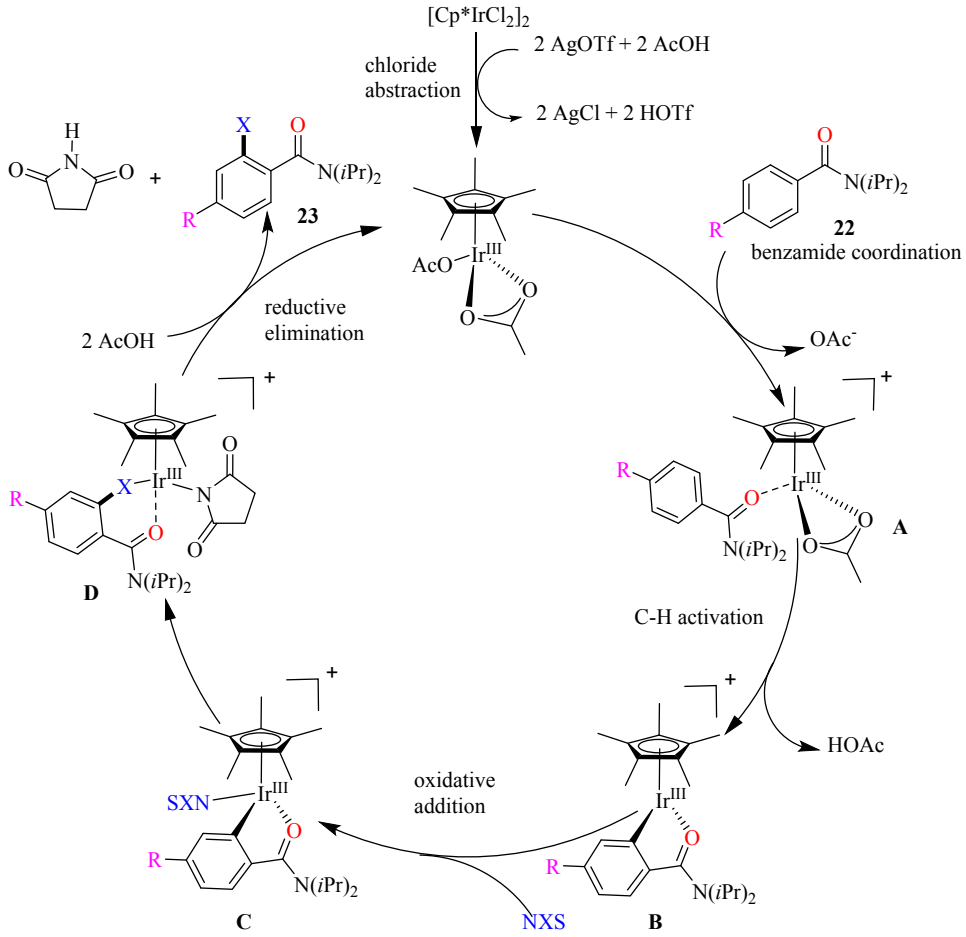
ortho-halogenation



Representative examples



Proposed mechanism



Scheme 11. Ir-catalyzed iodination and bromination of *tert*-benzamides.

Tanaka *et al.* reported a pioneering rhodium-catalyzed method for regioselective bromination of *O*-phenyl carbamates. The reaction is accelerated by secondary amide pendant cyclopentadienyl ligand due to hydrogen bond between the acidic NH group of the ligand and the carbonyl group of NBS (**Scheme 12**). This strategy demonstrated good functional group

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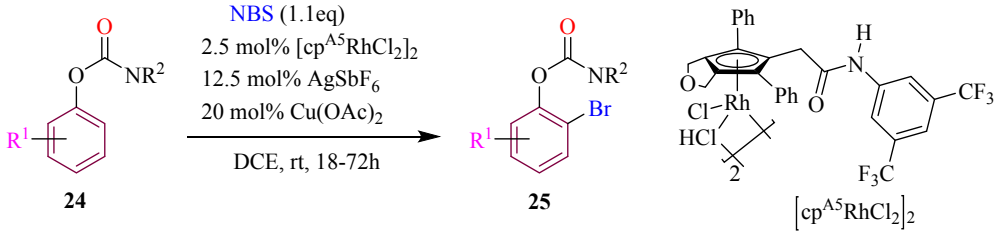
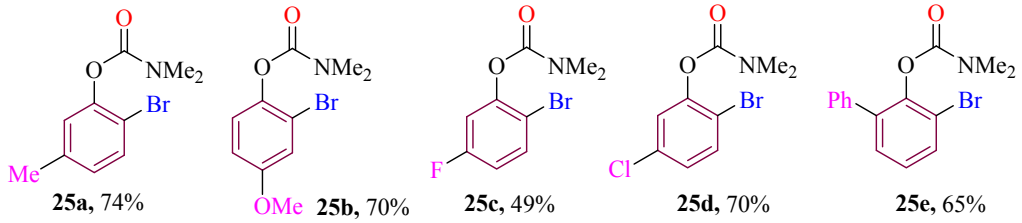
tolerance on aromatic rings, producing *ortho*-brominated product in satisfactory yields. Various mechanistic insights and DFT calculations were elucidated for possible catalytic cycle. In this cycle, the cleavage of the C−H bond with acetoxy ligand in intermediate **A** produced aryl rhodium **B** followed by coordination with *N*-bromosuccinimide (NBS) to form intermediate **C**. A concerted bromine transfer occurred through the transition state **TS-CD**, resulting in the formation of intermediate **D**. The subsequent formation of Rh-N bond yielded rhodiumamide **E**. Coordination of substrate **24** then released product **25** and generated rhodiumamide **F**. However, an alternative pathway might also exist in the catalytic cycle, where the C−H bond of **24** is cleaved with the succinimidyl ligand in **F**, creating aryl rhodium **C** *via* intermediate **G**.[61]

Regioselective bromination



Representative examples



Proposed mechanism

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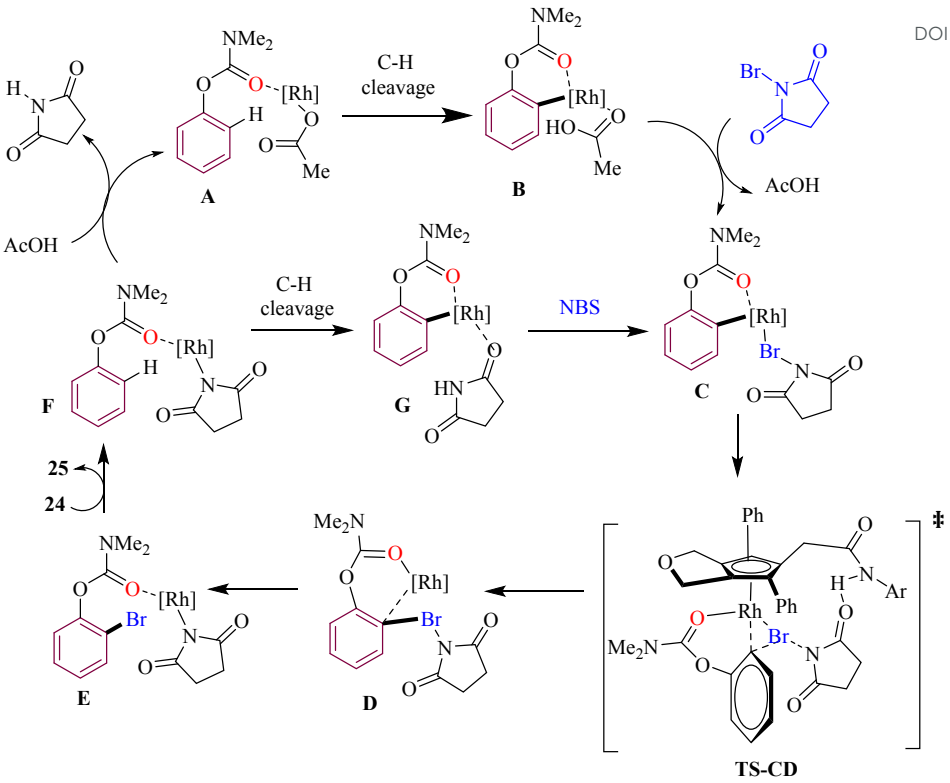
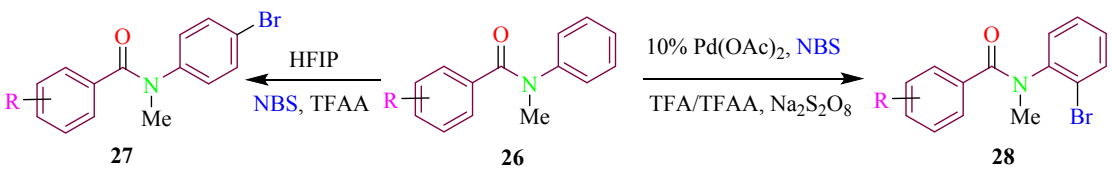


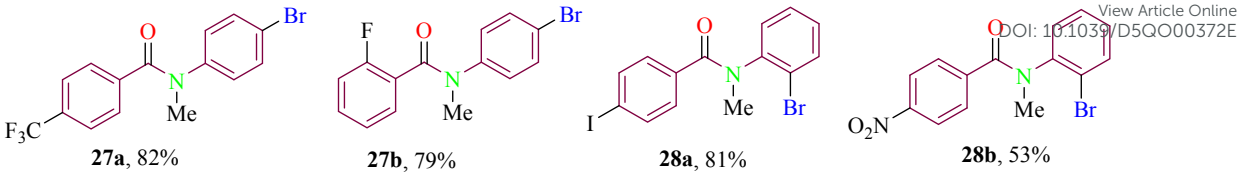
Scheme 12. Rhodium-catalyzed carbamate directed *ortho* C−H bromination of *O*-phenyl carbamates.

Recently, Sun *et al*. reported the regioselective synthesis of brominated derivatives of benzanilide guided by the amide bond as a directing group. The study demonstrated that different brominated regioisomers could be achieved by modulating site-selectivity through promoter choice (**Scheme 13**). The reaction conditions were optimized and applied to various functionalized substrates, with Pd(II) and HFIP as promoters, yielded the desired products efficiently. Detailed mechanism for *para*-bromination proposed in **Scheme 13** whereas *ortho*-bromination follows the general mechanistic pathway proceeding through C–H bond activation, oxidative addition and reductive elimination.[62]

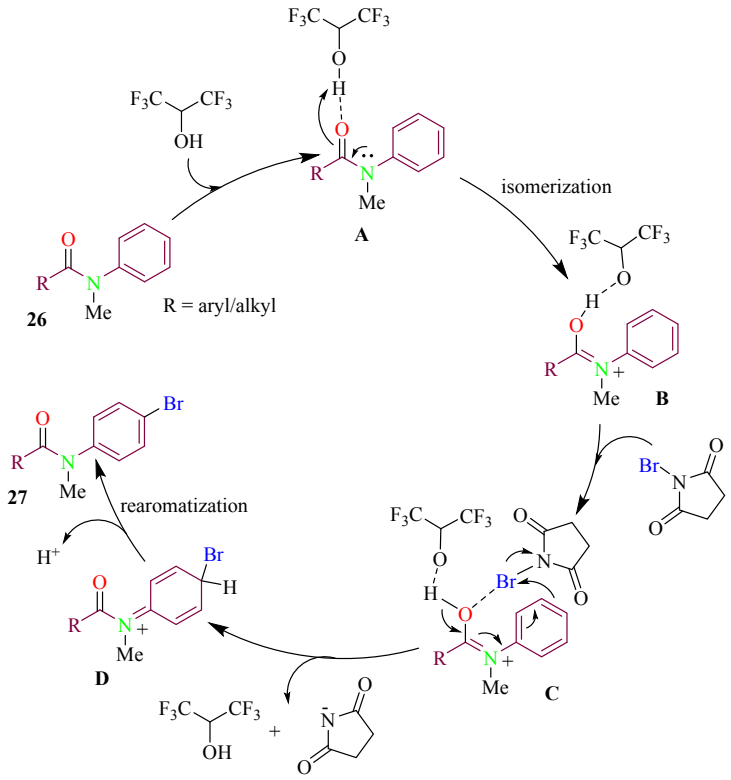
Brominated benzanilide



Representative examples



Proposed mechanism



Scheme 13. Switchable site-selective bromination of benzanilide

Weinreb amides (*N*-methyl-*N*-methoxyamides) are valuable intermediates in synthetic chemistry due to their distinct reactivity. Typically, the acyl group in the amide directs the metal during C–H activation. However, their weak coordination properties make them challenging substrates for C–H activation reactions.[63] These moieties utilized the labile N–O bond as an internal oxidant during C–H activation, eliminating the need for an external oxidant. Weinreb amides are readily synthesized from carboxylic acids, their chlorides, esters, aldehydes, or ketones, making them versatile and accessible building blocks in organic synthesis.

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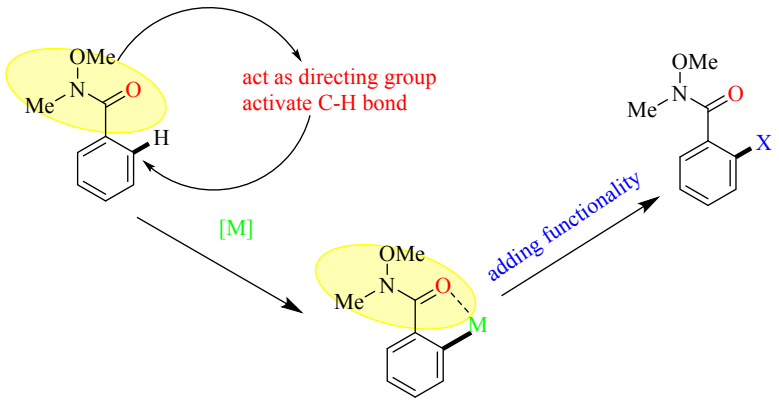
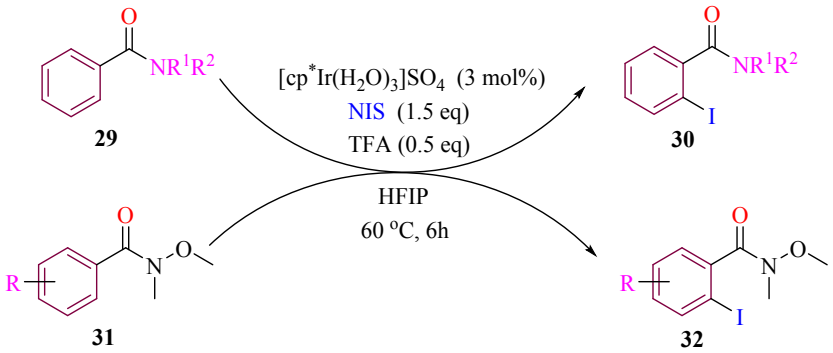
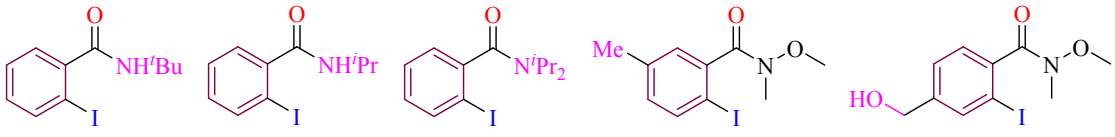


Matute group recently developed a method for selective *ortho* C–H iodination of Weinreb amides and benzamides. The approach employed iridium as a catalyst and *N*-iodosuccinimide (NIS) as the iodinating agent, with acid as a promoter (**Scheme 14**). The iodination reaction was conducted using mechanochemical methods, which reduced the reliance on HFIP, shorten reaction time, and eliminated the need for consecutive additions of NIS. This alternative approach delivered comparable or even improved yields and selectivity. The introduction of iodine provides a versatile handle for wide range of downstream functionalizations.[64]

***ortho*-iodination**



Representative examples



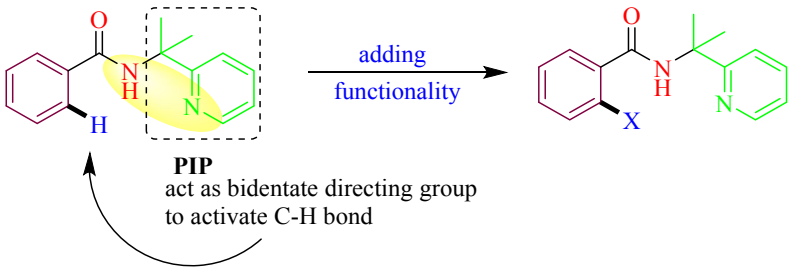
30a, 72% **30b,** 70% **30c,** 89% **32a,** 94% **32b,** 66%

Scheme 14. Iridium-catalyzed regioselective C−H iodination of benzamides and Weinreb amides

2.4. 2-(Pyridine-2-yl)isopropylamine (PIP) as directing group

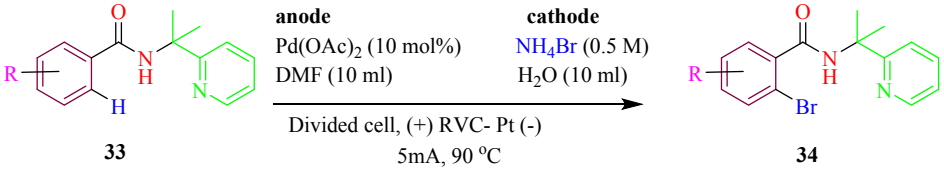
Inspired by the structure of aminoquinoline, researchers recognized the importance of an anionic binding site and a strongly coordinating neutral site in activating methylene C−H bonds. Leveraging the Thorpe-Ingold effect, which facilitated cyclometalation through bond

angle compression and entropic constraint, the 2-(pyridine-yl)isopropylamine (PIP) was designed as a directing group (DG). This DG features a *gem*-dimethyl group and a pyridyl group, which upon transformation into the corresponding PIP amide, enables selective *β* C−H activation. Additionally, modifying the two methyl groups into distinct functional groups or replacing the pyridyl group with a chiral oxazoline offers potential for creating chiral auxiliaries, paving the way for asymmetric C−H functionalization. The versatility of PIP as a bidentate directing group lies in its ability to be readily removed post-reaction *via* a nitrosylation/hydrolysis sequence or under acidic conditions.[65] Since its introduction, PIP has shown immense potential for directing C−H functionalization, demonstrating compatibility with various transition-metal catalysts such as Ni, Cu, Co, and Pd.



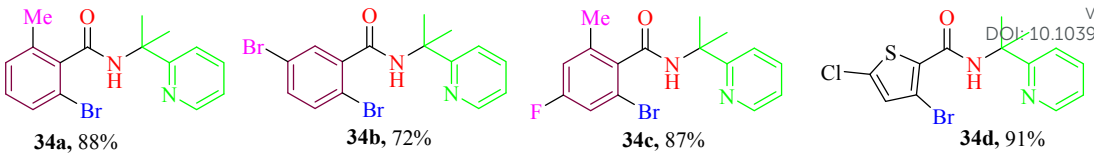
In 2019, Mei and co-workers employed a fascinating approach, forming a C–Br bond by activating the C–H bond of benzamide derivative with the assistance of optimal PIP directing group, guided by a versatile palladium redox catalyst which could operate under various cycles and oxidation states in a divided cell (**Scheme 15**). In this transformation, NH_4Br served not only as the brominating agent but also acted as the electrolyte, enabling the successful synthesis of arene derivatives substituted with diverse, well-tolerated functional groups at various positions, with yields ranging from good to excellent. The proposed mechanistic pathway involved the coordination of palladium with benzamide, which further proceeded through palladation, delivering Br_3^- or Br_2 generated *in-situ* to high-valent Pd species, followed by reductive elimination, resulting in brominated product after ligand exchange.[66]

Regioselective bromination

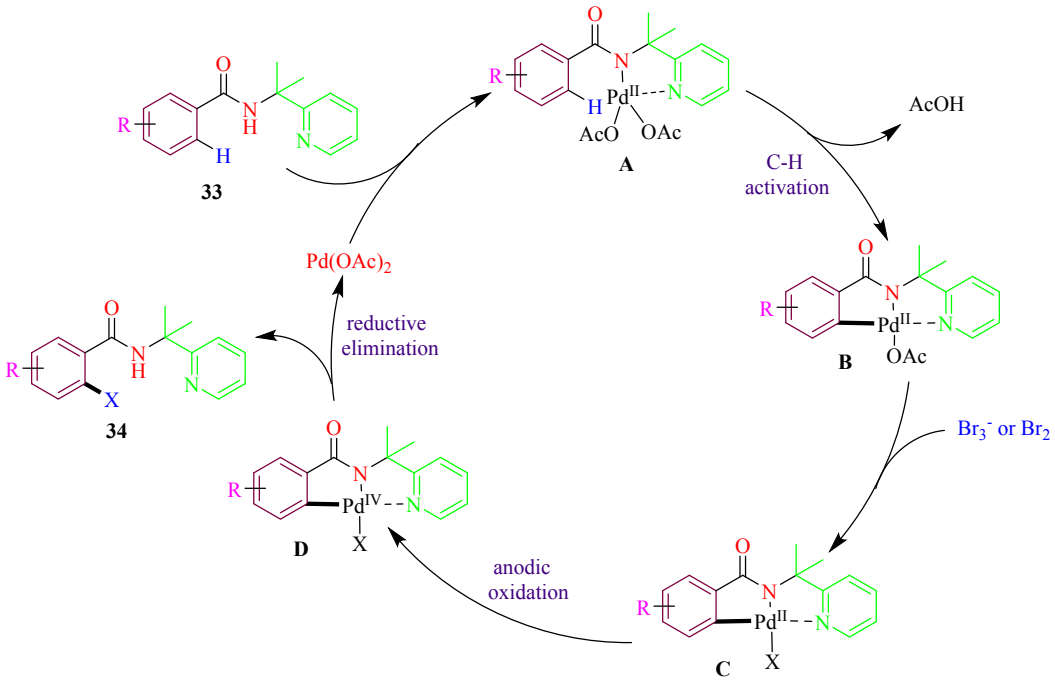


33 34

Representative examples



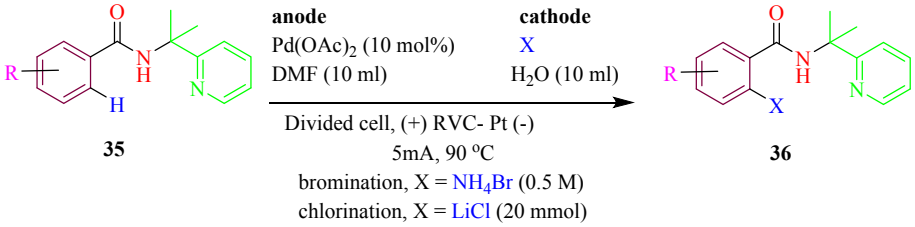
Proposed mechanism



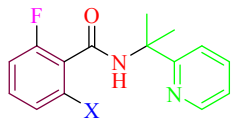
Scheme 15. Bromination of substituted arenes directed by PIP using electrochemical setup

Similar to this, Mei group in 2020, performed the same methodology as above for chlorination and bromination of benzamide derivatives possessing PIP as directing group where NH_4Br and LiCl acted as electrolytes as well as brominating and chlorinating agents, respectively (**Scheme 16**). However, the reaction proceeded through a catalytic cycle involving the coordination of benzamide derivative with palladium catalyst, activating *ortho* C–H bond, *in situ* generation of Br_3^- or Br_2, followed by reductive elimination to afforded the desired brominated product.[67]

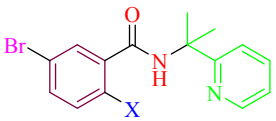
Chlorination and bromination



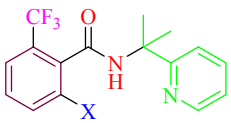
Representative examples



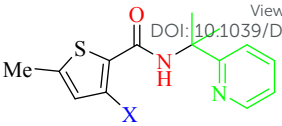
36a
X = Cl (81%), Br (95%)



36b
X = Cl (66%), Br (72%)

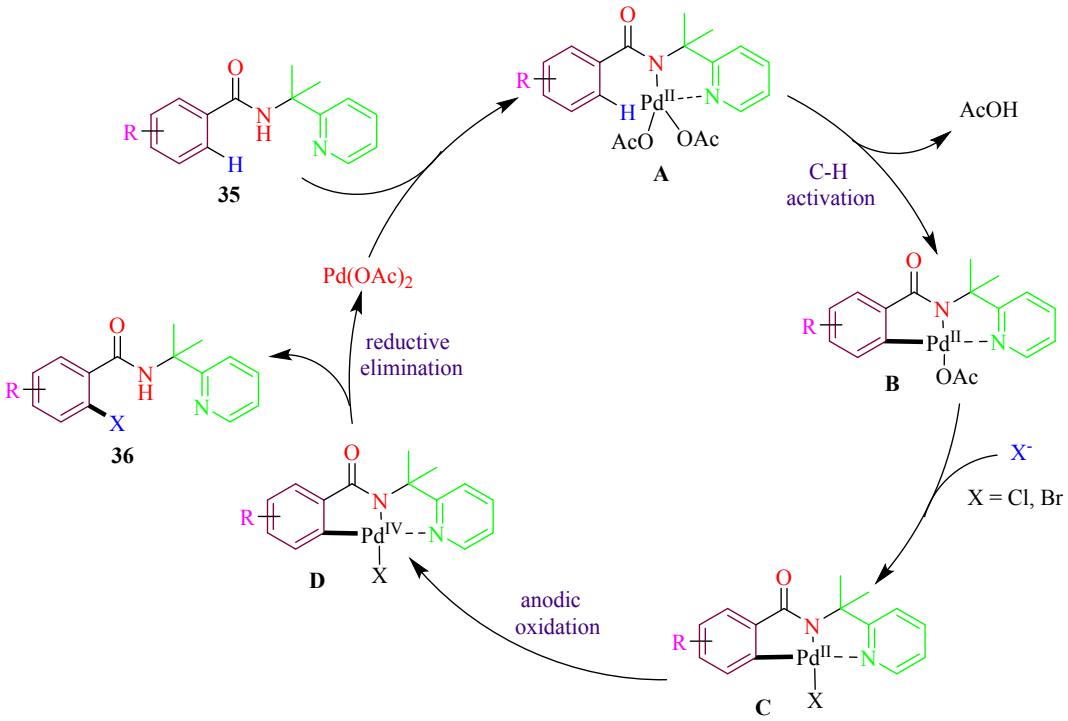


36c
X = Cl (78%), Br (78%)



36d
X = Cl (85%), Br (93%)

Proposed mechanism



Scheme 16. Chlorination and bromination of substituted benzamide directed by PIP using electrochemical setup

2.5. Pyridine as directing group

Murai and Chatani pioneered the use of pyridine as a directing group in C–H functionalization, a breakthrough that has since been expanded by various research groups. Pyridine has become a key player in C–H functionalization due to its simplicity and the ease of its incorporation into aliphatic chains or aromatic rings through diverse methods. However, when pyridine is attached *via* a carbon-carbon (C–C) bond, its removal from the substrate is not feasible; cleavage is only possible when the attachment involves a carbon-heteroatom bond.[68] Although significant progress has been made in C–C bond formation chemistry, methods for C–X bond formation remain underdeveloped.

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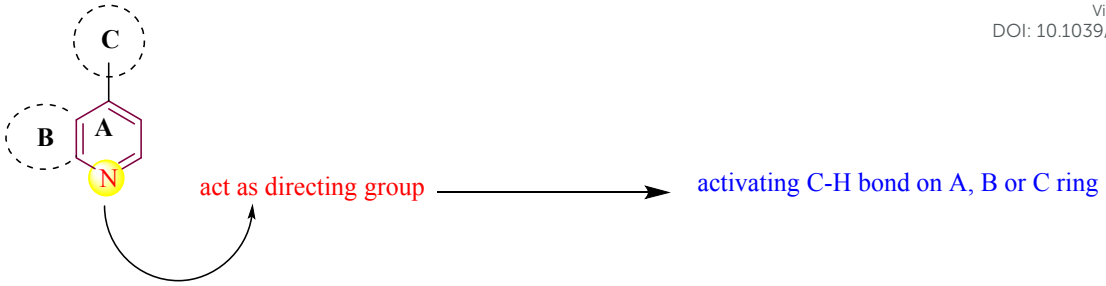
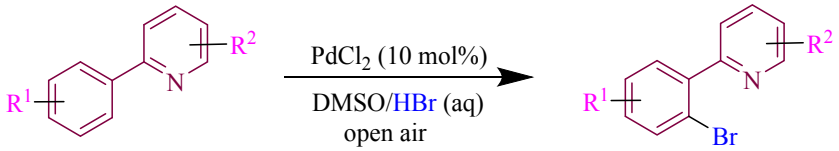


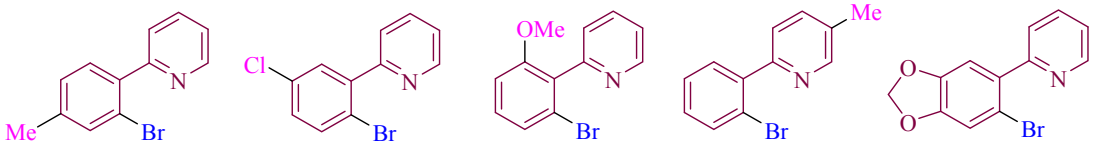
In 2019, Jiao group developed an efficient method for Pd-catalyzed directed *ortho* C–H bromination of arenes utilizing pyridine directing group in which dimethyl sulfoxide (DMSO) was employed as an oxidant with hydrobromic acid (aq) as bromide source (**Scheme 17**). The optimized method was evaluated for its substrate scope that successfully produced brominated 2-phenylpyridines with good to excellent yields and high selectivity. Various control experiments were performed to gain insight into the mechanistic pathway, revealing the coordination of directing group to Pd(II) centre, followed by C–H activation, cleavage of Pd-C bond through brominating agent $[(DMSO)_nBr^+(DMS)]Br^-$, which was formed under acidic conditions. Finally, the product dissociated from Pd(II) centre, regenerating Pd(II) catalyst and completing the catalytic cycle.[69]

Brominated arenes



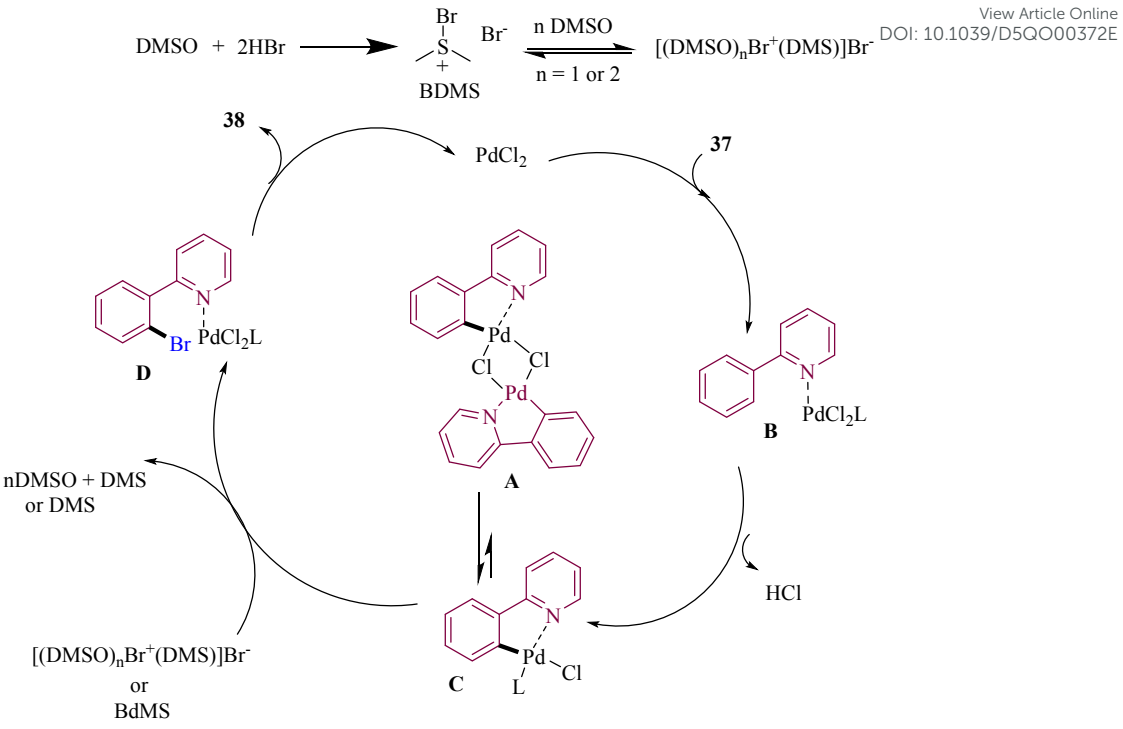
37 **38**

Representative examples



38a, 89% **38b**, 71% **38c**, 94% **38d**, 96% **38e,** 81%

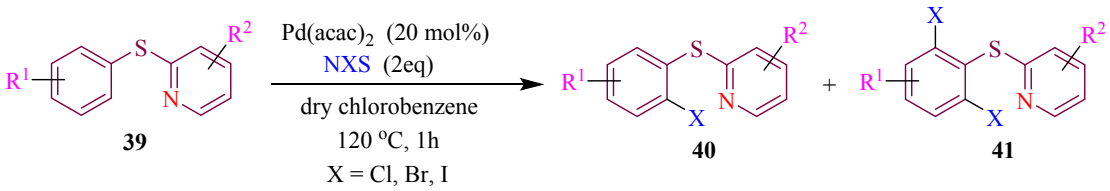
Proposed mechanism



Scheme 17. Pd-catalyzed *ortho* C−H bromination of arenes directed by pyridine

Guilbaud *et al*. introduced a method for palladium-catalyzed, pyridyl-directed selective oxidative *ortho* C−H halogenation of S-unprotected aryl pyridyl sulfides (**Scheme 18**). This approach avoids both sulfur oxidation and direct electrophilic halogenation of pyridine moiety, enabling rapid reactions (85% yield in just 40 minutes). This represents a significant improvement over slower C−H halogenation methods that rely on S-oxidized pyridyl sulfoxides and sulfones. The new methodology enabled the direct functionalization of C−H bonds in sulfides and eliminated the need for reduction steps or protection/deprotection of sulfoxides and sulfones, which could be challenging due to their high thermodynamic stability. The reactions were carried out under strictly anhydrous conditions in chlorobenzene, using a controlled amount of halosuccinimide or PIDA as the halogen source. This approach allows for both mono- and *ortho*-dihalogenation of highly functionalized pyridyl aryl sulfides, offering a versatile tool for halogenation in complex molecular settings.[70]

***ortho*-halogenation**



Representative examples

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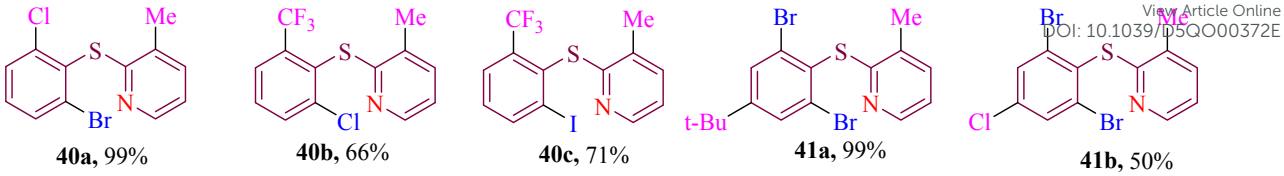
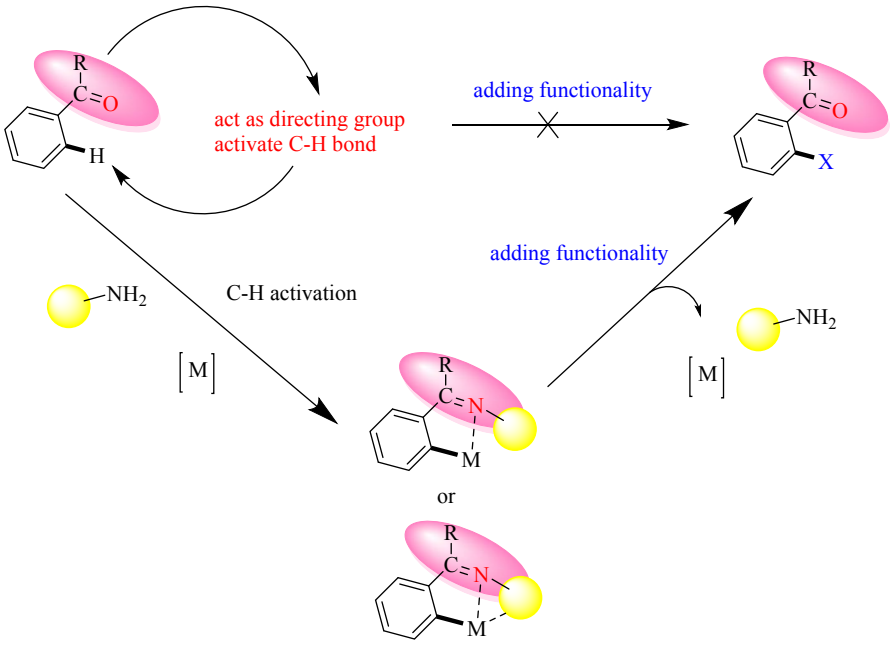


40a, 99% **40b,** 66% **40c,** 71% **41a,** 99% **41b,** 50%

Scheme 18. Direct C−H halogenation of pyridyl sulfides

2.6. Aldehyde and ketone as directing groups

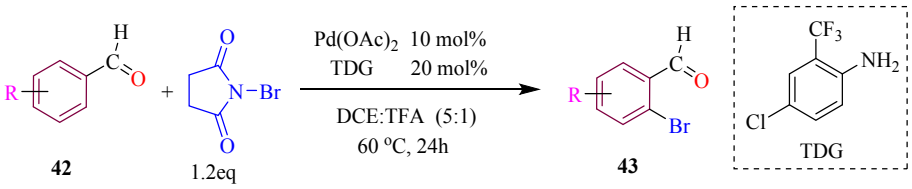
Reactive functional groups such as aldehydes and ketones present significant challenges in C–H functionalization, spurring innovative research into more efficient strategies through transient directing group strategy. One such approach leverages amines to form an imine *in situ*, which acts as a directing group (DG) during the reaction.[71] This imine can serve as either a monodentate or bidentate ligand, facilitating the crucial C–H activation step.[72] Subsequently, metal-catalyzed C–H functionalization occurs on the imine derivative, yielding a newly functionalized product while regenerating the amine. This strategy, referred to as the Transient Directing Group (TDG) approach, simplifies the C–H activation process by eliminating the need for additional DG installation or removal steps, significantly enhancing the overall efficiency and practicality of the method.



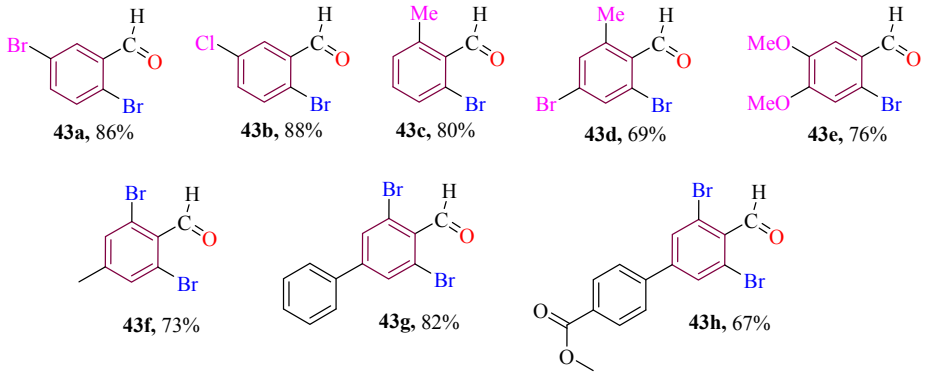
In 2019, Yonga *et al.* utilized the monodentate transient directing group strategy by employing 2-amino-5-chlorobenzotrifluoride to generate *in situ* an imine which facilitated the development palladium-catalyzed regioselective C–H bromination of benzaldehydes under

mild reaction condition without the requirement for an external ligand or silver salts (**Scheme 19**). The protocol was compatible with various electron-donating and electron-withdrawing groups, delivering good to excellent yields of conjugates. Additionally, the strategy was also explored to obtain dibrominated benzaldehyde derivatives, achieving excellent yields when the loading of NBS was increased from 1.5 to 2.5 equivalents.[73]

Regioselective bromination



Representative examples



Scheme 19. Palladium-catalyzed *ortho* C−H bromination of benzaldehydes

Zhang group developed an efficient method for chlorination utilizing *N*-chlorosuccinimide (NCS) to functionalize a variety of substituted benzaldehydes, achieving high yields (**Scheme 20**). By utilizing 4-trifluoromethylaniline as a transient directing group, in combination with a pyridone ligand, the chlorination of benzaldehydes was carried out with excellent yields. The reaction demonstrated broad functional group tolerance, accommodating nitrile, ester, and sulfonamide functionalities on aldehyde component. Furthermore, a celecoxib derivative could undergo chlorination at a late-stage transformation, where the imine directing group took precedence over any other coordinating functionalities on the substrate. Pyrroles, indoles, and benzothiophene carboxaldehydes were also subjected to chlorination; however, these reactions yielded lower results. Additionally, a dimeric palladacyclic intermediate was isolated, which was amenable to chlorination under the standard conditions used in this study.[74]

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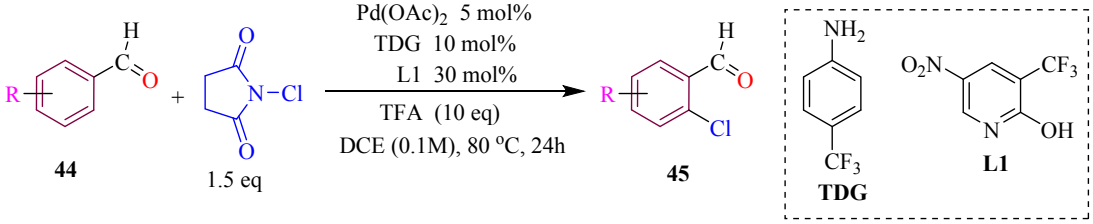
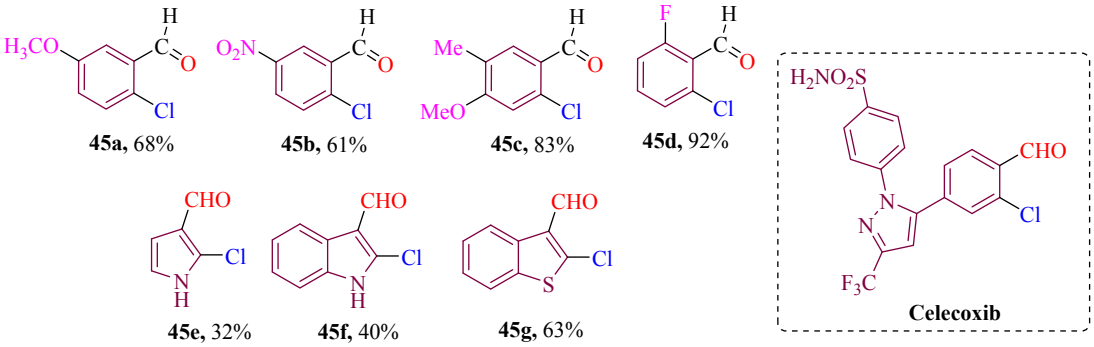
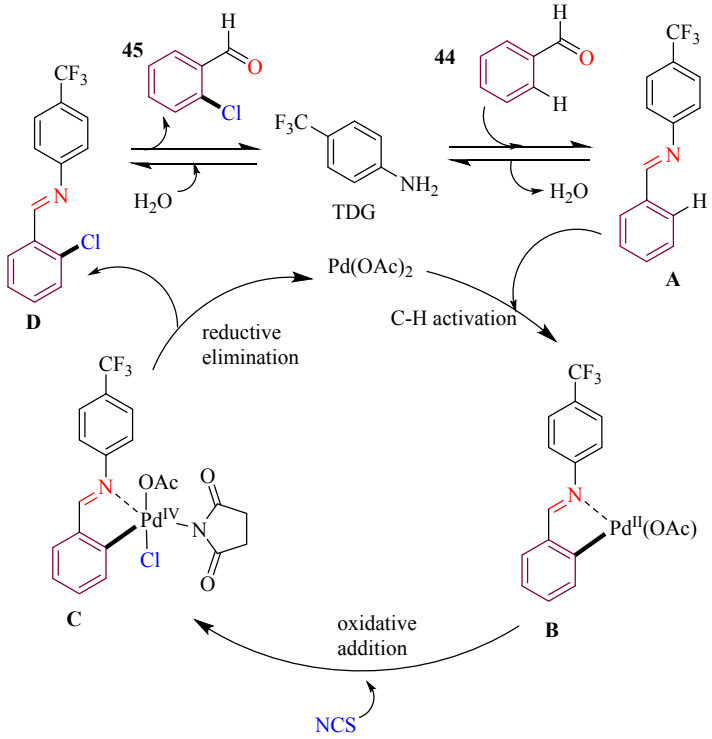
Regioselective chlorination



Representative examples



Proposed mechanism

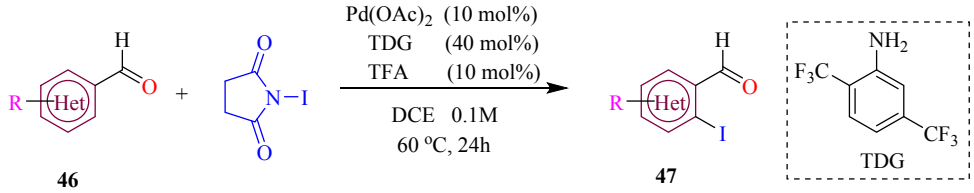


Scheme 20. Palladium-catalyzed *ortho* C−H chlorination of benzaldehydes

In 2021, La *et al*. introduced the first palladium-catalyzed direct *ortho* C−H iodination of benzaldehydes using optimal monodentate transient directing group 2,5-

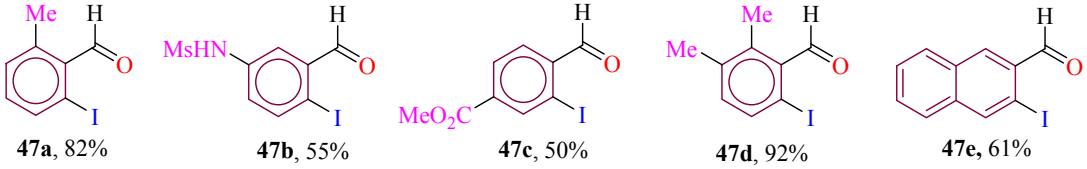
bis(trifluoromethyl)aniline under mild optimized reaction conditions (**Scheme 21**). The method demonstrated broad substrate scope and practicality, with benzaldehydes and heteroaromatic aldehydes reacting well with readily available *N*-iodosuccinimide (NIS) to deliver moderate to good yields. The synthetic utility of this methodology was further showcased in two-step total synthesis of the natural product hernial, involving a subsequent copper-catalyzed cross-coupling reaction. The mechanism involved *in situ* condensation of benzaldehyde with MonoTDG to form a transient imine, which then coordinated with palladium acetate, leading to *ortho* C−H activation, oxidative addition, followed by reductive elimination, formed the iodinated product, regenerating both the transient directing group and the palladium catalyst.[75]

ortho-iodination



46 **47**

Representative examples



47a, 82% **47b**, 55% **47c**, 50% **47d**, 92% **47e,** 61%

Proposed mechanism

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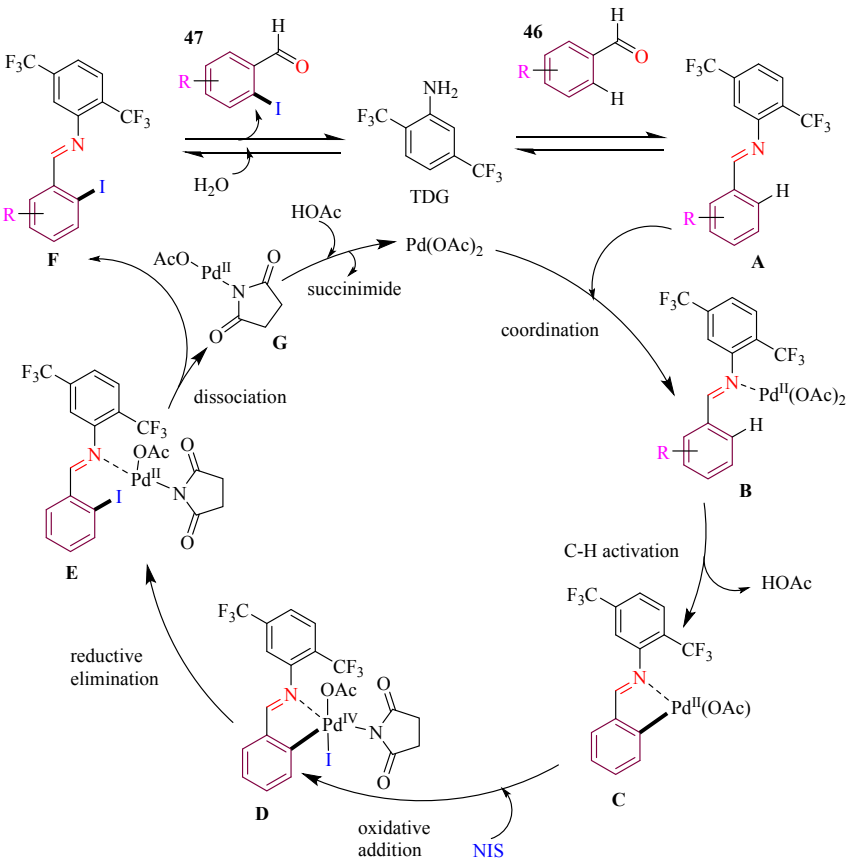
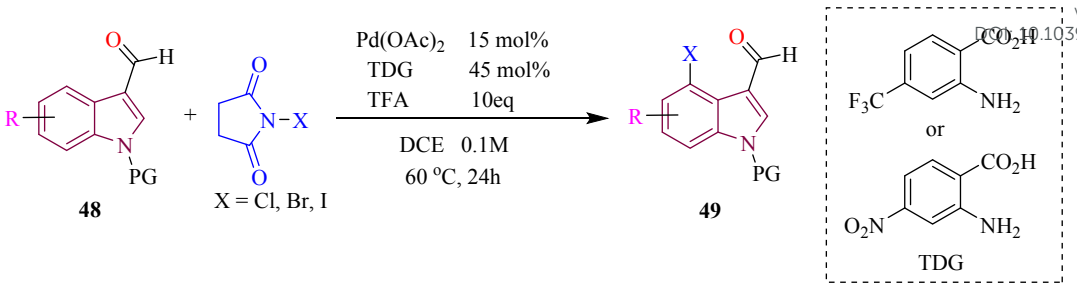


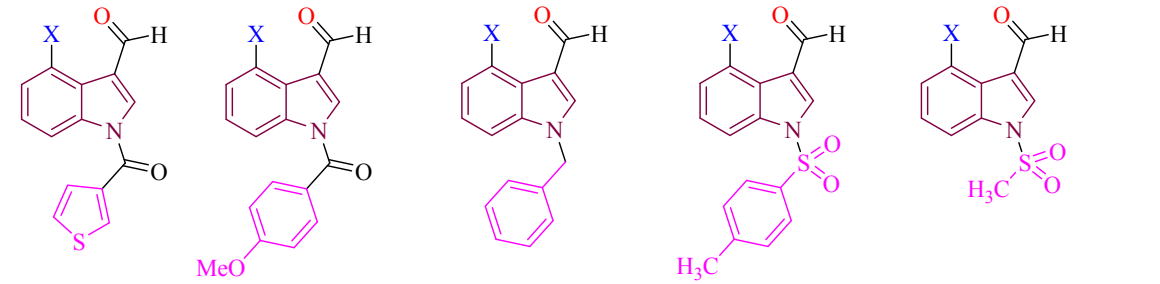
Scheme 21. Palladium catalyzed *ortho* C−H iodination of benzaldehyde and aromatic aldehyde.

In the same year, Zhou and co-workers developed a protocol to direct palladium-catalyzed site-selective C–H chlorination, bromination and iodination of indole-3-carbaldehydes with the assistance of anthranilic acid as a suitable bidentate transient directing group (**Scheme 22**). The optimized reaction condition probed for its substrate scope, delivering desired targets in good to excellent yields, possessing various electron-donating and electron-withdrawing groups without the influence of a protecting group on the reaction. It has been found that adding silver salts improved the yields for bromination but had negligible effect on chlorination and iodination. The protocol's applicability was demonstrated in the total synthesis of lysergic acid, Suzuki, Sonogashira, Stille and Miyaura couplings. The experimental results led to the catalytic cycle where imine is generated *in situ* through condensation, acting as a bidentate coordinating group and coordinating with the palladium centre.[76]

Halogenated indole-3-carbaldehydes

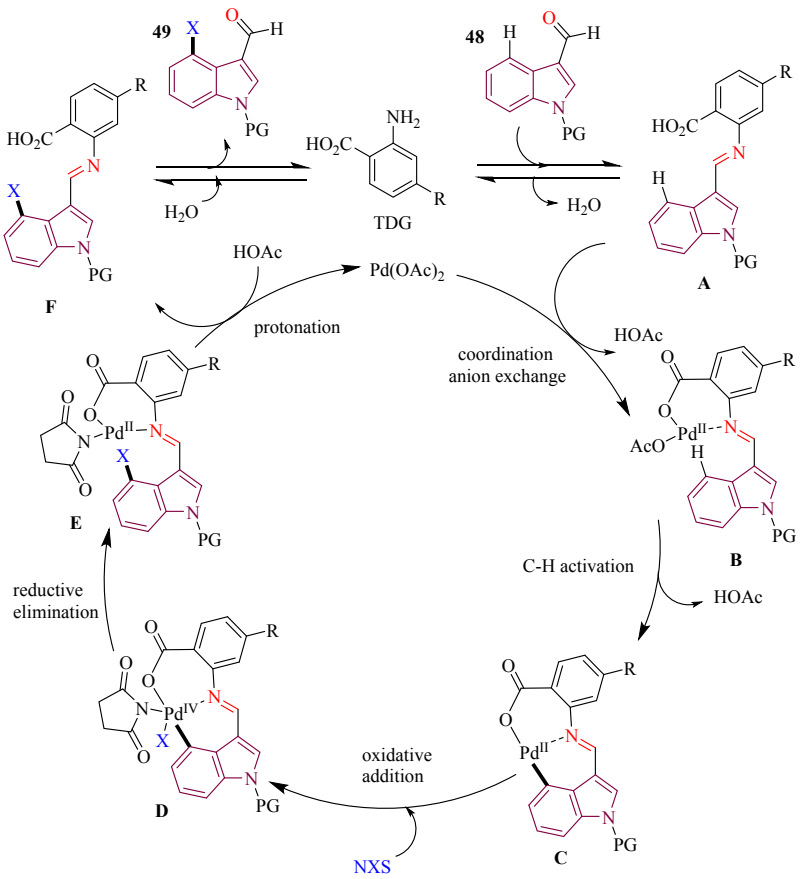


Representative examples



49a, X= Cl (68%) Br (76%) I (45%)
49b, X= Cl (65%) Br (50%) I (45%)
49c, X = Cl (85%) Br (76%) I (54%)
49d, X = Cl (83%) Br (61%) I (53%)
49e, X = Cl (84%) Br (53%) I (56%)

Proposed mechanism



Scheme 22. Site-selective C−H halogenation of indole-3-carbaldehydes

In 2021, Wu *et al*. successfully achieved the *ortho*-fluorination of aromatic ketones utilizing palladium acetate and the additives carbamate and nitrate (**Scheme 23**). This

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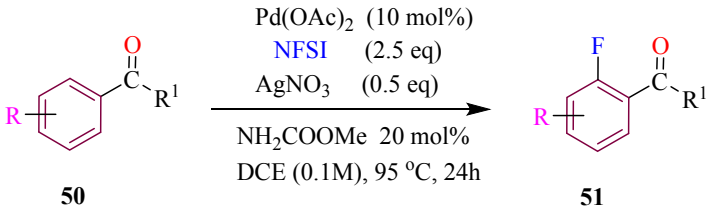
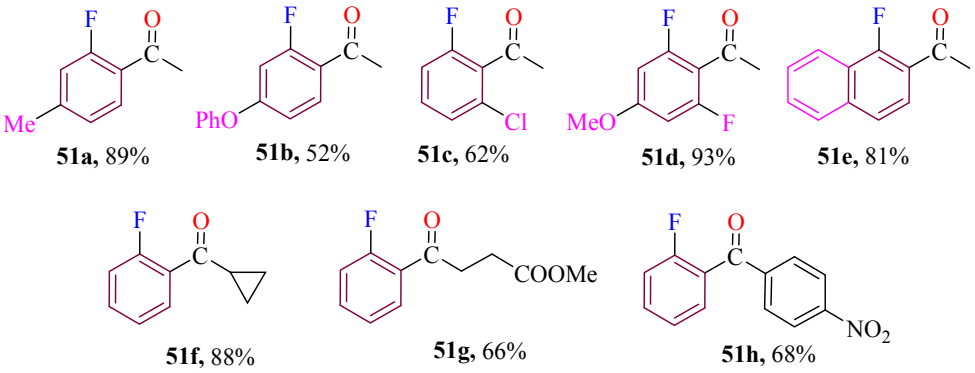
developed protocol showed good tolerance for a variety of electron-donating and electron-withdrawing groups, resulting in good to excellent yields. Additionally, experiments were also conducted without carbamate additive, highlighted its significance in promoting fluorination, as it facilitates the *in- situ* generation of imine during the reaction.[77]

***ortho*-fluorination**



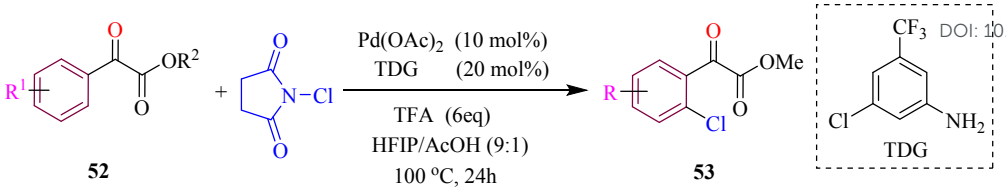
Representative examples



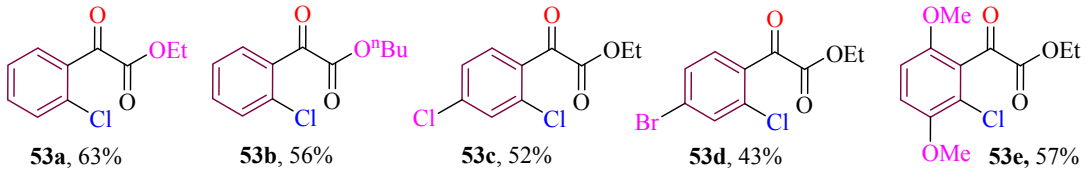
Scheme 23. Palladium-catalyzed *ortho* C−H fluorination of aromatic ketones

Wang *et al.* developed a palladium-catalyzed method for regioselective *ortho* C–H chlorination of α-ketoesters using commercially available aniline as an efficient monodentate transient directing group (MonoTDG) under mild conditions (**Scheme 24**). The strategy was tested on a variety of substituted α-ketoesters, yielding good to excellent results. Remarkably, even in cases where the *ortho*-reactive site was sterically hindered, the C–H chlorination proceeded efficiently with excellent site selectivity, highlighting the robust directing capability of this MonoTDG approach. Based on experimental findings, the proposed catalytic cycle begins with *in situ* condensation of the aryl α-ketoester with TDG to form a transient imine. This is followed by *ortho* C–H activation, oxidative addition, and reductive elimination, ultimately delivering the desired chlorinated products.[78]

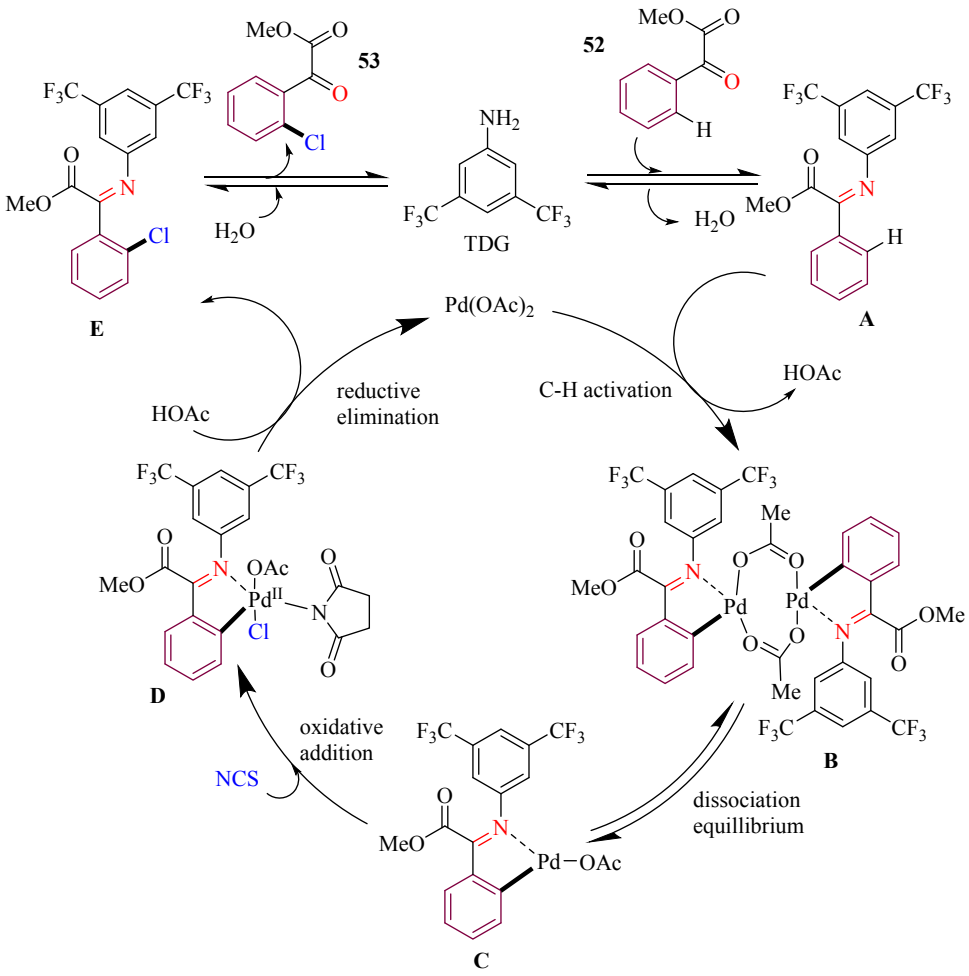
Chlorinated α-ketoesters



Representative examples



Proposed mechanism



Scheme 24. Palladium-catalyzed *ortho* C−H chlorination of *α*-ketoesters

2.7. Carboxylic acid as directing group

Various directing groups are available to achieve C–H activation and further functionalization. The ideal directing group can be considered as omnipresent, small and capable of being easily transformed or removed after C–H functionalization step. Carboxylate group is considered as attractive functionality to fulfil these specifications by regioselective C−H bond activation and

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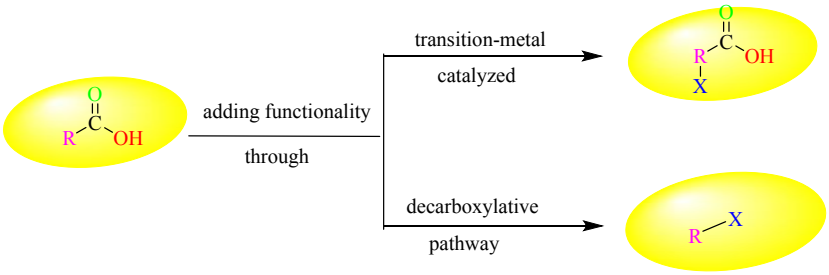
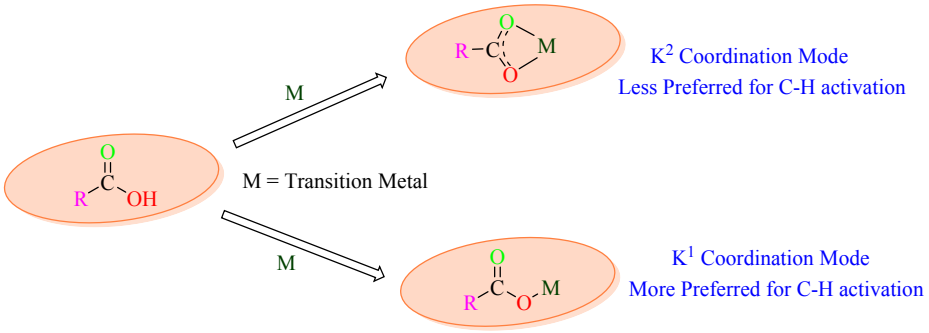
can also act as a traceless directing group. This group shows its versatile activity with its abundance in organic molecules, its ability to be removed CO_2 tracelessly by catalytic extrusion, conversion to other moieties. Additionally, the carboxylate group can act as a leaving group in decarboxylative couplings, facilitating the formation of C–C or C–X bonds at the *ipso* position.[79] Although the carboxylate group is inherently *meta*-directing, transformations mediated by transition metal carboxylates can direct functionalization to the *ortho* position. This unique behavior further underscores the carboxylate group's utility in directed C–H functionalization.



Moreover, two coordination modes utilized by carboxylate group mediated by metal to carry out transformation namely, K^1 and K^2 coordination modes. In K^1 mode, metal coordinated with one oxygen and activated the target C–H bond by remaining intact in a better conformation. However, in K^2 coordination mode, both the oxygen atoms coordinated with metal and secluded from the target C–H bonds. Different metals prefer different coordination modes but K^1 is considered to be the effective strategy. In this perspective, to carry out C–H activation, carboxylate group proved to be a better alternative.



In 2019, Zhang *et al*. developed a metal-free method for synthesizing 2-halo pyridine derivatives. This methodology involved decarboxylative bromination and chlorination of 2-picolinic acids using a dihalomethane reagents in the presence of *t*-BuOCl and $NaHCO_3$ under an air or oxygen atmosphere (**Scheme 25**). The same reaction conditions could also be extended to decarboxylative halogenation of carboxylic acids derived from quinoline and isoquinoline, yielding halogenated products. However, when performing decarboxylative bromination of

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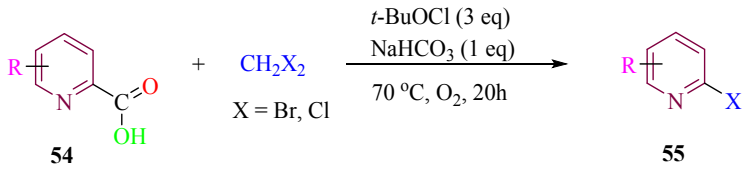
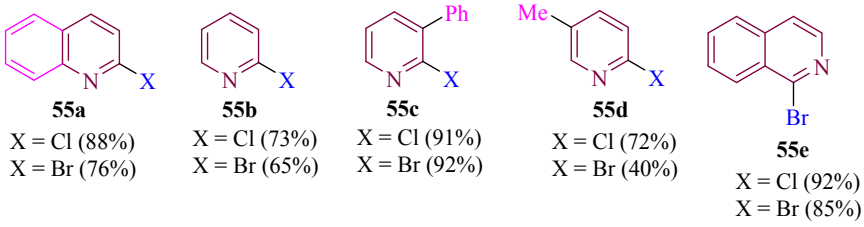
heteroaryl carboxylic acids with CH_2Br_2, the reaction produced desired heteroaryl bromides along with small amount of chlorinated biproducts. This is due to *in-situ* generation of a mixed dihalomethane (CH_2BrCl) during the reaction. The proposed reaction pathway includes the generation of Cl^+ and *t*-BuO^- in the presence of oxygen followed by decarboxylative process to form a ylide, which transforming into a carbene intermediate, and ultimately leading to the desired product.[80]

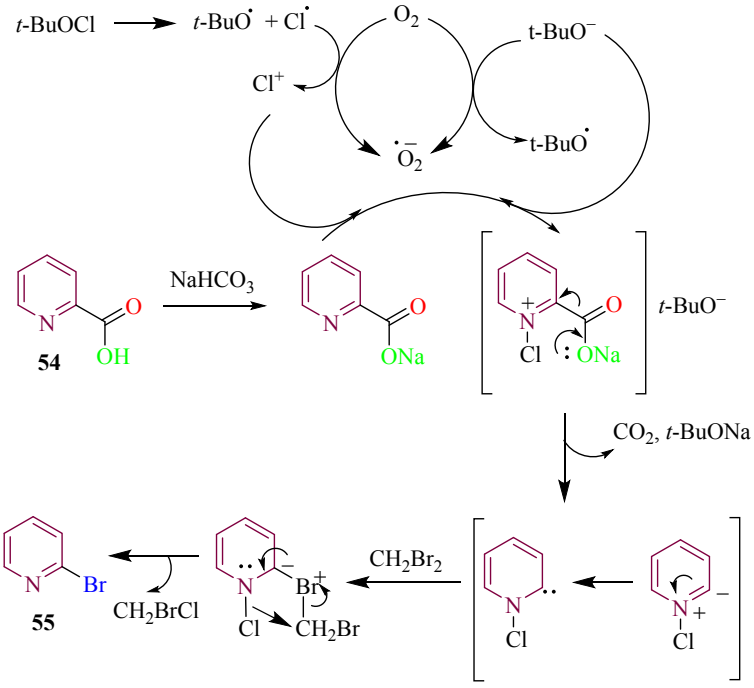
Decarboxylative bromination and chlorination



Representative examples



Proposed mechanism

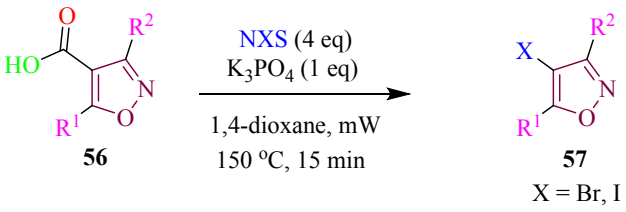


Scheme 25. Decarboxylative bromination of 2-picolinic acid

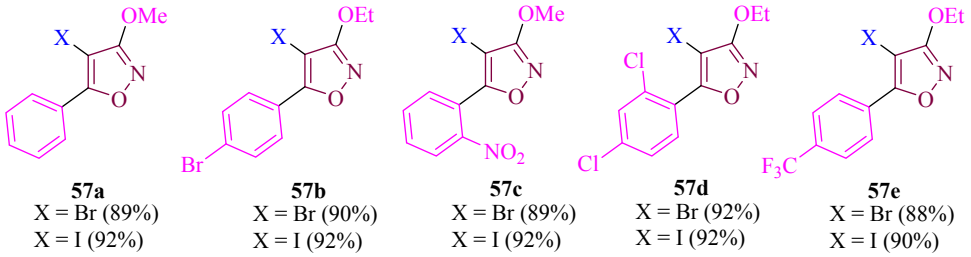
Barak *et al*. reported a method for microwave-assisted decarboxylative bromination and iodination of 4-isoxazole carboxylic acids. This approach utilized readily available NXS (where X = I or Br) as halogen source, with K_3PO_4 as the base in 1,4-dioxane at 150 °C. This

method efficiently yielded bromo- or iodo-isoxazoles in good yields (**Scheme 26**). Interestingly, proto-decarboxylation products were formed when the reaction was conducted at a higher temperature of 210 °C, in the presence of K_3PO_4 regardless of whether NCS or NBS was included. Methoxy (OMe) group at 3-position of isoxazole exhibited significantly higher reactivity compared to fluorine (F), nitro (NO_2), and amino (NH_2) groups. Moreover, only 3-nitro derivatives could yield iodinated products, while hydrazine and amino groups did not produce any halogenated products. The mechanistic pathway was proposed to proceed *via* a concerted decarboxylation that led to formation of halogenated products.[81]

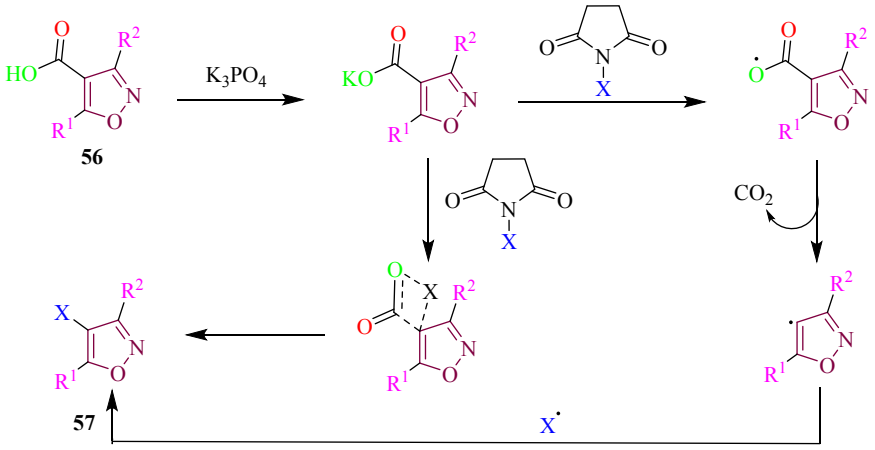
Decarboxylative bromination and iodination



Representative examples



Proposed mechanism

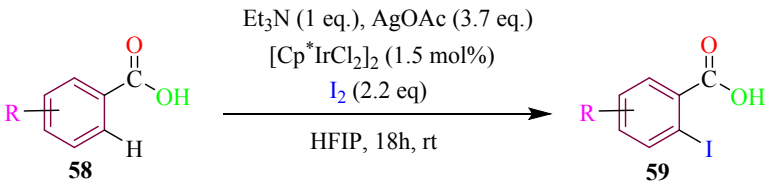


Scheme 26. Decarboxylative bromination and iodination of 4-isoxazole

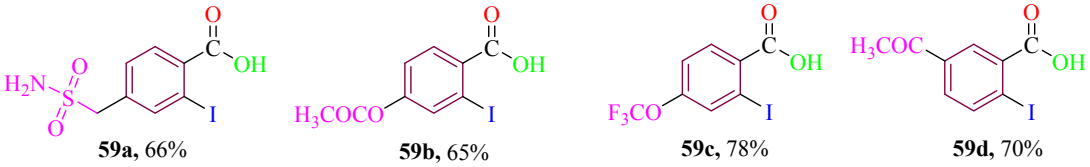
In 2020, Matute and co-workers performed a mild and simple method for Ir-catalyzed regioselective monoiodination of benzoic acids. This approach utilized iridium catalyst and iodine as an iodinating agent in protic solvent of HFIP at room temperature for 18 h (**Scheme**

27). The method was compatible with nearly all functional groups attached to the benzoic acid even in the presence of competing directing groups as substituents in benzoic acids. However, the silver salt was crucial for the selective iodination of the benzoic acid substrates. These reactions outlined a catalytic cycle that proceeded through C–H activation, oxidative addition, and reductive elimination. These findings indicated that the rate-limiting step in C–H activation occurred *via* concerted metalation-deprotonation pathway, ultimately leading to the desired products.[82]

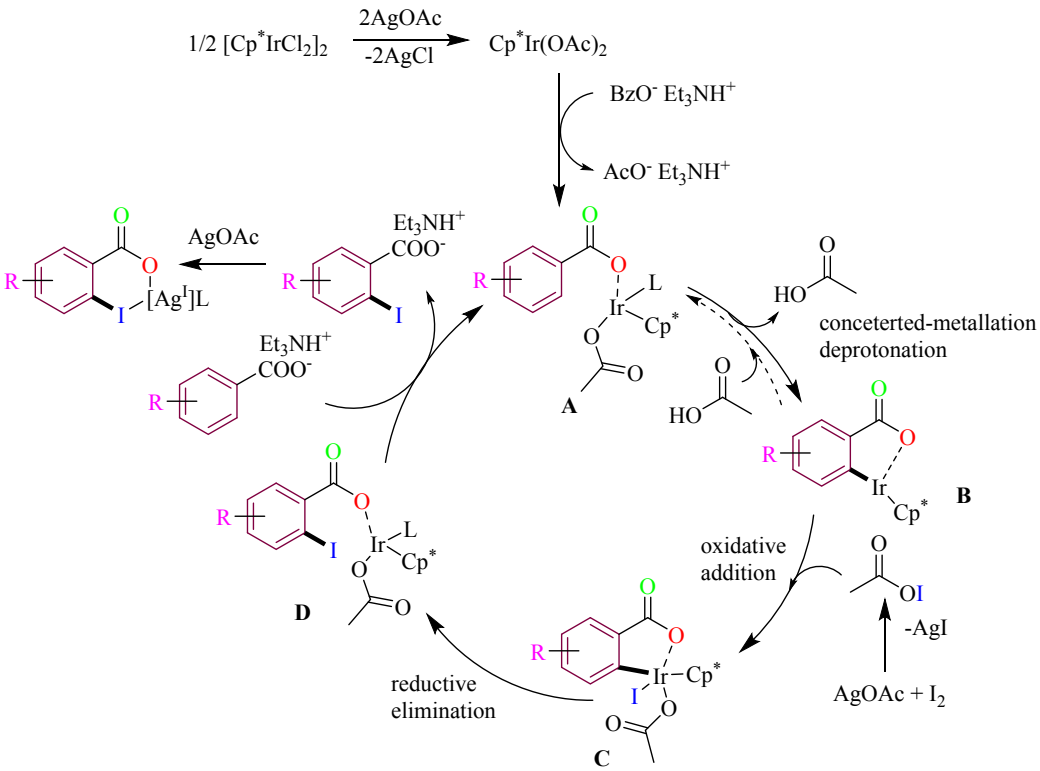
Regioselective monoiodination



Representative examples



Proposed mechanism



Scheme 27. Regioselective iodinated derivatives of various substituted benzoic acid scaffolds

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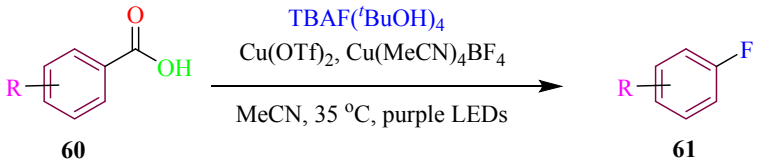
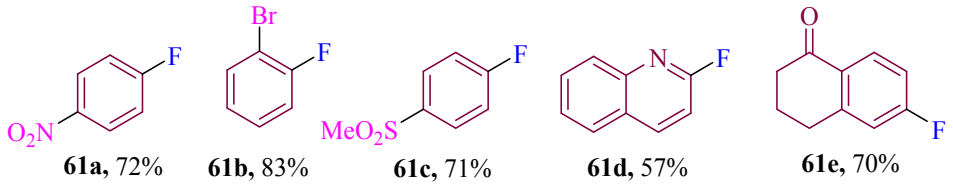
Ritter and group utilized a mild and versatile approach for aromatic fluorination (**Scheme 28**) through a low-barrier photoinduced ligand to metal charge transfer (LMCT)-enabled radical decarboxylative carbometallation that formed high-valent aryl copper(III) intermediates. The optimized protocol overcome the harsh reaction conditions, limited substrate scope, and poor functional group tolerance typically associated with aromatic decarboxylation. The selective LMCT excitation−homolysis sequence of copper(II) carboxylates allowed for late-stage fluorination of several complex small molecules.[83]

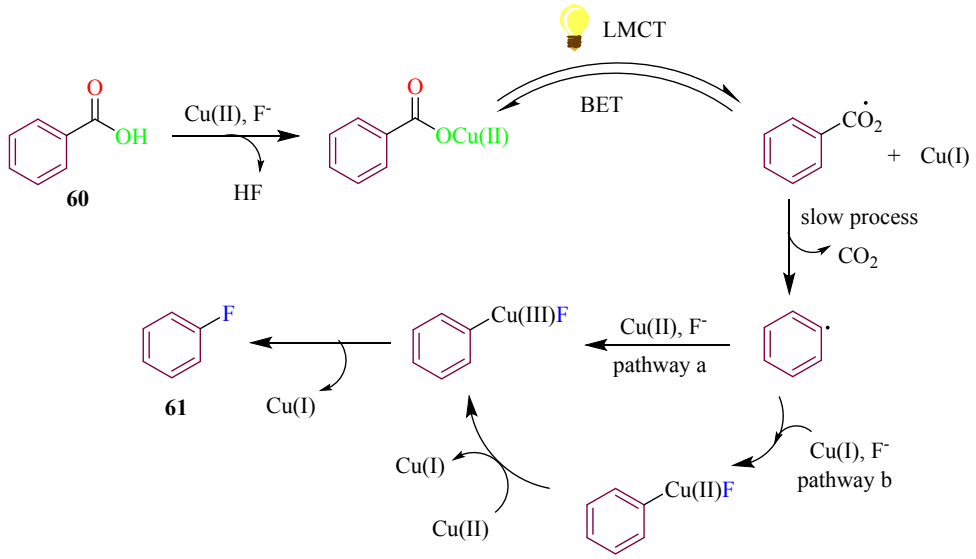
Aromatic fluorination



Representative examples



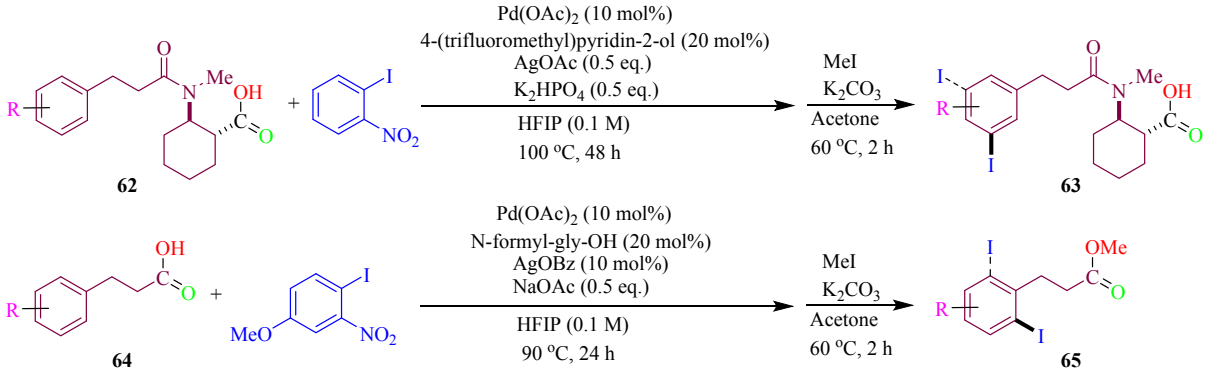
Proposed mechanism



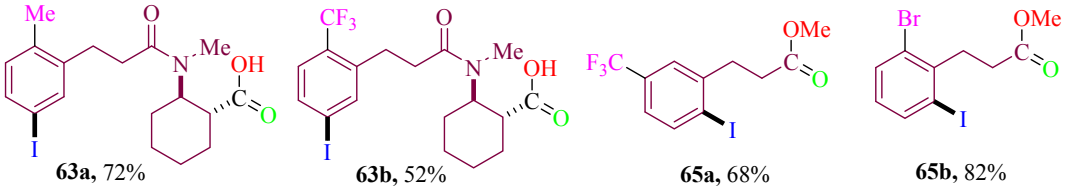
Scheme 28. Decarboxylative fluorination of aromatic benzoic acids

In another approach, Li group performed Pd(II)-catalyzed selective *ortho*- and *meta*-C–H iodination of arenes assisted by aliphatic carboxylic acid directing group *via* formal metathesis. The protocol utilized 2-nitrophenyl iodide as the iodinating agent where a range of iodinated hydrocinnamic acids and arenes were obtained in good yields (**Scheme 29**). To gain insights into the mechanistic pathway, a series of control experiments was conducted. These experiments suggested a catalytic cycle that involved the initial coordination of the active palladium catalyst with substrate, followed by metalation-deprotonation process. Subsequently, oxidative addition occurred, culminating in reductive elimination to yield the desired product.[84]

***ortho*- and *meta*- C–H iodination**



Representative examples



Proposed mechanism

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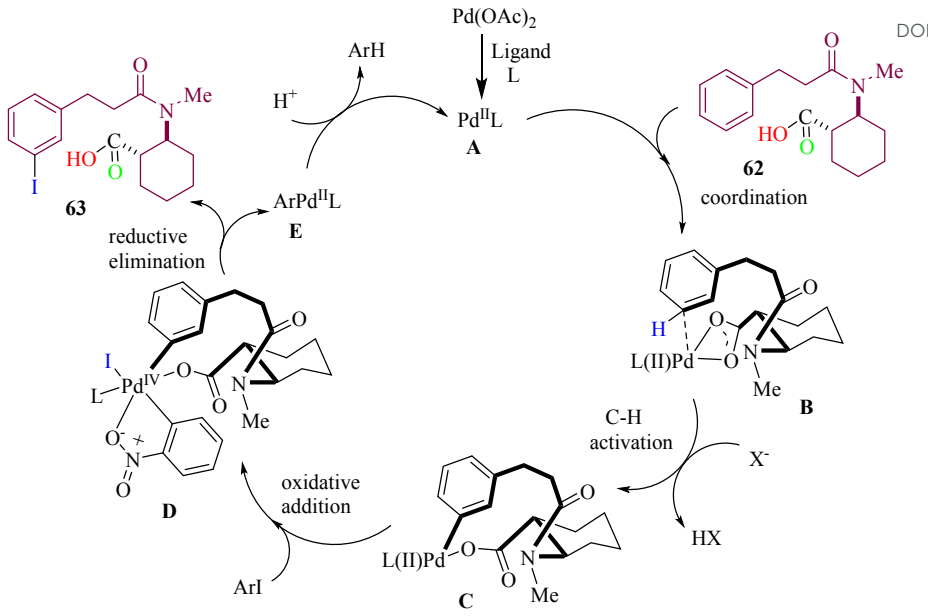
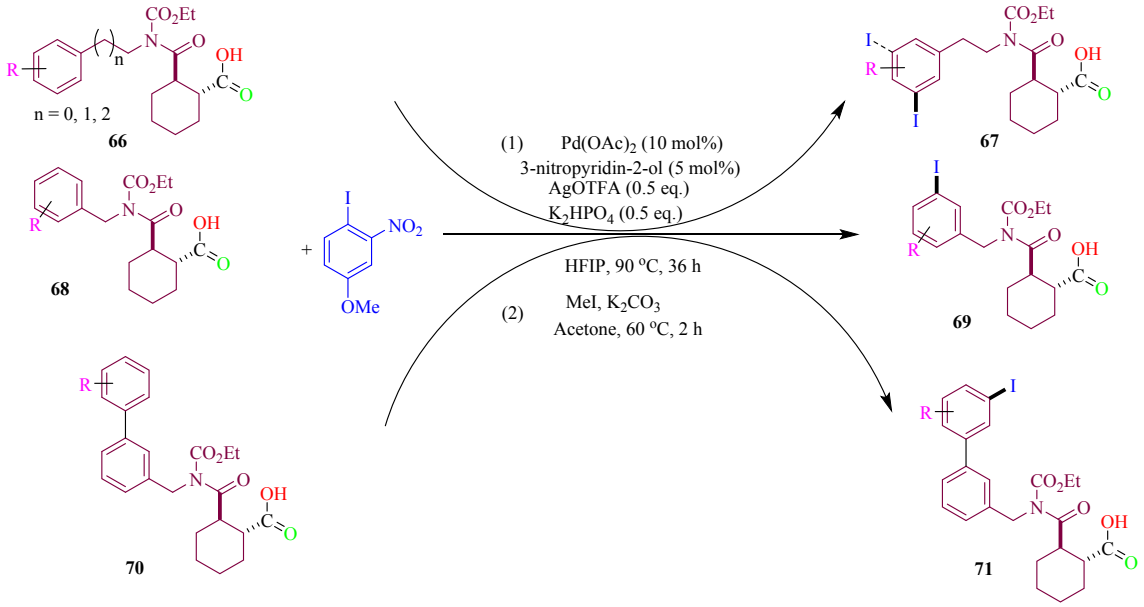


Scheme 29. Pd-catalyzed C−H iodination of arenes using aryl iodide

The Li group reported similar research on the Pd(II)-catalyzed carboxylic group-assisted regioselective and chemoselective iodination of phenethylamines, benzylamines, and 2-aryl anilines (**Scheme 30**). This method employed 1-iodo-4-methoxy-2-nitrobenzene as a mild iodinating reagent. As a result, various valuable *meta*-iodinated and even multi-halogenated amines were smoothly synthesized.[85]

Regio- and chemo-selective iodination



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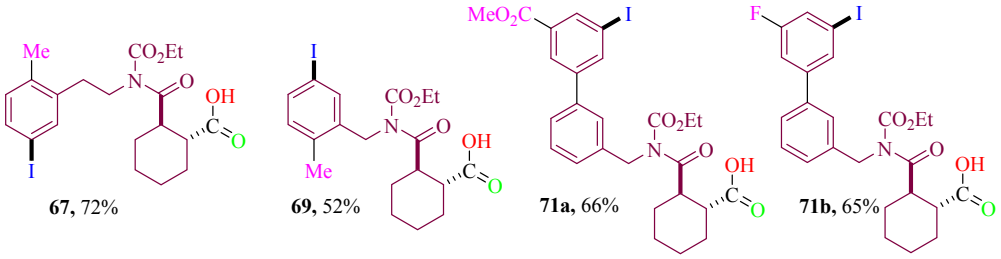
DOI: 10.1039/D5QO00372E

Representative examples



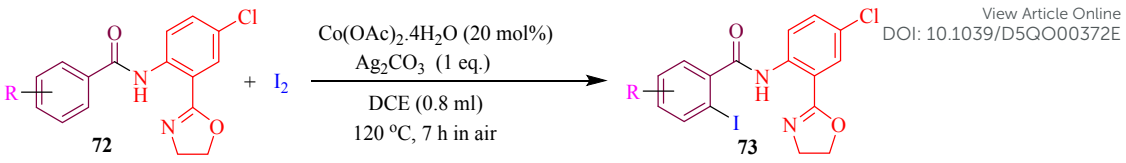
Scheme 30. Carboxylic group- assisted *meta*-iodination of phenethylamines, benzylamines, and 2-arylanilines

2.8. Other heterocycles as directing group

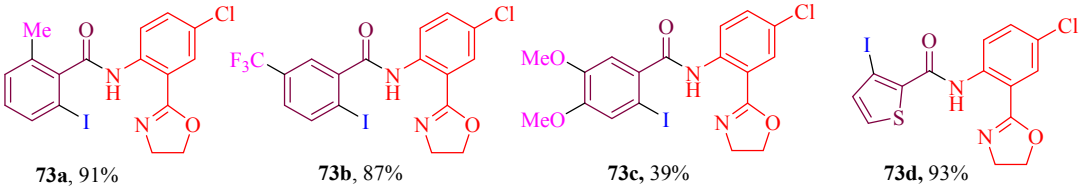
Like other directing groups discussed so far, heterocycles serve as a common structural motif used to direct C–H functionalization. The C(sp^2)-hybridized nitrogen atoms in heterocyclic directing groups act as coordinating sites, facilitating the formation of metallacyclic intermediates crucial for C–H functionalization. This property has garnered significant interest due to the prevalence of heterocycles in bioactive molecules. Heterocyclic directing groups offer advantages such as the absence of a need for installation or removal, making them suitable for late-stage modifications. When installation is required, it can be achieved through various straightforward methods. Additionally, substitutions on heterocyclic scaffold can modulate their coordinating properties, enabling customization for specific transformations.

In 2019, Kommagalla *et al*. reported cobalt-catalyzed chelation-assisted C−H iodination of aromatic amides using molecular iodine as an iodinating reagent. The reaction was carried out in an atmosphere of air using $Co(OAc)_2 \cdot 4H_2O$ as an efficient catalyst with 4-chloro-2-(4,5-dihydrooxazol-2-yl)aniline serving as the directing group (**Scheme 31**). The reaction showed a wide range of functional group tolerance. Studies revealed that Ag_2CO_3 was an essential component of the reaction for promoting the iodination and eliminating the formation of byproducts. Kinetic studies and Hammett study revealed that the present C−H iodination approach was likely to proceed through the coordination of **72** with Co(II) species, formation of an arenium ion intermediate, attack of I_2 on **C** and further the protonation of intermediate **E** gives the iodination product **73** with the regeneration of the Co(III) species.[86]

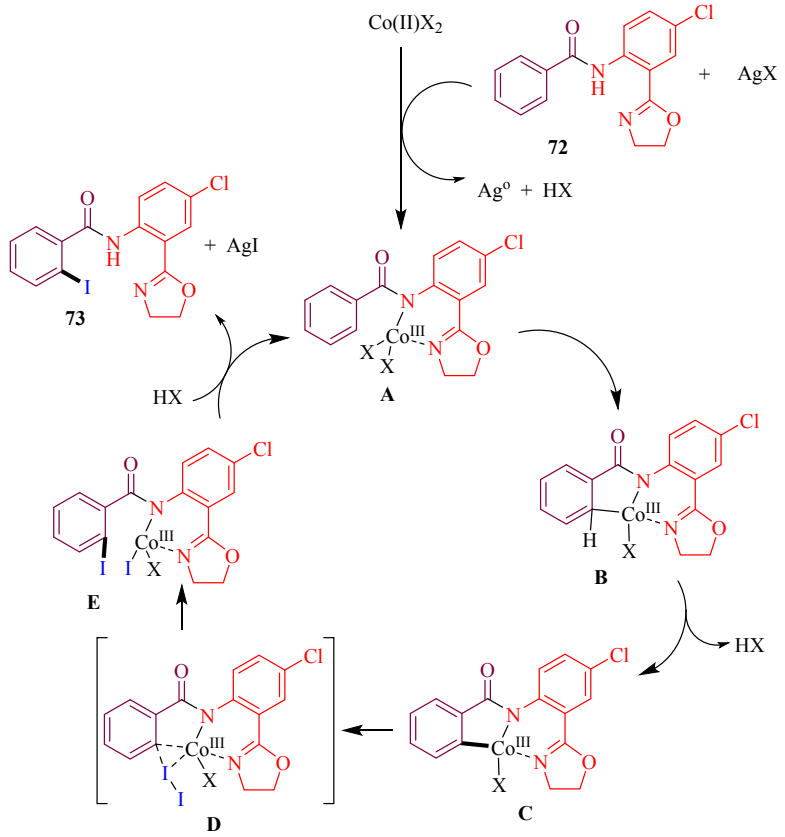
Chelation-assisted iodination



Representative examples



Proposed mechanism

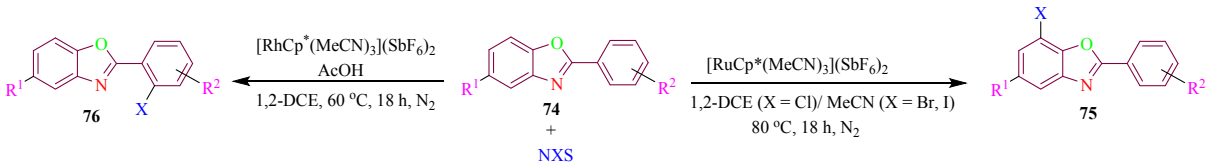


Scheme 31. Cobalt-catalyzed direct C−H iodination of aromatic amides

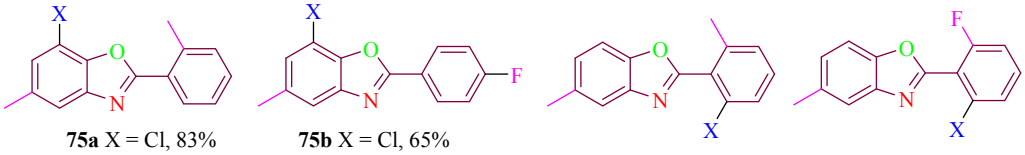
Hong *et al*. designed a method for C–H chlorination, bromination and iodination of 2-arylbenzo[*d*]oxazoles in different catalytic systems. In the presence of ruthenium catalyst, halogenation occurred at C-7 position whereas when rhodium catalyst was used, *ortho*-selective product was formed with C7-halogenation on 5-methyl-2-(*p*-substituted)arylbenzo[*d*]oxazoles as a side reaction (**Scheme 32**). The established systems delivered products with good to excellent yields, suggested that the reaction was tolerable to various substrates. Mechanistic experiments and DFT calculations revealed that C7-halogenation catalyzed by Ru proceeded *via* single-electron-transfer (SET) radical process,

while the Rh catalyzed *ortho*-selective halogenation occurred through a redox-neutral SN2 type mechanism. Moreover, the charge difference between benzo[*d*]oxazolyl and aryl rings led to the different selectivity of Rh catalyzed halogenations.[87]

Halogenated 2-arylbenzo[*d*]oxazoles



Representative examples



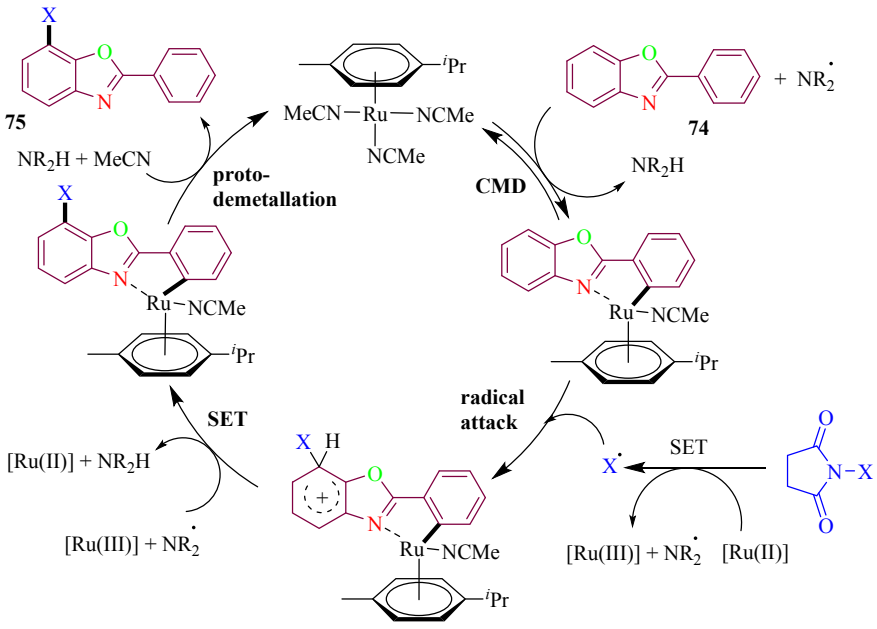
75a X = Cl, 83%
Br, 73%
I, 75%

75b X = Cl, 65%
Br, 92%
I, 95%

76a X = Br, 96%
I, 95%

76b X = Br, 75%
I, 79%

Proposed mechanisms



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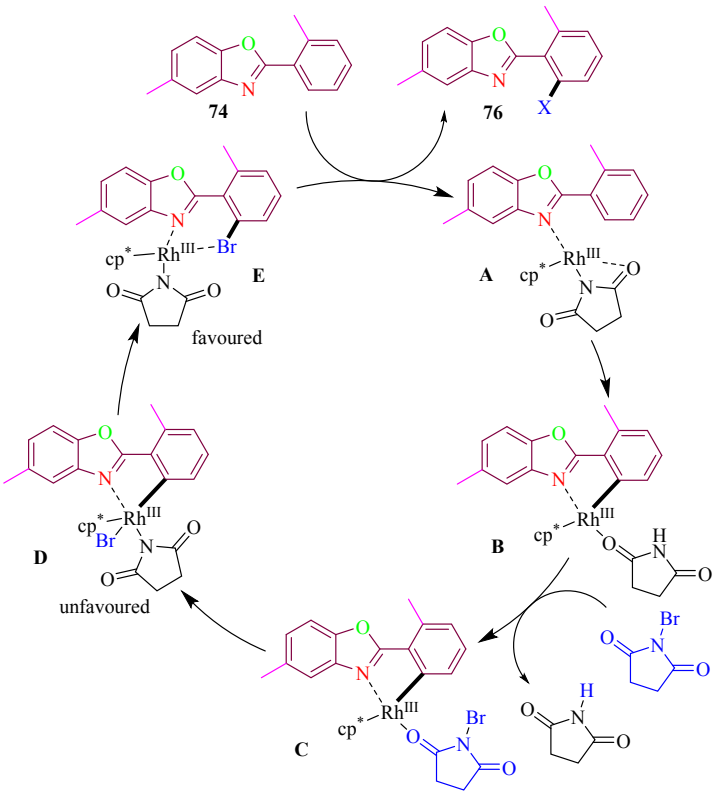
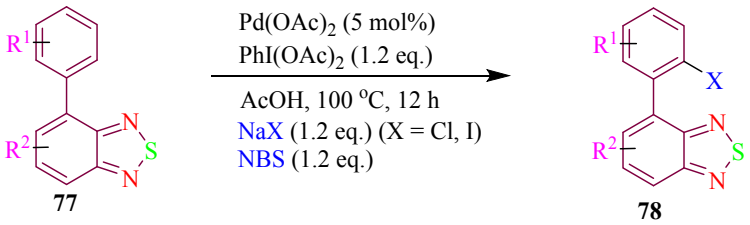


Scheme 32. Ru & Rh catalyzed C7 and *ortho*-selective halogenation of 2-arylbenzo[*d*]oxazoles

Further, in 2020, He *et al*. synthesized palladium catalyzed direct mono- and poly-halogenated derivatives of benzothiadiazole (BTD) where BTD ring acted as both important nuclei of material science and directing group, which would allow the rational tuning of the physical and chemical properties of BTD derivatives. Here PIDA is used as oxidant, acetic acid as additive, NaX as halogenating agent for chlorination and iodination but for bromination NBS gave the best results (**Scheme 33**). The designed strategy was well-tolerated by various substituted benzothiadiazole candidates where electron-rich substrates reacted much faster than the electron deficient. These derivatives exhibit good solubility and absorb strongly in the 230 to 380 nm UV range, which have potential applications in material science.[88]

Halogenated benzothiadiazole



Representative examples

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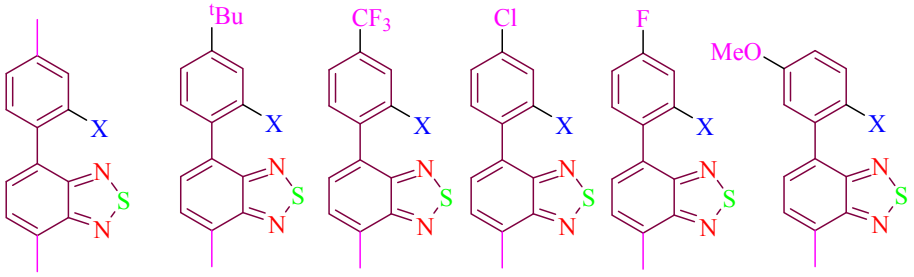
DOI: 10.1039/D5QO00372E

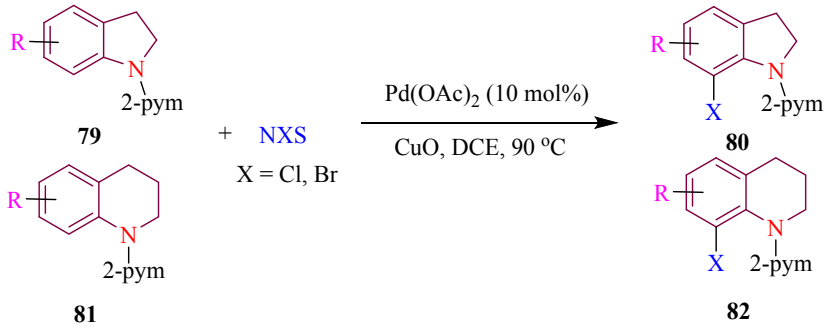


78a	78b	78c	78d	78e	78f
X = Cl (80%)	X = Cl (80%)	X = Cl (80%)	X = Cl (80%)	X = Cl (80%)	X = Cl (80%)
X = I (91%)	X = Br (83%)	X = Br (85%)	X = Br (92%)	X = Br (65%)	X = Br (80%)
	X = I (91%)	X = I (91%)	X = I (91%)	X = I (91%)	X = I (91%)

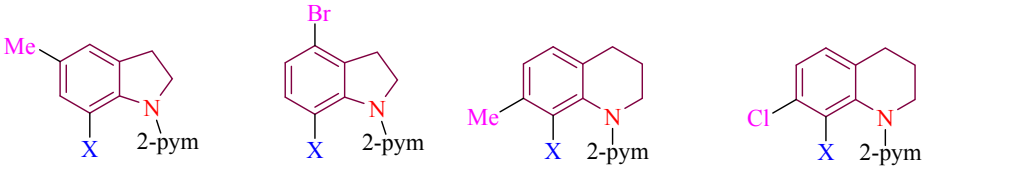
Scheme 33. Palladium catalyzed direct halogenation of benzothiadiazole derivatives

Koley & co-workers explored palladium-catalyzed regioselective *ortho*-chlorination and bromination of indolines and tetrahydroquinolines. The method required the addition of CuO to avoid the formation of side products (**Scheme 34**). The optimized reaction conditions were well tolerated on various substrates bearing electron-donating and electron-withdrawing groups, obtained in good to excellent yields. The applicability of the designed method was demonstrated by synthesizing various valuable synthetic scaffolds, including primaquine and precursors of hippadine and pratosine.[89]

Regioselective halogenation



Representative examples



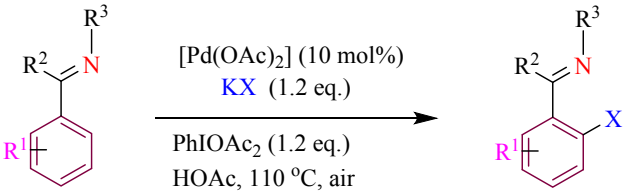
80a	80b	82a	82b
X = Cl (69%), Br (55%)	X = Cl (69%), Br (55%)	X = Cl (56%), Br (75%)	X = Cl (73%), Br (80%)

Scheme 34. Pd-catalyzed chlorination and bromination of indolines and tetrahydroquinolines

In 2022, Roger group developed a palladium-catalyzed, *N*-directed selective *ortho*-halogenation protocol under atom-economic conditions (**Scheme 35**). The method is compatible with various functionalized aromatic rings, including pyridine, pyrimidine,

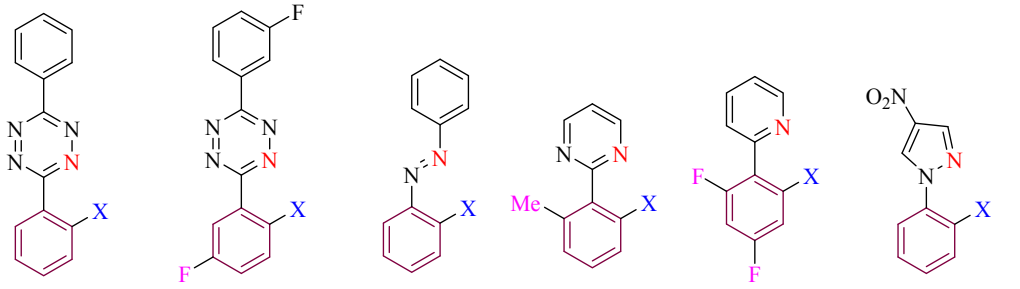
pyrazole, oxazoline, naphtho[1,2-*d*]thiazole, azobenzene, and selectivity-challenging nitrogen-rich s-aryltetrazines. The protocol employed alkali halides as nucleophilic halogen source and PIDA as the oxidant. The use of microwave irradiation significantly reduced the reaction time and enhancing the efficiency of the synthesis.[90]

Regioselective halogenation



83 **84**
X = Cl, Br, I

Representative examples



84a
X = Cl (35%)
X = Br (48%)
X = I (61%)

84b
X = Cl (28%)
X = Br (35%)
X = I (35%)

84c
X = Br (60%)
X = I (39%)

84d
X = Br (61%)
X = I (65%)

84e
X = Cl (70%)
X = Br (51%)

84f
X = I (62%)

Scheme 35. Selective halogenation of s-tetrazines and other heteroaromatics using alkali halides

Recently, Zheng *et al*. disclosed a novel strategy for enantioselective C–H iodination of isoquinolines under mild reaction conditions. NIS was used as iodinating agent catalyzed by chiral CpRh(III) complex afforded a series of axially chiral biaryl iodides in excellent yields with enantioselectivity (**Scheme 36**). The protocol was also compatible with atroposelective C−H chlorination and bromination. The obtained iodide products could be further transformed to other compounds containing C-C, C-N and C-P bonds. Experimental results suggested a plausible catalytic cycle where the desired products comprised two pathways: (a) oxidative addition of NIS to form CpRh(V) complex, followed by reductive elimination assisted by AcOH, or (b) direct nucleophilic substitution of NIS with rhodacycle.[91]

Enantioselective iodination

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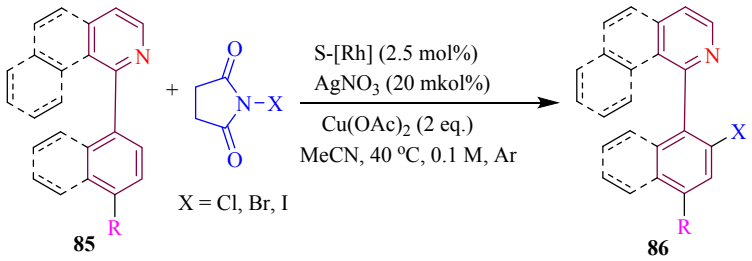
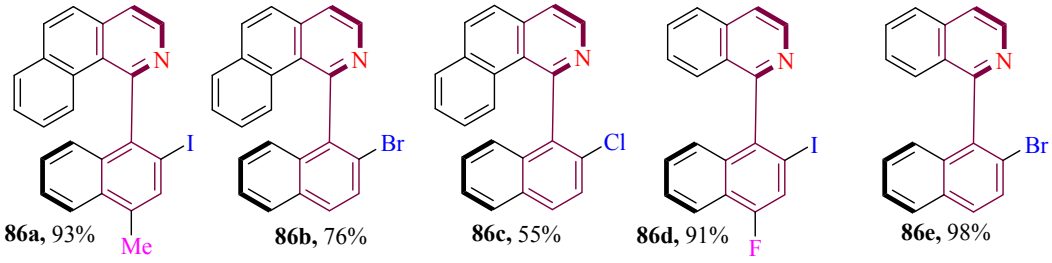
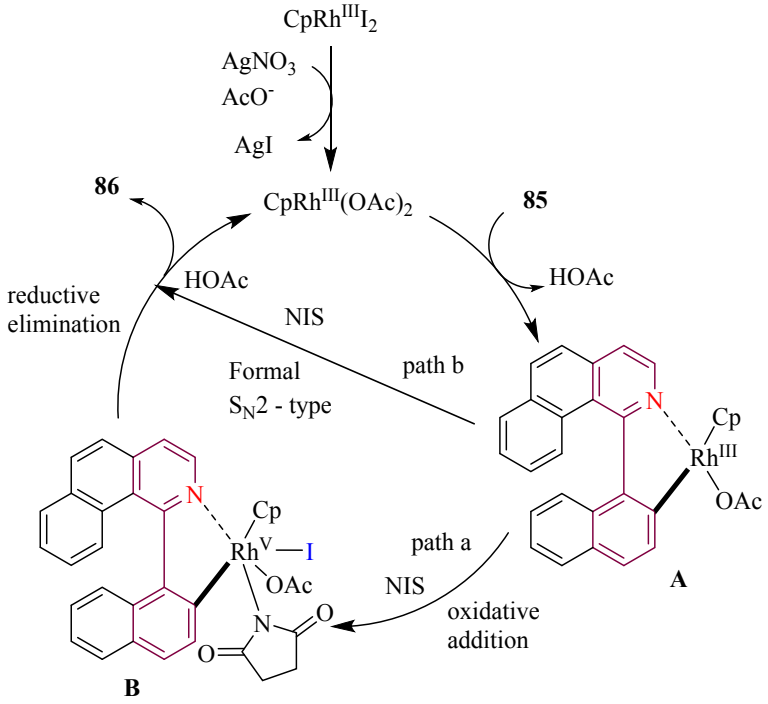


Representative examples



Proposed mechanism



Scheme 36. Rh-catalyzed enantioselective C−H iodination of isoquinolines

2.9. Miscellaneous directing group

Sunoj and Yu reported the fluorination of methylene and methyl groups in aliphatic substrates *via* F^+ oxidants, with distinct methodologies tailored for each substrate class (**Scheme 37**). Both methods employed 2-hydroxylnicotinaldehyde as a transient directing group and a pyridone ligand. Methylene fluorination required silver salts, while methyl fluorination proceeded without silver, highlighting the contrasting roles of silver in these reactions. *N*-Fluorosuccinimide (NFSI) was identified as the most effective oxidant and fluorine source for

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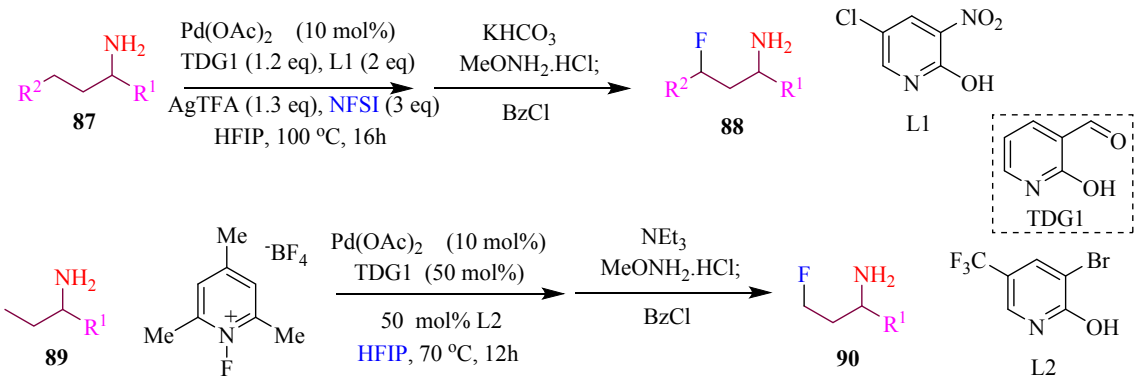
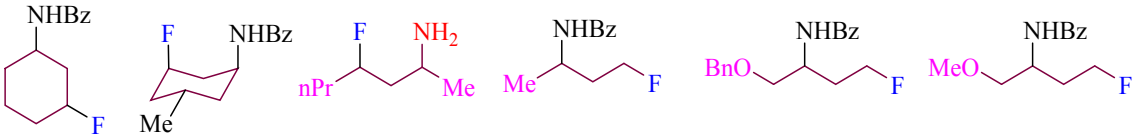
methylene substrates. It was employed alongside silver trifluoroacetate, pyridone A in superstoichiometric amounts, and a mixed solvent system of HFIP and PhCl. The resulting fluorinated amines were isolated as benzoyl-protected derivatives. Mechanistic studies suggested a Pd(II)/(IV) catalytic cycle involving three key steps: (a) C−H activation, (b) oxidative addition to N−F bond, and (c) reductive elimination, which formed the desired C−F bond. This efficient methodology expanded the toolbox for selective aliphatic fluorination.[92]

Methylene fluorination



Representative examples



88a, 70% **88b,** 66% **88c,** 49% **90a,** 48% **90b,** 32% **90c,** 62%

Proposed mechanism

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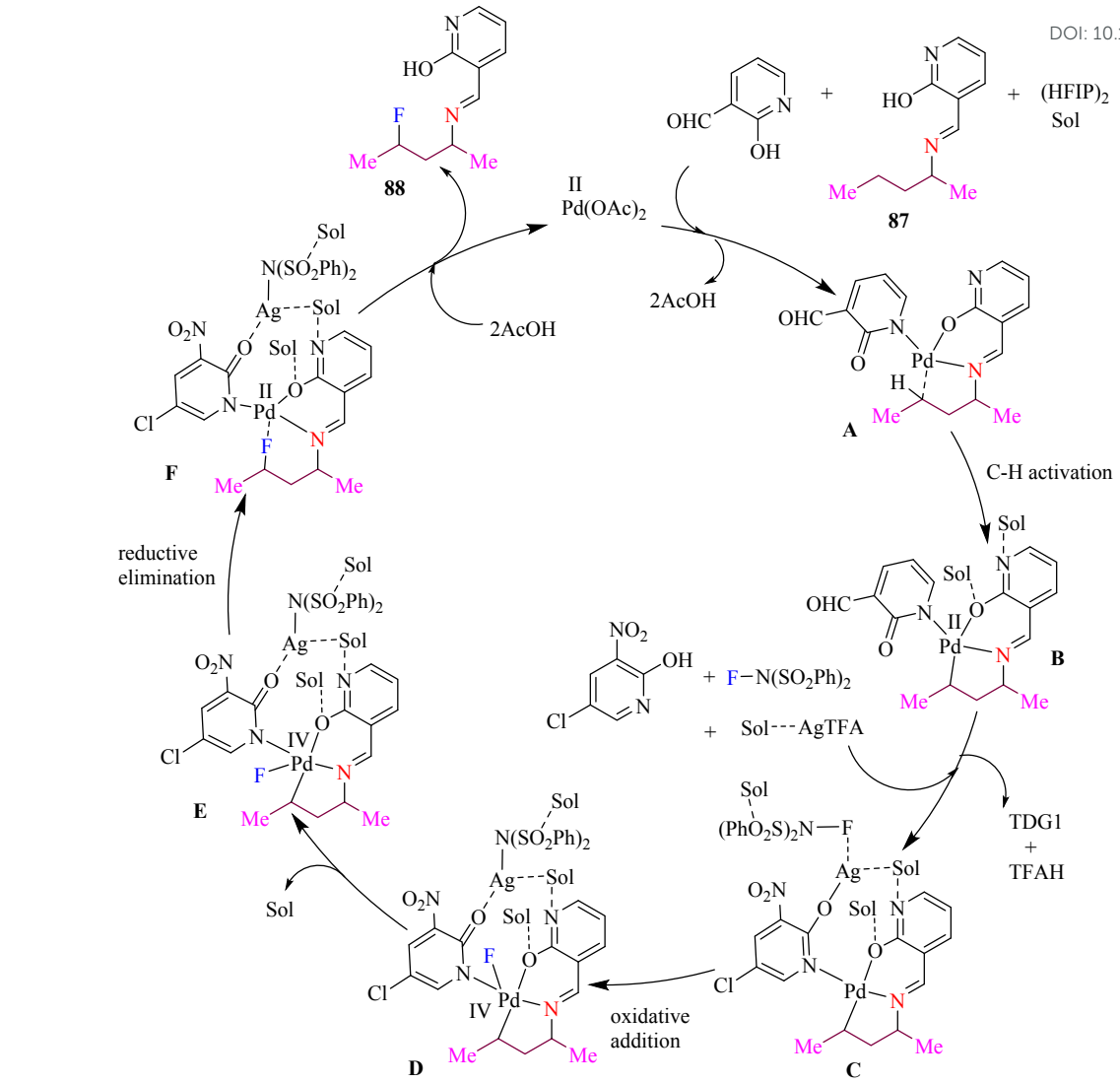

Scheme 37. C(sp^3)-H fluorination of aliphatic amines catalyzed by palladium

In 2021, Chan and group designed a fascinating approach for site-selective chlorination of aliphatic γ C–H bonds of ketones, enones and alkylbenzenes without the use of transient directing group. The cheap and mild protocol utilized copper triflate as a catalyst and dichloramine-T as a chlorinating agent at room temperature (**Scheme 38**). The optimized reaction condition's efficiency was determined by employing a series of secondary or tertiary γ-carbon centres of ketones, (*E*)-enones and alkylbenzenes. Mechanistic studies supporting DFT calculations which proposed that the reaction pathway proceeded through a single electron mechanism, showing the possibility of two different pathways, i.e., inner-sphere and outer-sphere mechanisms, which competed with generation of radicals and formation of metal complexes.[93]

Site-selective chlorination

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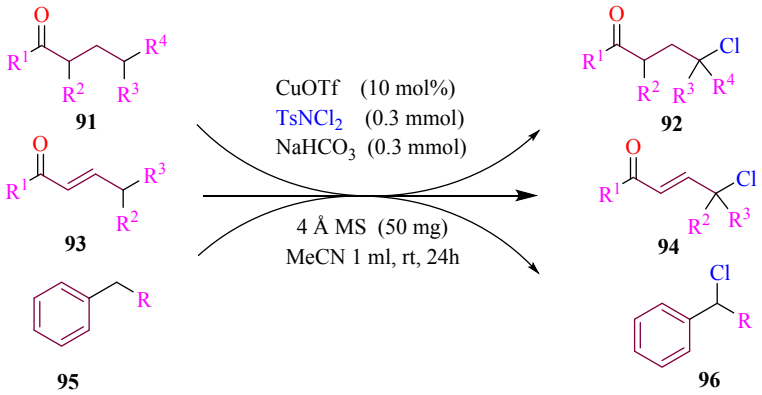
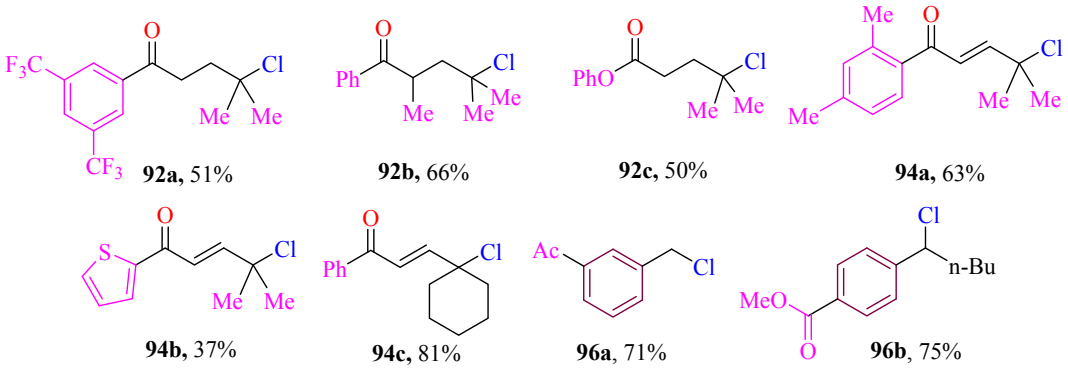
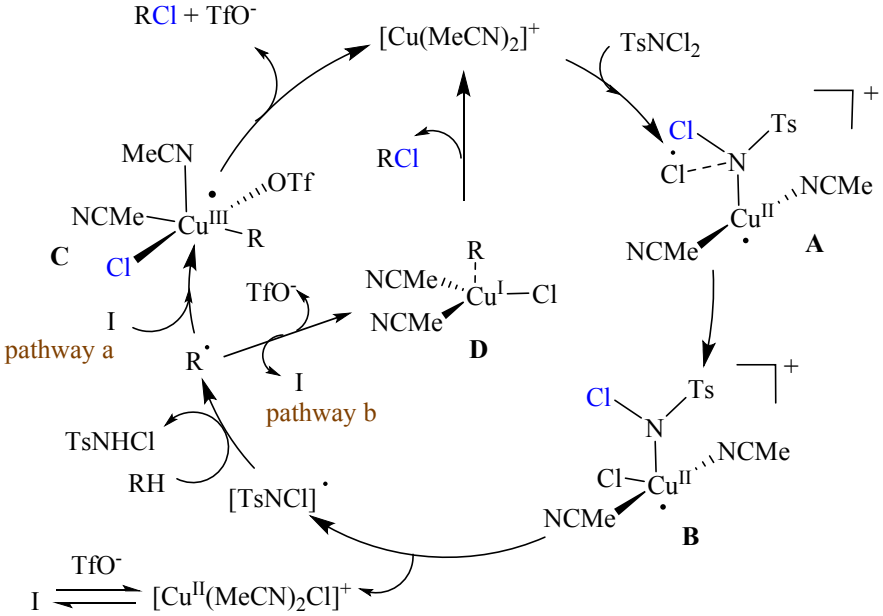


Representative examples



Proposed mechanism

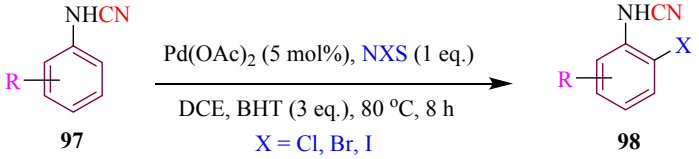


Scheme 38. Site-selective chlorination of ketones, (*E*)-enones and alkylbenzenes by dichloramine-T

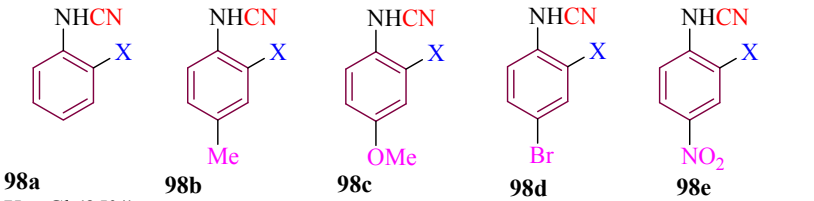
Bollikolla group established *ortho*-chlorination, bromination and iodination of arylcyanamide using Pd(II) catalyst under mild reaction condition (**Scheme 39**). The optimized reaction condition readily delivered the desired products in moderate to good yields with both

electron-donating and electron-withdrawing groups. The mechanism is following with metal coordinating to the directing group, followed by the formation of a palladacycle through ligand-assisted C–H bond activation. Subsequently, oxidative addition of NXS formed a Pd complex, which underwent reductive elimination to yield the desired product.[94]

Halogenation arylcyanamide



Representative examples



98a
X = Cl (95%)
X = Br (91%)
X = I (91%)

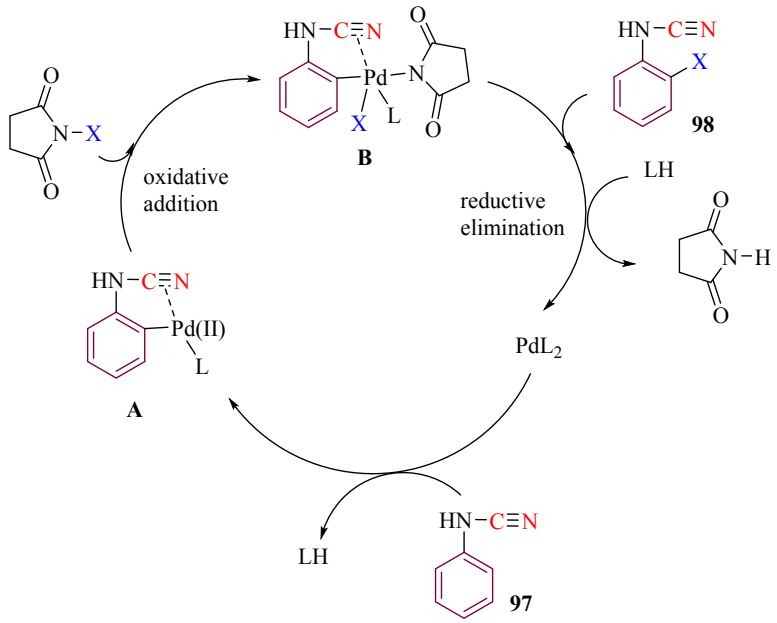
98b
X = Cl (96%)
X = Br (94%)
X = I (89%)

98c
X = Cl (97%)
X = Br (95%)
X = I (92%)

98d
X = I (90%)

98e
X = Cl (78%)
X = Br (75%)
X = I (71%)

Proposed mechanism

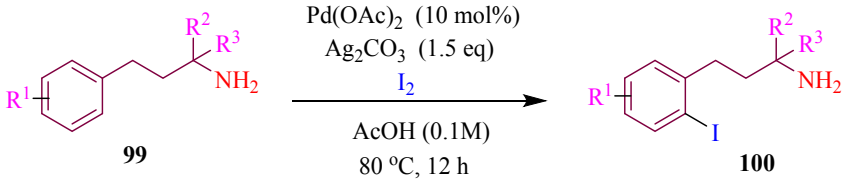


Scheme 39. Pd-catalyzed regioselective halogenation of arylcyanamide

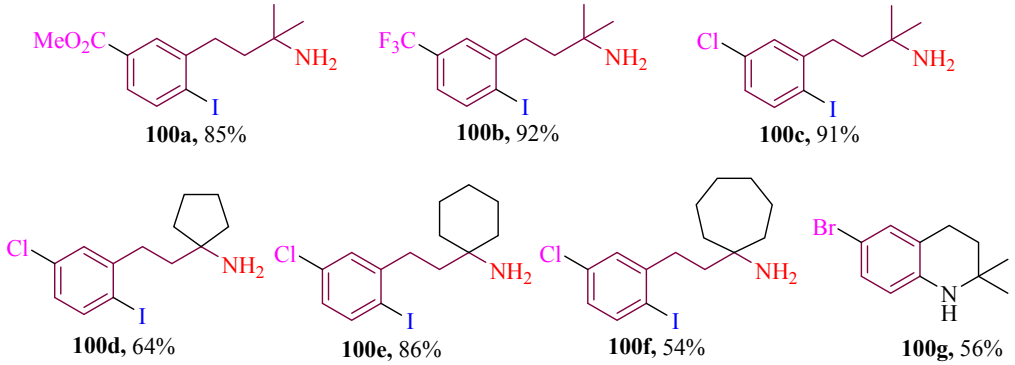
Recently, Feng *et al*. reported the first selective ε-C(sp^2)−H iodination of 3-arylpropan-1-amines using the unprotected NH_2 group as a native directing group, with palladium as the catalyst (**Scheme 40**). This reaction proceeded *via* the formation of seven-membered palladacycle, which was less kinetically favourable than five- or six-membered palladacycles. Under optimized conditions, the reaction displayed broad substrate scope, with substituted

amines delivering the desired iodinated products in excellent yields. Furthermore, the iodination products can undergo copper-catalyzed cyclization in a single step to form 1,2,3,4-tetrahydroquinolone, a key structural motif in drugs, dyes, and natural products.[95]

Selective ε-C(sp^2)−H iodination



Representative examples



Scheme 40. Palladium assisted *ortho*-selective C−H iodination of primary amines

2.10. Regioselective electrophilic halogenation

The direct halogenation of compounds is one of the most fundamental and frequently used reactions in organic chemistry. Regioselective electrophilic halogenation, influenced by directing groups, has gained prominence in recent years. In this approach, the electronics of the substituent guide the substitution process, utilizing various halogenating reagents under mild reaction conditions. This method does not require transition metal chelation and can proceed through different techniques, including photochemical, electrochemical, and radical halogenation.

Xiong *et al*. achieved the simultaneous C5- and C7-dihalogenation and acylation of 8-hydroxyquinolines under catalyst free condition using acyl halides as halogenating agent. However, on slightly changing reaction conditions and directly using *O*-acylated 8-hydroxyquinoline, regioselective C5-halogenation could be achieved (**Scheme 41**). Further, the optimized reaction conditions speculated to find the substrate scope providing the desired products in moderate to good yield. On the basis of various control experiments, it has been found that dihalogenation proceeded through free radical pathway while the selective halogenation occurred through electrophilic mechanism.[96]

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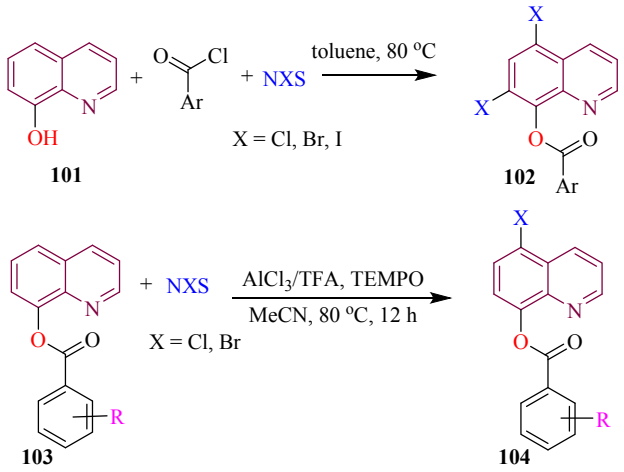
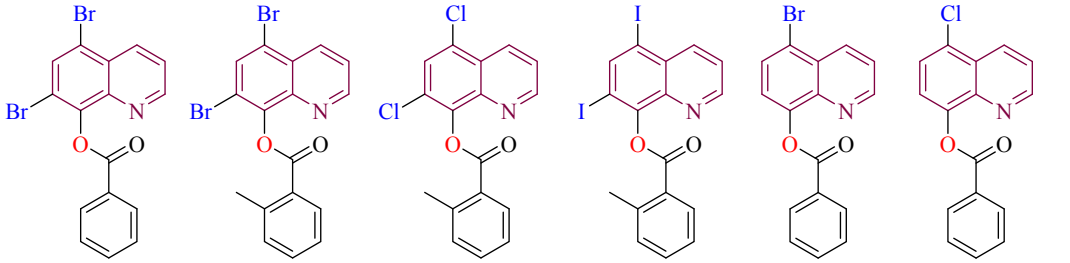
Acylation and halogenation

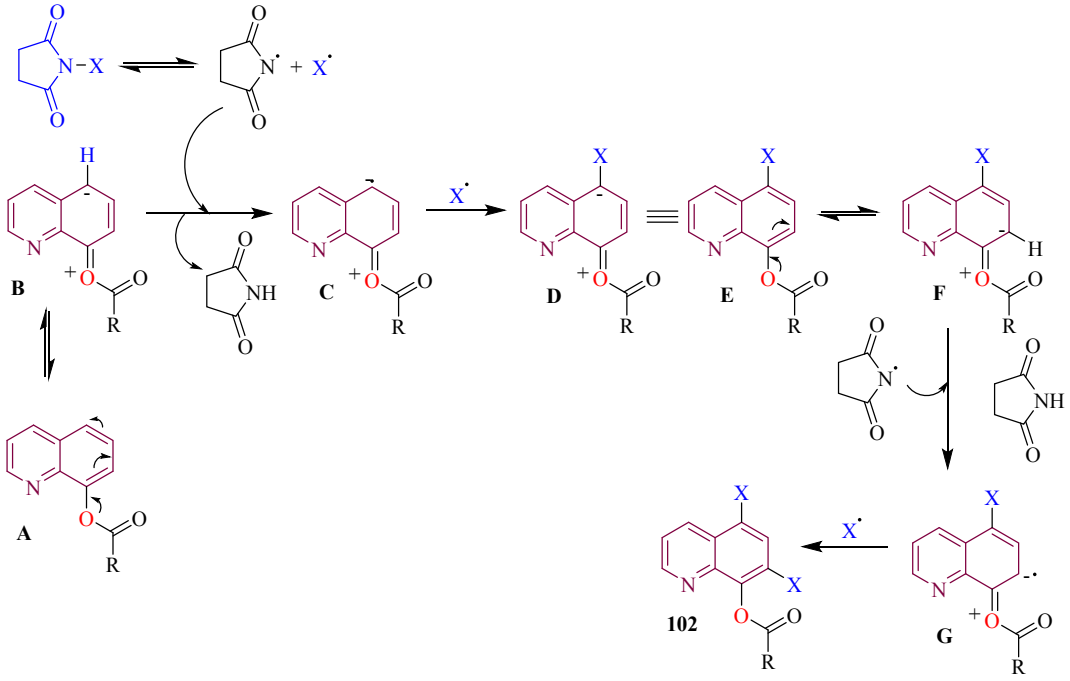


Representative examples



102a, 75% **102b,** 69% **102c,** 60% **102d,** 66% **104a,** 67% **104b,** 60%

Proposed mechanism



Scheme 41. C5- and C7-dihalogenation, and selective C5-halogenation of 8-hydroxyquinoline

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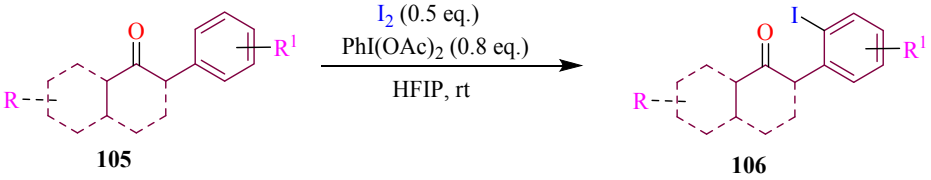
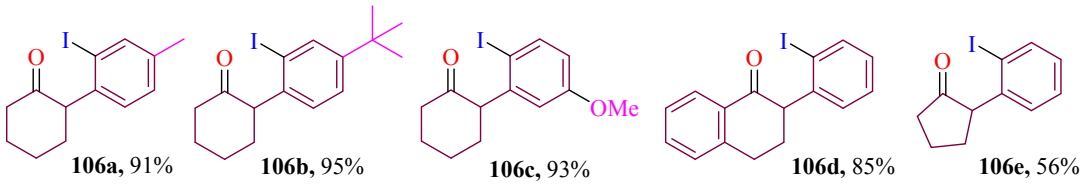
In 2020, Bian *et al*. developed a transition-metal-free methodology that employed cyclic and acyclic aliphatic ketones as directing groups for site-selective γ-C(sp^2)−H iodination of aryl compounds (**Scheme 42**). This transformation offered a broad substrate scope and operated under mild conditions with free from air and moisture. The reaction occurred rapidly and was easy to perform, making it both environmentally friendly and scalable. Based on several control experiments, a possible reaction mechanism was outlined which illustrated that the combination of I_2 and PIDA was crucial for the iodination process.[97]

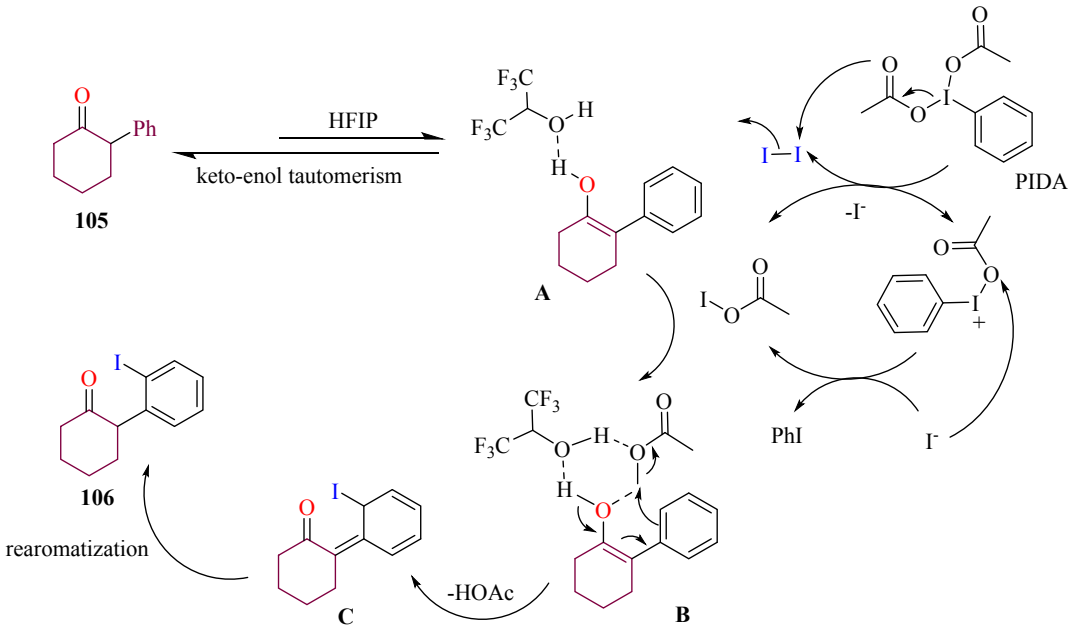
γ-C(sp^2)−H iodination



Representative examples



Proposed mechanism

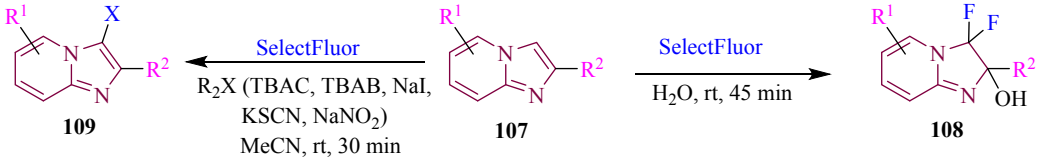


Scheme 42. Aliphatic ketone directed site-selective mono-iodination of arenes

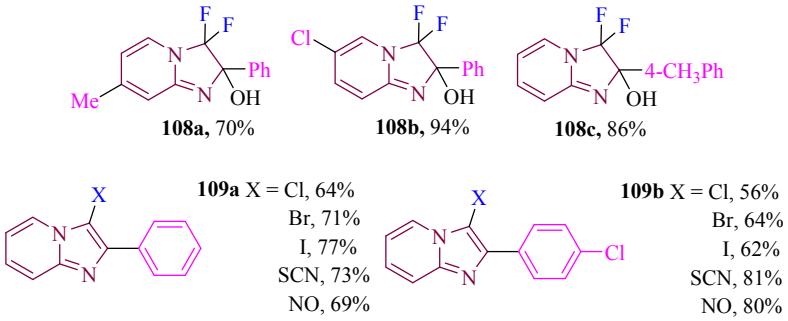
In 2021, Rode's group reported a facile protocol for C–H functionalization of imidazo[1,2-*a*]pyridines with different nucleophilic species including TBAC, TBAB, NaI,

KSCN, and $NaNO_2$ (**Scheme 43**) in acetonitrile. The product showed a dominant functionalization at the 3-position of imidazo[1,2-*a*]pyridines, giving reaction yields ranging from 62% to 81% under mild conditions. The reaction showed a good group tolerance with 2-aryl substitution. Importantly, the C–H fluorination in absence of any nucleophile proceeded apparently through an ionic mechanism *via* electrophilic aromatic substitution. In the presence of water, a hydroxylated-fluorinated product was obtained, being essential for the effective C–H functionalization with a nucleophile. No mechanistic evidence was provided for reactions involving a nucleophile, but it is possible to suppose a radical mechanism. The strategy provided a viable route for the halogenation (e.g., chlorination, bromination, and iodination) of imidazo[1,2-*a*]pyridines, with potential to be extended to other *N*-heterocyclic systems.[98]

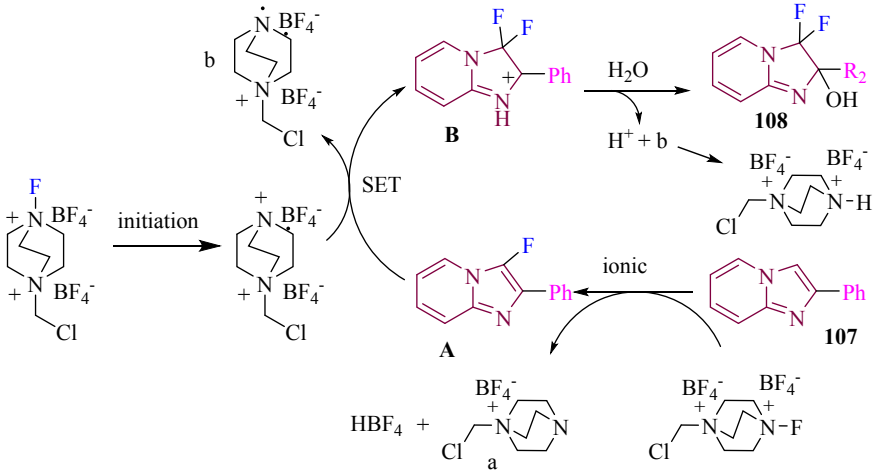
Selective fluorination



Representative examples



Proposed mechanism



Scheme 43. C-3 functionalization of imidazopyridine using Selectfluor

Sun group developed an efficient, regioselective and metal-free protocol for *para* C–H

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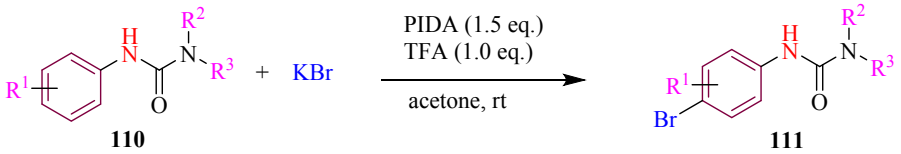
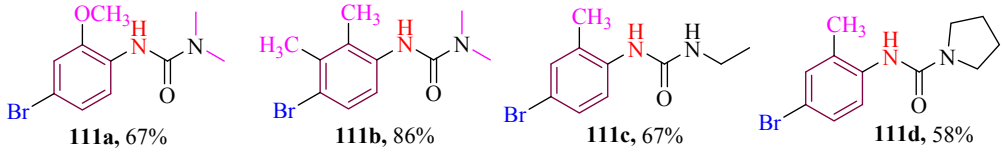
bromination of phenylurea. The method used simple and readily available KBr as bromide source, TFA as an additive and PIDA as an oxidant in acetone at room temperature (**Scheme 44**). The method tolerated a variety of functional groups and allowed the synthesis of diverse 4-brominated phenylurea derivatives in moderate to excellent yields. Series of control experiments performed to find out the reaction pathway where, initially, iodonium intermediate **A** was formed through a nucleophilic attack of urea. Then, cleavage of N-I bond furnished iodobenzene and nitrenium ion **B**, which was stabilized by the charge delocalization on the phenyl ring. Finally, the extensively charge delocalized intermediate **C** reacted with Br to give the *para*-brominated products **111**.[99]

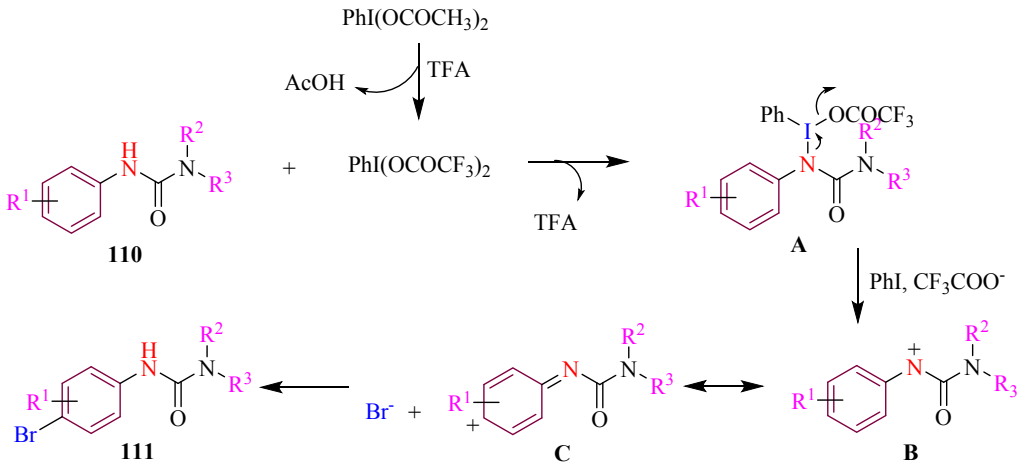
Regioselective bromination



Representative examples



Proposed mechanism

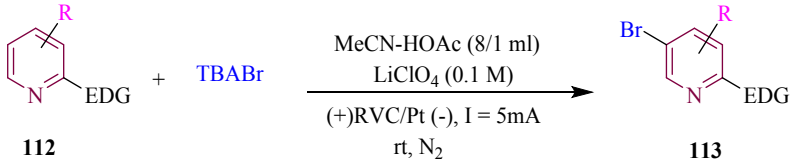


Scheme 44. Regioselective C−H bromination of urea

In 2021, Chen & co-workers developed an economical, user-friendly, and environmentally benign method for selective *meta*-bromination of pyridines. A sustainable electrochemical approach was developed, combining installation and removal steps using TBAB, NaBr, and LiBr as brominating salts at room temperature. This method operated without the need for catalysts or oxidants (**Scheme 45**), offering an environmentally friendly

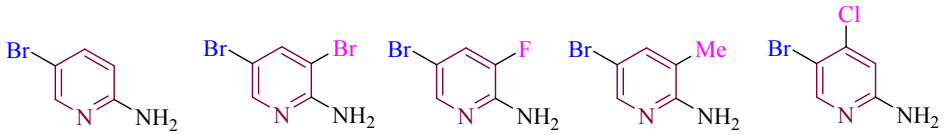
alternative. A wide range of brominated pyridine derivatives was synthesized in good to excellent yields. The proposed reaction pathway, supported by various control experiments showed the electrophilic aromatic substitution of pyridine conjugates.[100]

***meta*-bromination**



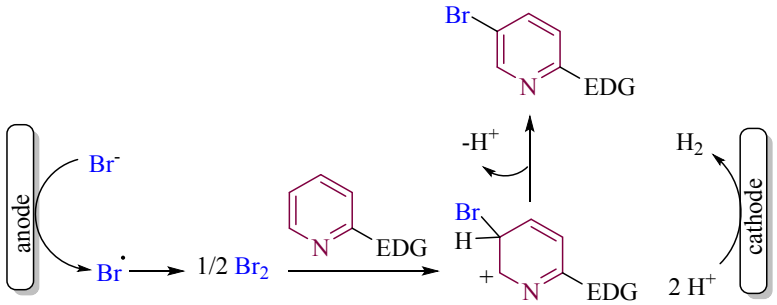
112 **113**

Representative examples



113a, 93% **113b,** 83% **113c,** 60% **113d,** 66% **113e,** 76%

Proposed mechanism

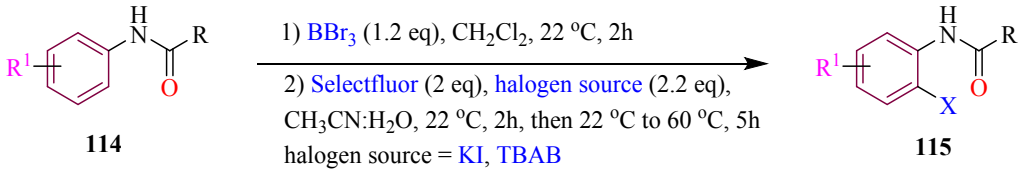


Scheme 45. Electrochemical *meta*-bromination of pyridines

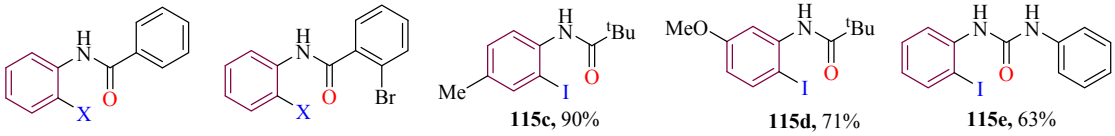
In 2023, Shinde *et al*. reported a new protocol for regioselective *ortho*-halogenation of *N*-aryl amides and urea through an oxidative halodeboronation approach. After optimizing the reaction conditions, the scope of the method was explored by testing various *para*-substituted *N*-aryl amides containing electron-donating, halogenated, and electron-withdrawing groups. The protocol successfully produced *ortho*-iodinated and brominated products with moderate to excellent yields (**Scheme 46**). The method demonstrated versatility by yielding desirable products from electron-rich heteroaromatics and alkyl-based groups. Control experiments and DFT studies revealed a proposed mechanism in which Selectfluor played a dual role as both a fluoride source and an oxidant. The process involved an oxidative ligand exchange removed boron, followed by *ipso*-addition and release of the boron species to form the final product. This innovative reactivity of C–B and B–X bonds offer a promising

alternative for the functionalization of a broad range of *N*-heterocycles, opening new avenues in synthetic chemistry.[101]

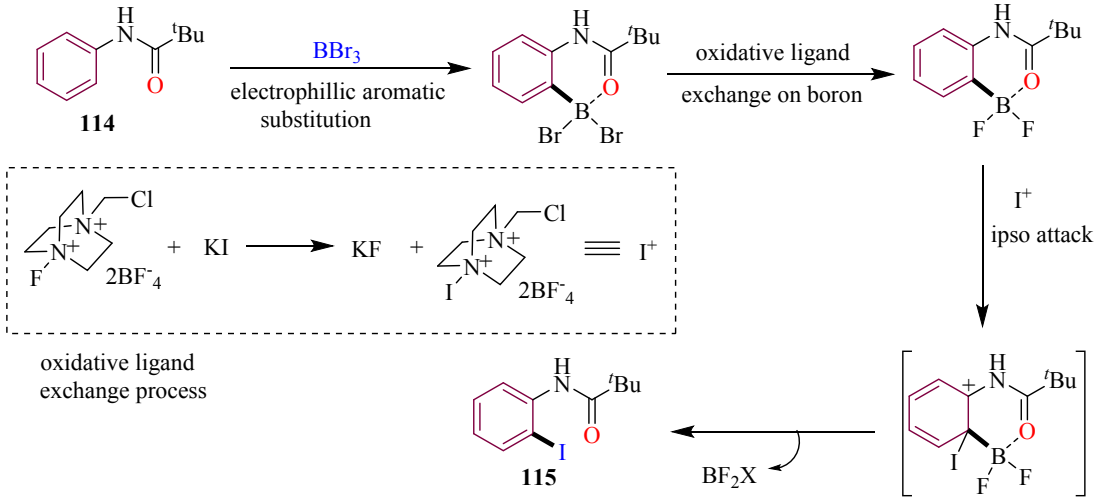
Oxidative halodeboronation



Representative examples



Proposed mechanism

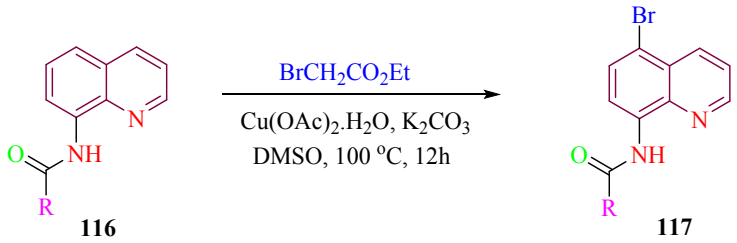


Scheme 46. Regioselective *ortho*-iodination and bromination of *N*-aryl amides and urea

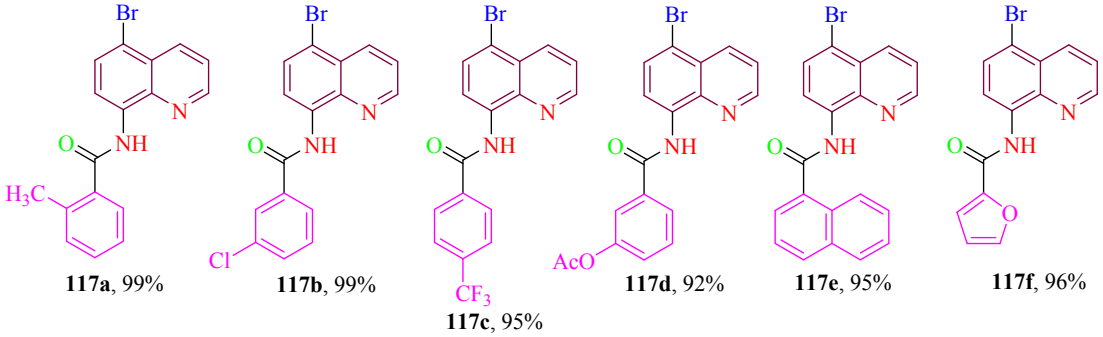
Recently, Zhang and group attempted to use activated and un-activated alkyl bromides to synthesize the regioselective brominated derivatives of 8-aminoquinoline amide in the presence of copper catalyst. The optimal method was employed on various 8-aminoquinoline amides, functionalized with different electron-donating and electron-withdrawing groups **(Scheme 47)**. Activated alkyl bromides gave the desired targets in excellent yield, while un-activated alkyl bromides proceeded with low efficiency following the reactivity order primary

> secondary > tertiary. The proposed reaction mechanism began with the dipolar protic solvent DMSO, attacking ethyl bromoacetate to form intermediate **A**. This intermediate combined with a bromide ion to produce intermediate **B**, which subsequently interacted with another bromide ion to generate either dimethylsulfonium bromide or a dimethyl thioether/molecular bromine complex (intermediate **C**). Intermediate **C** then reacted with 8-aminoquinoline amides *via* copper-promoted aromatic electrophilic substitution, resulting in regioselective C5 brominated product.[102]

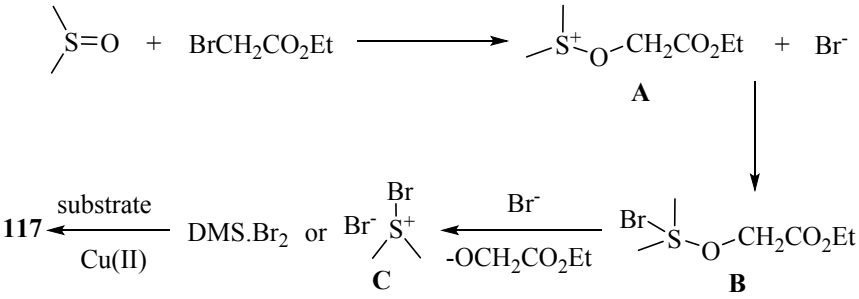
Regioselective bromination



Representative examples



Proposed mechanism

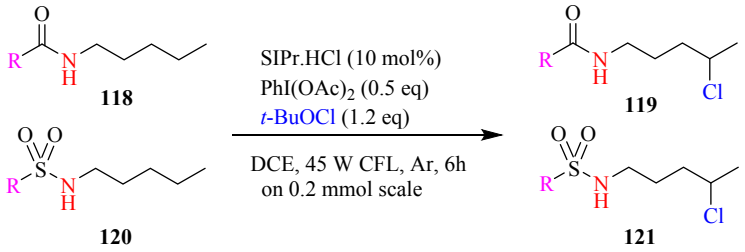


Scheme 47. Copper assisted C5 bromination of 8-aminoquinoline amide using alkyl bromide

In 2020, Yu group developed a new photochemical method for selective chlorination of aliphatic amides. This approach utilized *tert*-butyl hypochlorite as the chlorinating agent and household CFL as the light source **(Scheme 48)**. The reaction proceeded *via* a radical mechanism, following a tandem sequence of *N*-chlorination and photoinduced 1,5-chlorine atom transfer. This process was enabled by the combined action of *N*-heterocyclic carbene

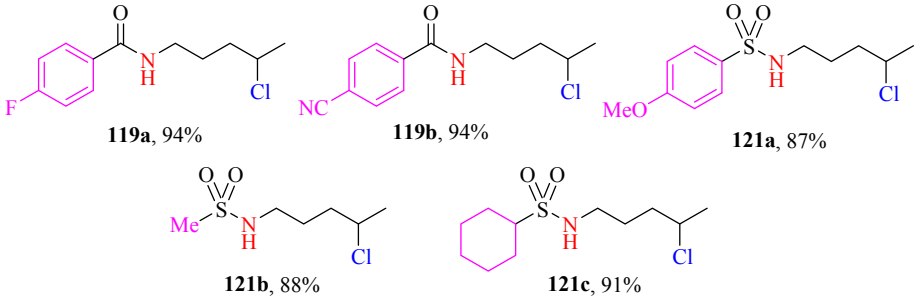
(NHC)·SIPr·HCl and (diacetoxyiodo)benzene (DIB), which promoted N-H chlorination and facilitated the generation of an amide radical through N–Cl cleavage. Under these conditions, a variety of carboxamides and sulfonamides yielded *δ*-chlorinated products with good efficiency and high selectivity. Notably, the reaction conditions were also compatible with phosphonamides, extending the scope of the methodology. This protocol provides a practical and efficient approach for site-selective chlorination of methyl, methylene, and methine hydrogens, paving the way for advancements in selective aliphatic chlorination.[103]

Selective chlorination



118 **119** **120** **121**

Representative examples



119a, 94% **119b**, 94% **121a**, 87%

121b, 88% **121c**, 91%

Proposed mechanism

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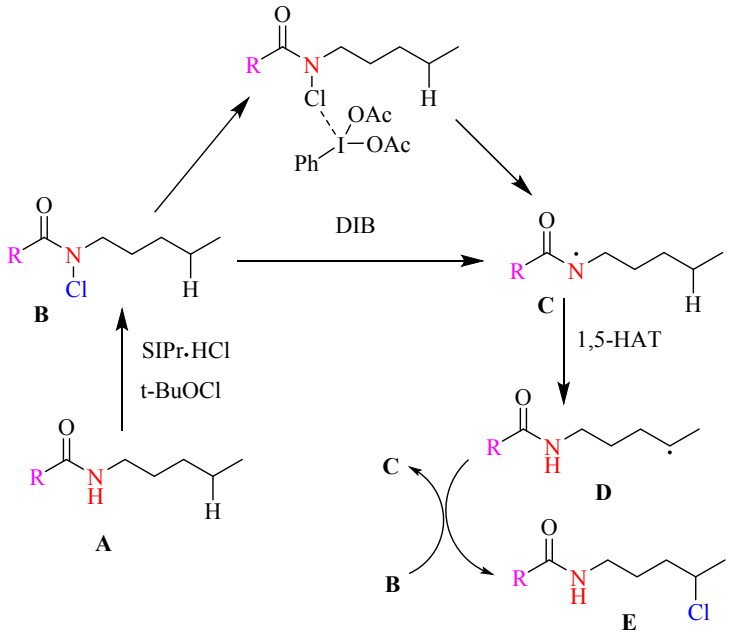
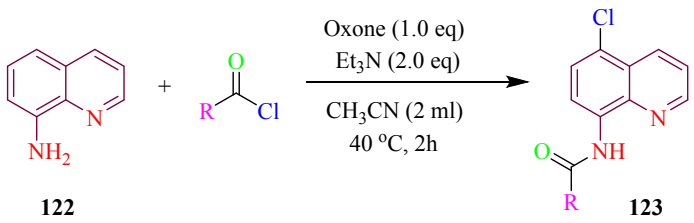


Scheme 48. Photoinduced selective chlorination of aliphatic amides

Under transition-metal-free and mild reaction conditions, Xu and co-workers (2019) achieved one-pot synthesis of highly functionalized *N*-acetylated and selectively C-5 chlorinated conjugates of 8-aminoquinoline. In this methodology, substituted acetyl chloride acted as both acetylating and halogenating agents (**Scheme 49**). Additionally, successful results were obtained with brominated derivatives of 8-aminoquinoline with increasing additive loading and extending reaction time. Based on prior literature and experimental findings, a plausible mechanism was proposed. Initially, 8-aminoquinoline (**122**) reacted with acyl halide to form intermediate **A**. Subsequently, oxone oxidized the halide anion in the ammonium salt to generate a halogen radical. This radical selectively attacked the C-5 position of intermediate, forming complex **B** *via* a single-electron transfer. Finally, the elimination of a proton from complex **B** yielded the desired product **(123)**.[104]

Acetylation and chlorination



122 **123**

Representative examples

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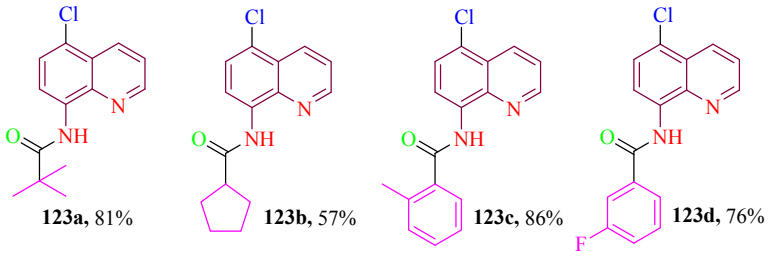
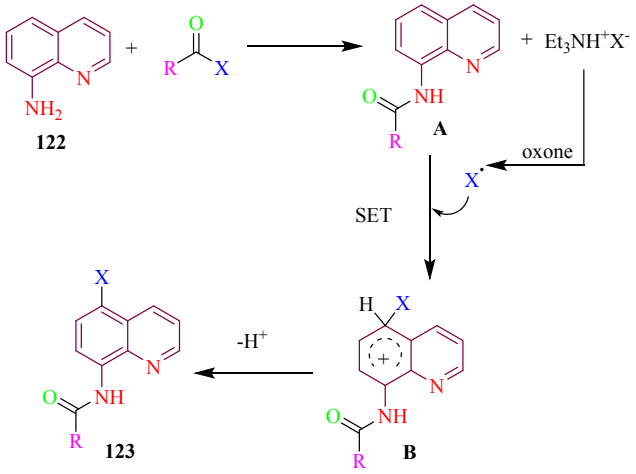


Proposed mechanism



Scheme 49. One-pot acetylation and C-5 chlorination of 8-aminoquinoline

In another notable study, Shu *et al*. developed a selective method for bromination and chlorination of 8-aminoquinoline using environmentally friendly and cost-efficient visible-light-induced processes. They utilized economical and effective halogenation reagents, specifically 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH), in a continuous flow, delivered the high yields of desired products within a short reaction time **(Scheme 50)**. The chlorination reaction required an additional oxidizing agent (TBHP), due to the poor reactivity of DCDMH, which extended the reaction time from 0.5 h to 1 h. Moreover, this approach was also successfully applied to sulfonamides, providing moderate to good yields of products. Under visible light irradiation, halogen radicals (Cl· or Br·) and complex **A** radicals are generated from DXDMH (X = Cl, Br). These radicals reacted with **124** to form radical intermediate **B** and HBr or complex **C**. Intermediate **B** could tautomerize into stable intermediates **D** and **E**. Additionally, HBr reacted with complex **A** to produce X_2, which subsequently halogenated intermediates **D** or **E** to yield C-5 halogenated product **125**. This product could also obtain through the reactions of halogen radicals with intermediates **B** or **E**.[105]

Regioselective halogenation

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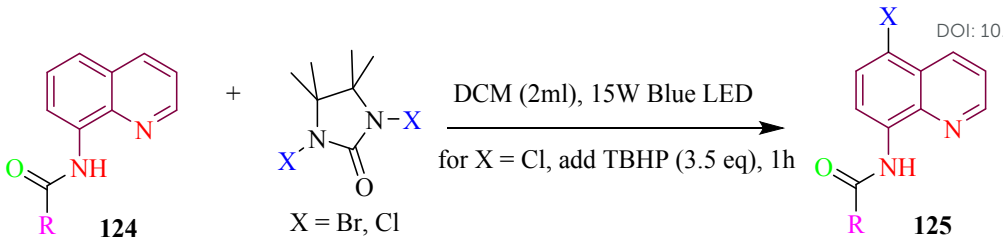
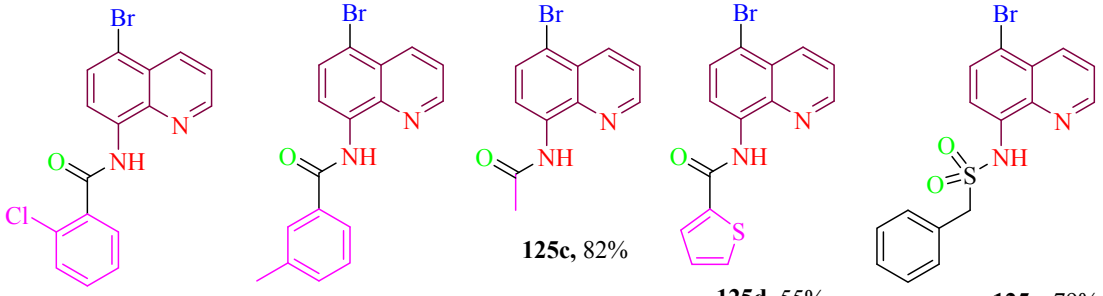
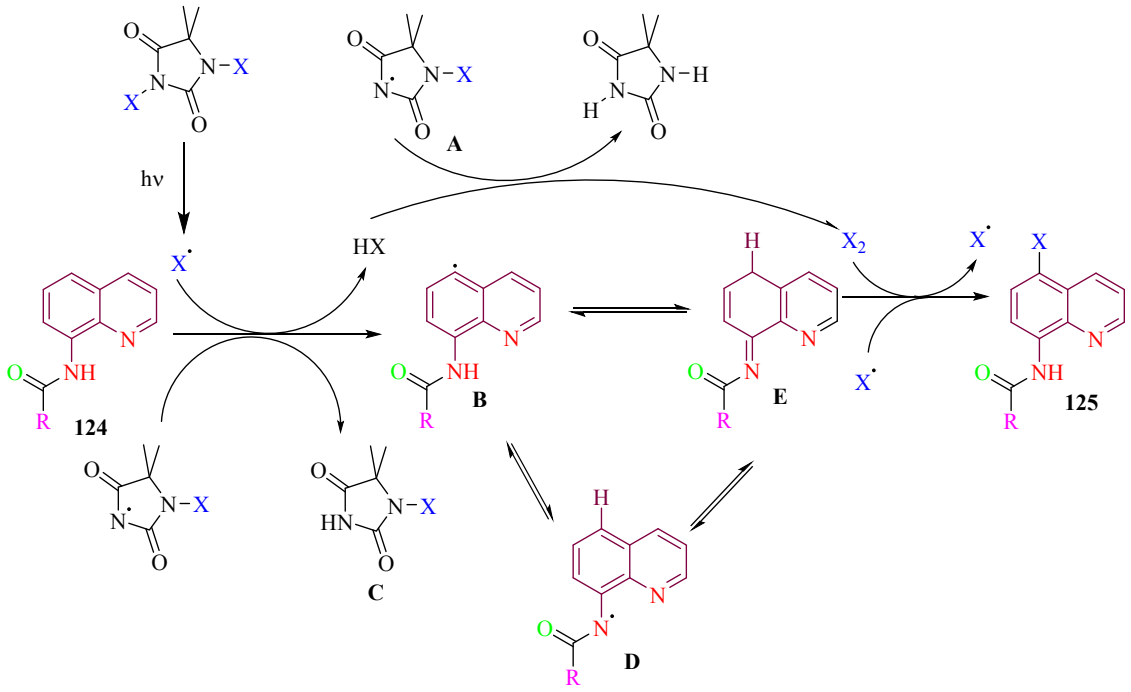
DOI: 10.1039/D5QO00372E



Representative examples



Proposed mechanism



Scheme 50. Visible light induced C-5 halogenation of 8-aminoquinoline

In 2019, Li and co-workers reported bromination and iodination of 8-aminoquinoline or *N*-acetanilide derivatives. Sodium halides (NaBr, NaI) were employed as halogenating agents at room temperature in the presence of oxidant *N*-fluorobenzenesulfonimide (NFSI) **(Scheme 51)**. Here, NFSI oxidized NaBr or NaI to obtained Br^+ or I^+ species which facilitated electrophilic halogenation of arene. This methodology accompanied by the formation of dibenzenesulfonimide as a byproduct. However, diphenylsulfonimide is a well- known starting

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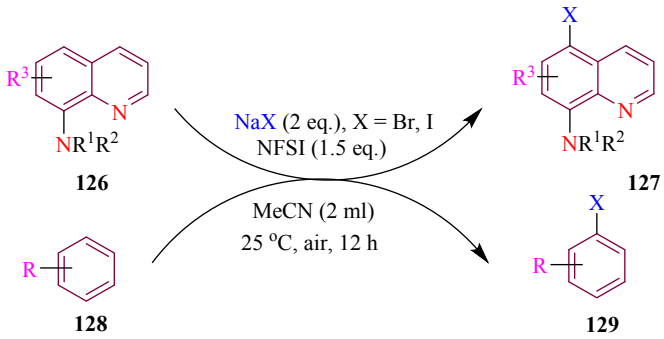
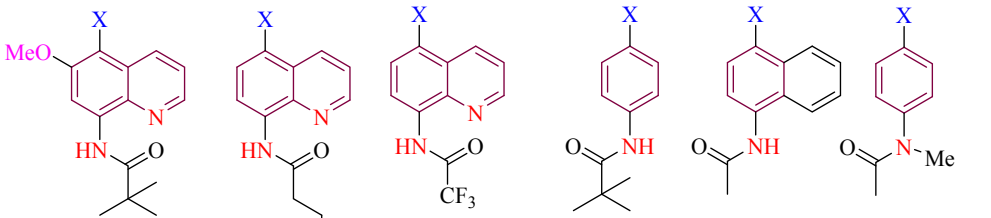
material to synthesize NFSI, making it a potential for recycling of this stoichiometric oxidant.[106]

Bromination and iodination



Representative examples



127a
X = Br, 95%
X = I, 94%

127b
X = Br, 95%
X = I, 83%

127c
X = Br, 67%
X = I, trace

129a
X = Br, 83%
X = I, 86%

129b
X = Br, 99%

129c
X = Br, 93%

Scheme 51. C–H bromination and iodination of arenes and 8-aminoquinolinamide using sodium halide.

Lei and co-workers developed a selective method for C-5 bromination of 8-aminoquinoline amides using carbon tetrabromide (CBr_4) as the bromine source, 10-phenylphenothiazine (PTH) as an organophotoredox catalyst, potassium carbonate (K_2CO_3) as the base, and a small amount of water. The reaction was performed under blue light irradiation in acetonitrile to produce the expected product **(Scheme 52)**. Both alkyl and aryl-substituted substrates were compatible for this approach. Visible light initially transformed the photocatalyst PTH into its excited form PTH*. A single-electron transfer (SET) process between PTH* and CBr_4 generates Br^-, $\bullet CBr_3$, and $PTH^{\bullet+}$. Subsequently, $^{\bullet}CBr_3$ oxidized substrate **130** to radical intermediate **A** and $HCBr_3$. Intermediate **A** reacted with $PTH^{\bullet+}$ to form the carbocation intermediate **B**, which combined with Br^- to generate intermediate **C** and underwent hydrogen atom transfer (HAT) process to deliver the target product **131**.[107]

C-5 bromination

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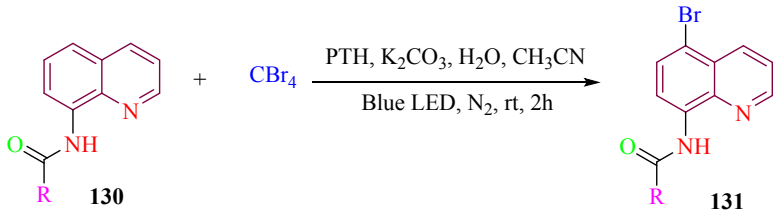
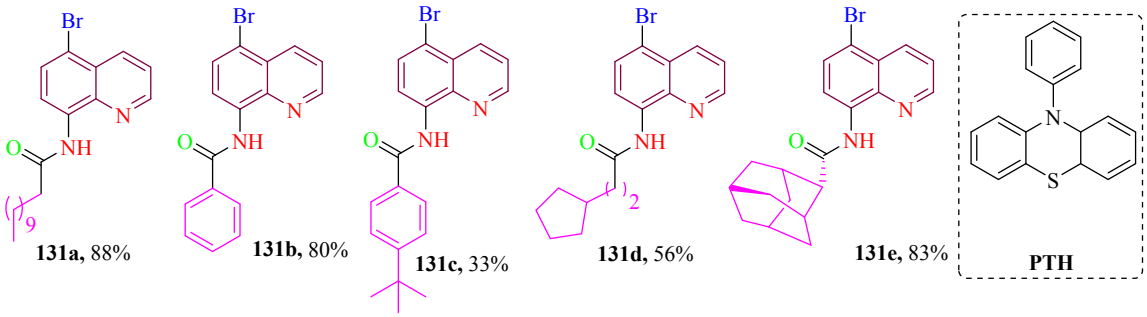
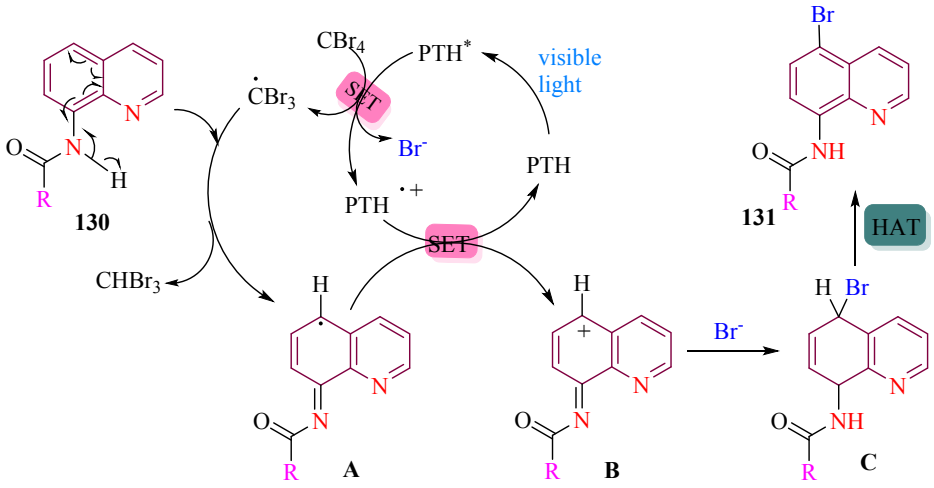
DOI: 10.1039/D5QO00372E



Representative examples



Proposed mechanism



Scheme 52. Organophotocatalyst mediated C5 bromination of 8-aminoquinoline amides.

In 2020, Xie group successfully achieved the dihalogenation of 8-aminoquinolines at C5 and C7 positions using NXS (Cl, Br) as the halogenating source through an electrocatalytic process without the use of transition metals and oxidants (**Scheme 53**). This method circumvents the limitations associated with copper catalysts. Additionally, reducing the reaction time to 3 min. under standard conditions achieved a 90% yield of monobrominated product, selectively halogenating the C5 position. Using this monobrominated compound as a reactant in the dihalogenation system led to 97% yield of the target product, demonstrating that the reaction can be controlled stepwise, with C5 position being more reactive than C7 position. The proposed mechanism, exemplified with bromination, involves the reduction of NBS at the cathode to generate Br^-, which was subsequently oxidized at the anode to produce $Br^{\cdot}$. The

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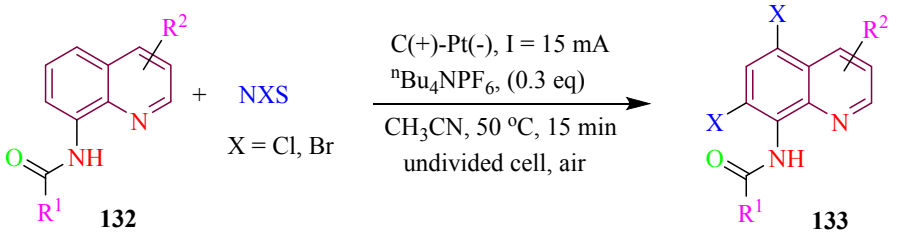
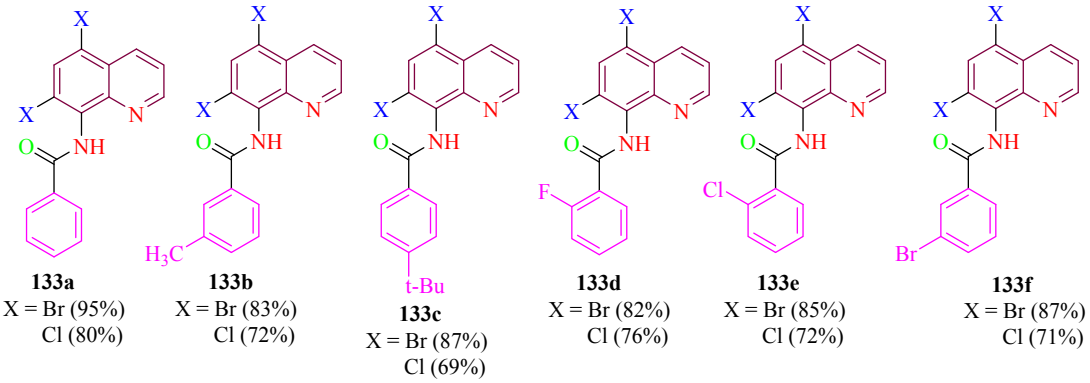
bromine radical cross-couples with radical intermediate **A**, formed *via* anodic oxidation, to create intermediate **B**. This intermediate underwent proton transfer to yield the monobrominated product **C**. The process repeated at the C7 position, forming the dibrominated product **133.**[108]

C-5 and C-7 dihalogenation



Representative examples



133a
X = Br (95%)
Cl (80%)

133b
X = Br (83%)
Cl (72%)

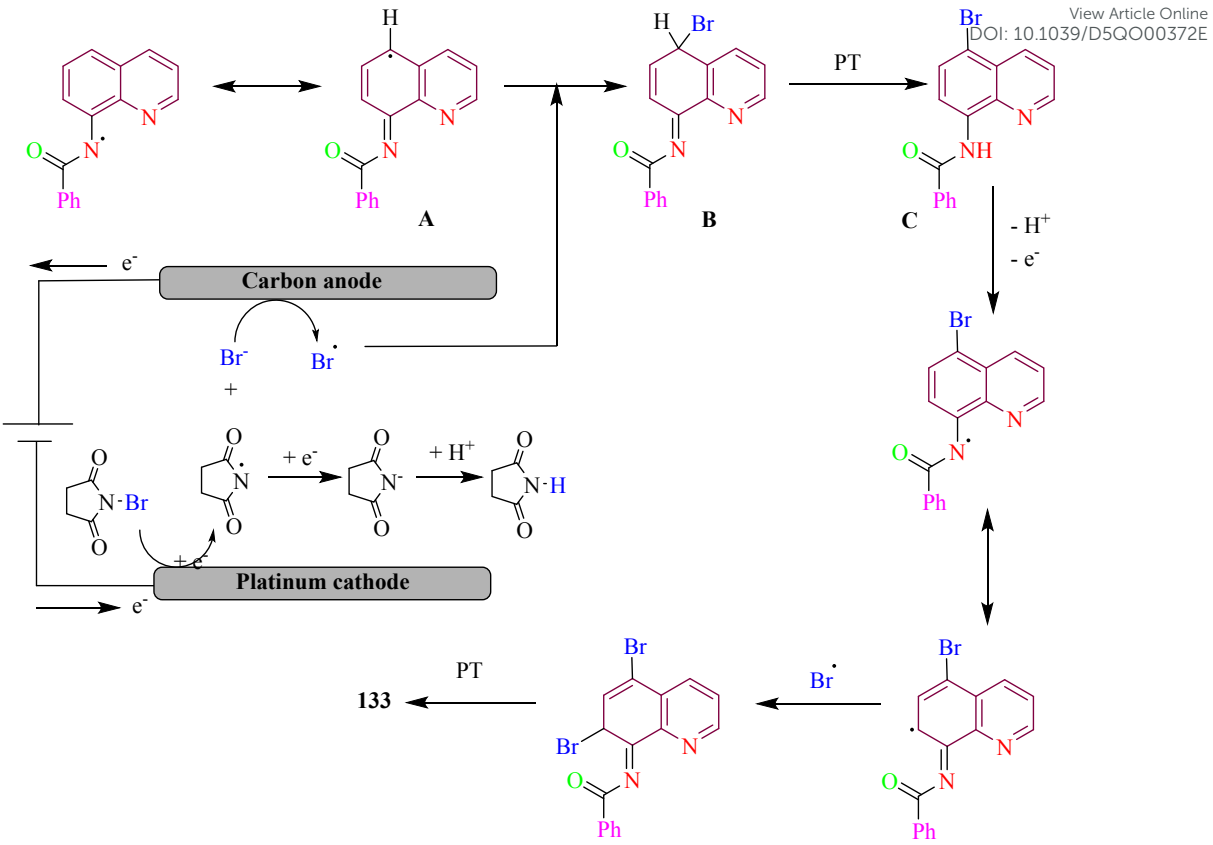
133c
X = Br (87%)
Cl (69%)

133d
X = Br (82%)
Cl (76%)

133e
X = Br (85%)
Cl (72%)

133f
X = Br (87%)
Cl (71%)

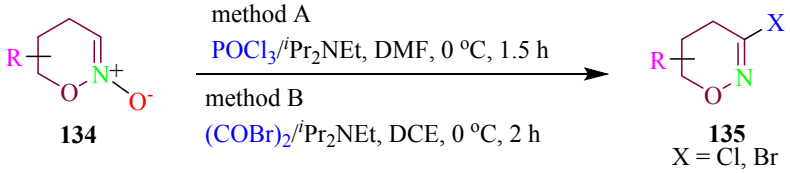
Proposed mechanism



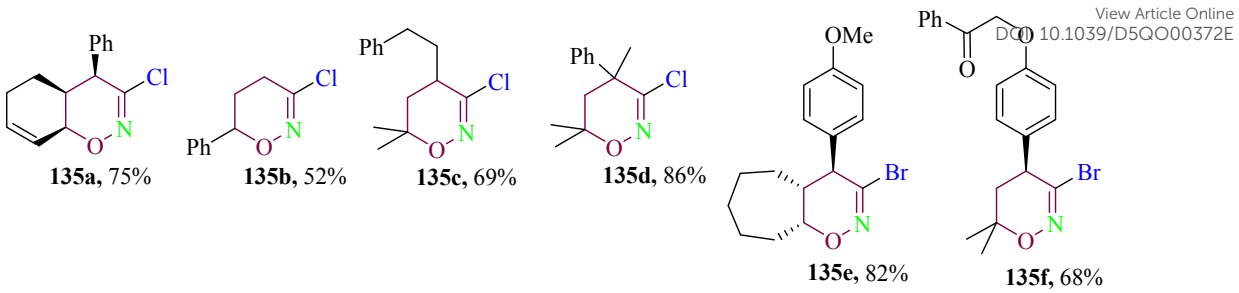
Scheme 53. Electrochemical oxidative dihalogenation at C5 and C7 positions of 8-aminoquinoline.

Further, Malykhin *et al*. established a method to access 3-halo-1,2-oxazines from 1,2-oxazine-*N*-oxides *via* nucleophilic halogenation utilizing phosphorus oxyhalides or oxalyl halides as halogenating agents. Assisted by TfOH or $BF_3 \cdot Et_2O$, the halogen substitution in 1,2-oxazines-*N*-oxide was accomplished under mild conditions (**Scheme 54**). Moreover, several side processes, including 1,2-oxazine ring contraction and [3,3]-sigmatropic rearrangement, were also observed. Introduction of azido group at C-3 position of 1,2-oxazine resulted in cyclization to hitherto unknown tetrazolo[1,5-*b*][1,2]oxazines. Fragmentation of 1,2-oxazine ring in 3-halo-1,2-oxazines upon action of strong electrophiles provided a route to unsaturated nitriles and imides.[109]

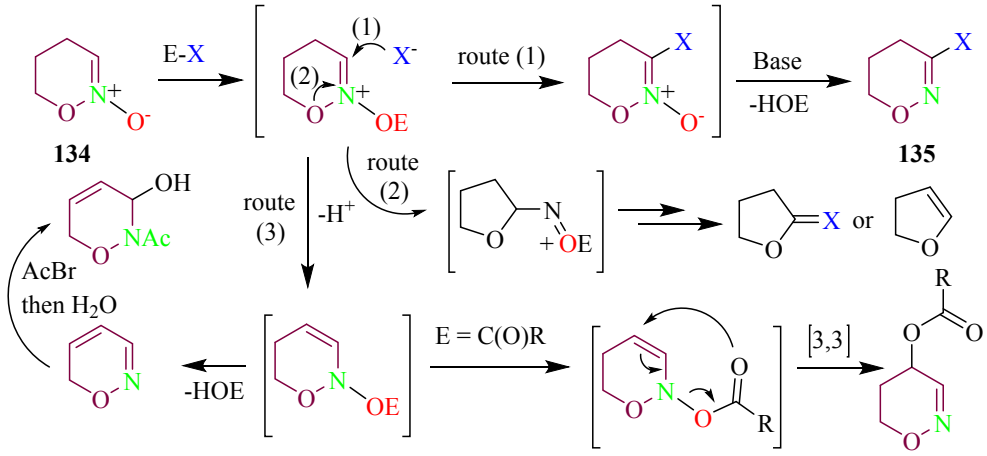
Nucleophilic halogenation



Representative examples



Proposed mechanism



Scheme 54. Nucleophilic halogenation of cyclic nitronates

Wang and co-workers reported novel one-pot synthesis of C3-sulfonate esters and C4-chlorides of quinoline *N*-oxides that is both chemo- and regioselective. This approach required no metal, oxidant, or additive and employed commercially available sulfonating and chlorinating reagents (**Scheme 55**). The methodology demonstrated good chemoselectivity and regioselectivity, operated under mild conditions, and exhibited broad functional group tolerance, making it suitable for a wide range of *N*-oxides. Initially, *N*-oxide reacted with sulfuryl chloride through *O*-acylation step, yielding intermediate **A** and a chloride ion. Intermediate **A** then underwent [3,3]-sigmatropic rearrangement to form intermediate **B**. Next, **B** is captured by another *N*-oxide *via* hydrogen bond interaction, resulting in the formation of intermediate **C**. Finally, intermediate **C** was reacted by the chloride ion through nucleophilic substitution, followed by an elimination, resulting in the formation of **137** and **138**.[110]

Sulfonate esters and chlorination

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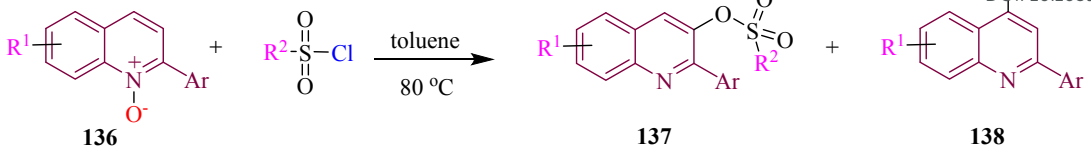
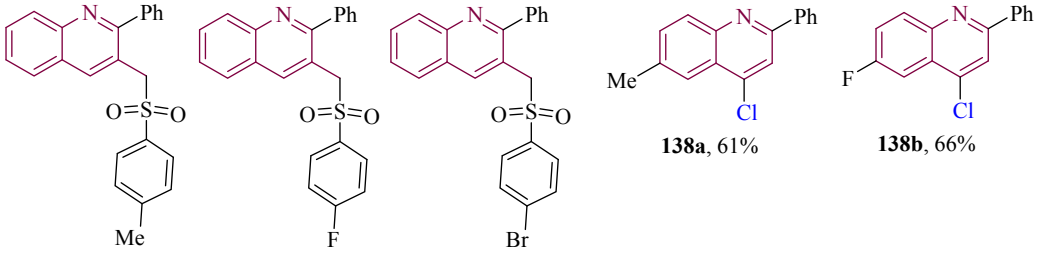


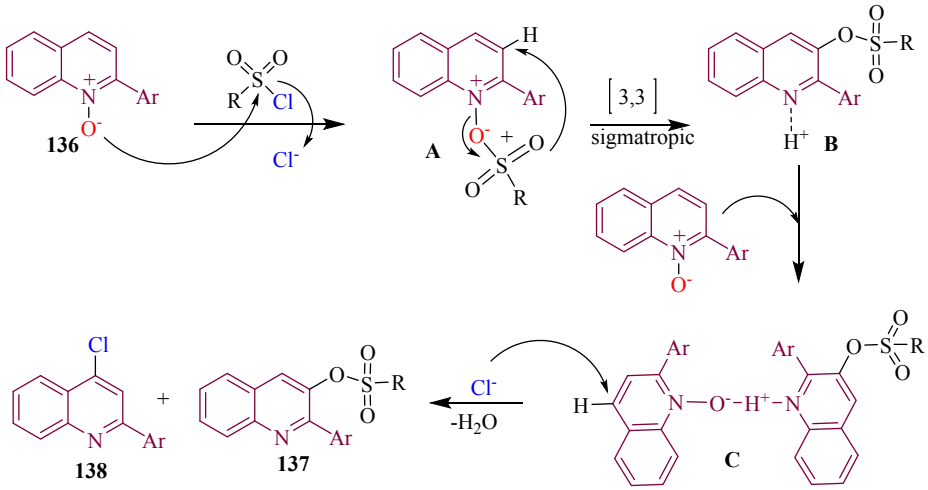
136 137 138

Representative examples



137a, 79% **137b**, 87% **137c**, 68% **138a**, 61% **138b**, 66%

Proposed mechanism

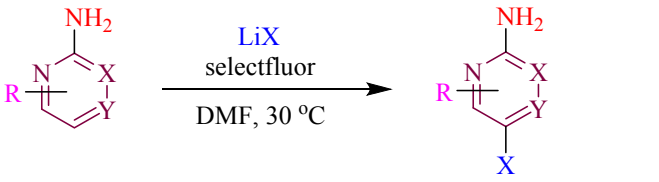


Scheme 55. Synthesis of C3-sulfonate ester and C4-chloride of quinolines from quinoline *N*-oxides.

In 2019, Hu *et al*. successfully generated C−H functionalized chlorinated and brominated products from pyridines and diazines under mild conditions, using lithium chloride (LiCl) and lithium bromide (LiBr) salts, where these achieved in good to excellent yields with high regioselectivity. The regioselectivity of halogenation in 2-aminopyridines and 2-aminodiazines was significantly influenced by the substituent patterns (**Scheme 56**). The presence of nitrogen heterocycle and *ortho*-amino group adjacent to heterocycle nitrogen were crucial for converting the starting materials into halogenated products. The authors proposed a radical pathway for the selector-mediated chlorination and bromination of 2-aminopyridines

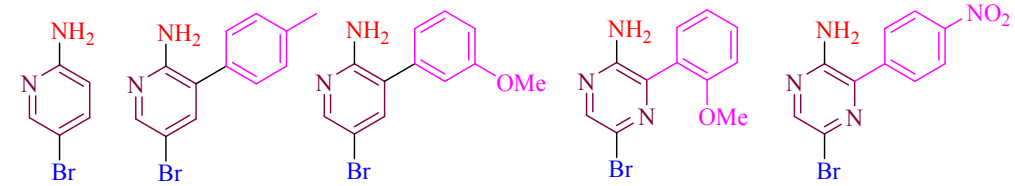
and 2-aminodiazines where a zwitterionic diradical adduct (**A**–**B**) which was formed through a SET mechanism from *N*-heteroarene, acting as an electron donor, to Selectfluor which served as the electron acceptor. Meanwhile, the cationic heterocyclic radical (**B**) underwent deprotonation to form a neutral *N*-heteroarene radical (**C**), which could isomerize to yield intermediate **D**. Intermediate **D** subsequently reacted with halogen radical to produce intermediate **F**, which underwent tautomerization to yield the desired halogenated product.[111]

Chlorination and bromination



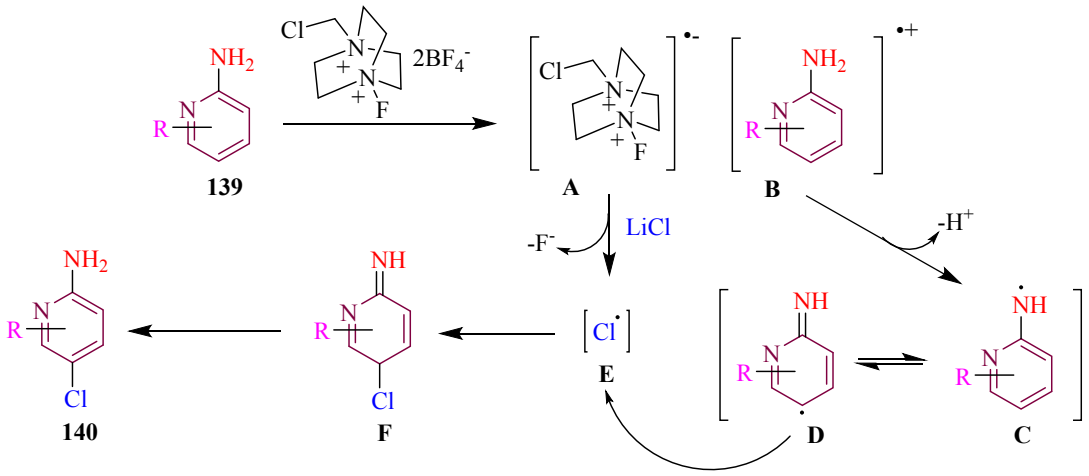
139 **140**, X = Cl, Br

Representative examples



140a, 75% **140b,** 70% **140c,** 70% **140d,** 80% **140e,** 75%

Proposed mechanism

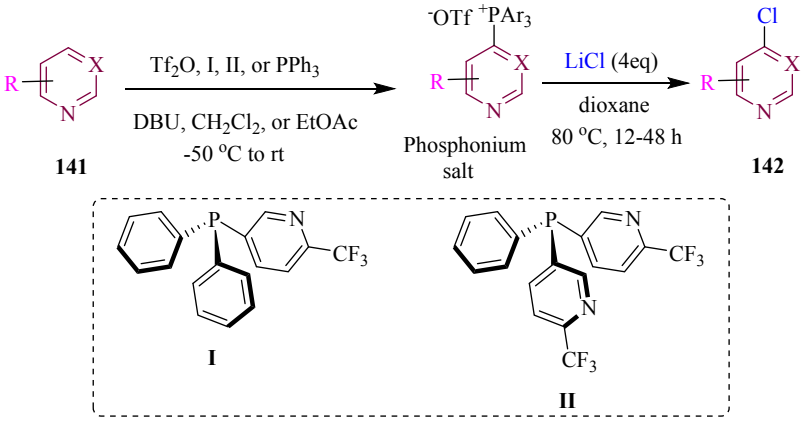


Scheme 56. Regioselective halogenation of 2-aminopyridine and 2-aminodiazines in the presence of selectofluor

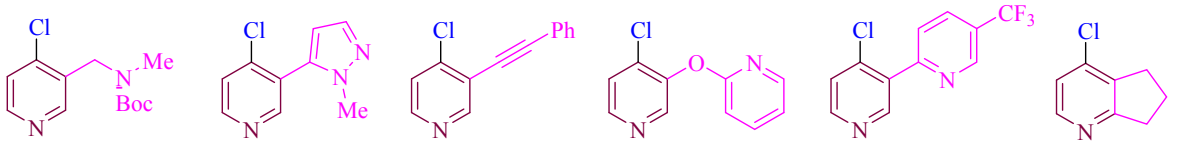
Levy *et al*. developed a strategy for selective chlorination of substituted 2-phenylpyridines and 3-phenylpyridines using a specially designed set of phosphine reagent (**Scheme 57**). The heterocyclic phosphines are introduced at 4-position of pyridines as phosphonium salts and are subsequently displaced by halide nucleophiles. In this process, the phosphine was added to triflate, activated 2- and 3,5-disubstituted pyridine rings, forming

dearomatized adducts. Computational studies revealed the formation of C−X bond through a stepwise SNAr pathway, which necessitates the *N*-activation of the pyridyl group. Steric interactions between the departing phosphine and the pyridyl substituents are particularly significant during the cleavage of C−P bond, which explained the differences in reactivity that observed between 2- and 3-substituted pyridines. This method allows for halogenation of a wide range of un-activated pyridines and is applicable for late-stage halogenation of complex pharmaceuticals.[112]

Selective chlorination



Representative examples

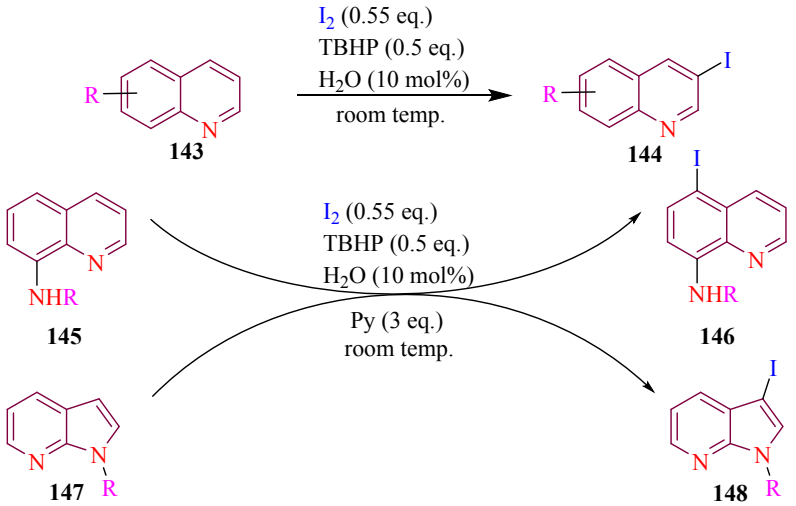


Scheme 57. Selective chlorination of pyridines using phosphine reagents

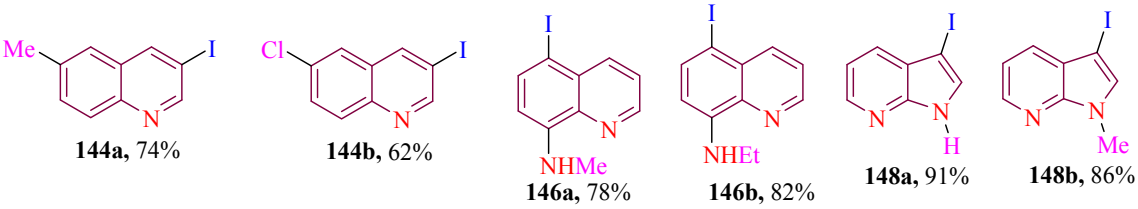
The Sekar group developed an atom-economical and facile protocol for electron-catalyzed C–H iodination of various heteroarenes, leveraging halogen-bond interactions at room temperature. The iodination was achieved using only 0.55 equivalents of I_2 and 0.50 equivalents of TBHP. Notably, the reaction efficiency improved with the addition of 10 mol% H_2O (**Scheme 58**). The success of the reaction relies on the halogen bond interaction between the heteroaryl substrates (electron donors) and iodine (electron acceptor). This interaction lowered the activation energy for electron transfer, prevented the unwanted Bray–Liebhafsky reaction, and reduced the amount of terminal oxidant required. A combination of control experiments, quantum chemical calculations, and spectroscopic analyses confirmed the formation of a halogen bond, its role in lowering the activation barrier, the regioselectivity of the reaction, and the presence of radical intermediates in the reaction mixture. Mechanistic investigations revealed that the reaction proceeds *via* a radical pathway, with both kinetically

controlled and thermodynamically controlled pathways, converging to produce a single regioisomer.[113]

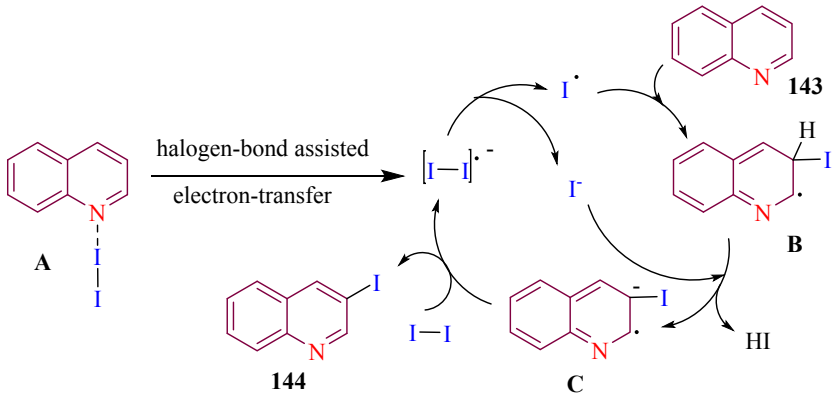
Electron-catalyzed C–H iodination



Representative examples



Proposed mechanism



Scheme 58. Electron-catalyzed iodination of heteroarenes at room temperature

In another approach, Du *et al*. developed a facile transition-metal free method for synthesizing *ortho*-bromoanilides from arylhydroxylamines. Here, thionyl bromide was used as halogenating agent under mild reaction conditions (**Scheme 59**). To evaluate the substrate scope, the optimized protocol employed on wide variety of substituted substrates delivered the desired targets in good to moderate yields. Several control experiments ruled out the free radical mechanism involving the intramolecular substitution.[114]

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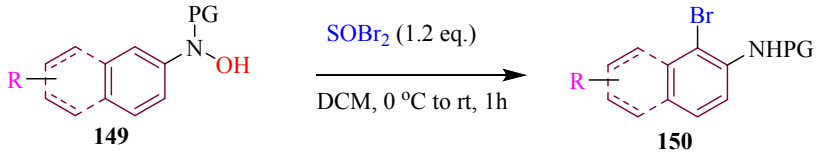
***ortho*-bromoanilides**



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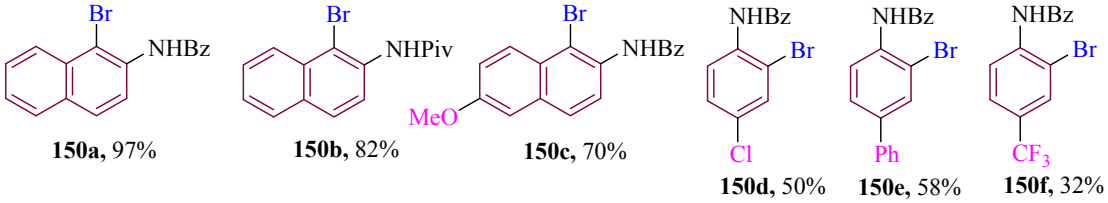

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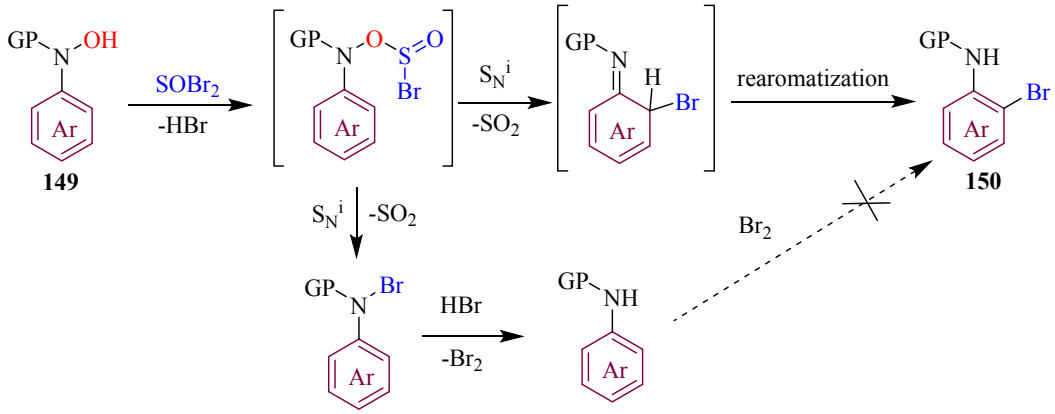

Scheme 59. Synthesis of *ortho*-bromoanilides using thionyl bromide

Further, Yu *et al*. performed electrochemical directed chlorination and bromination of electron-deficient C–H bond in different heterocycles such as quinones, coumarins, quinoxalines and 1,3-diketones. The protocol utilized the readily available halogen sources such as HCl and KBr under mild reaction conditions, yielding highly site-selective derivatives (**Scheme 60**). Moreover, a set of control experiments were performed to investigate the mechanistic pathway suggested the electrophilic process. Here, first cathodic reduction of benzoquinone could generate the corresponding hydroquinone, which underwent electrophilic chlorination with chlorine (from anodic oxidation of the chloride anion) to afford the chlorinated hydroquinone. Subsequently, anodic oxidation could give the desired product.[115]

Chlorination and bromination

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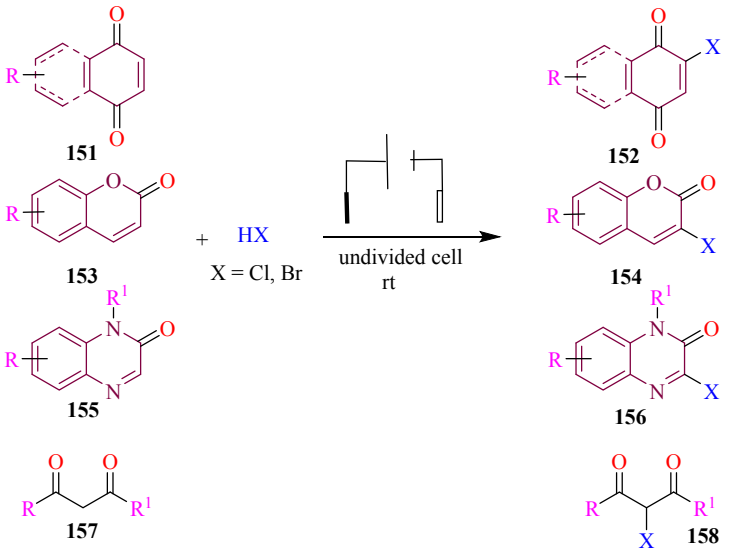

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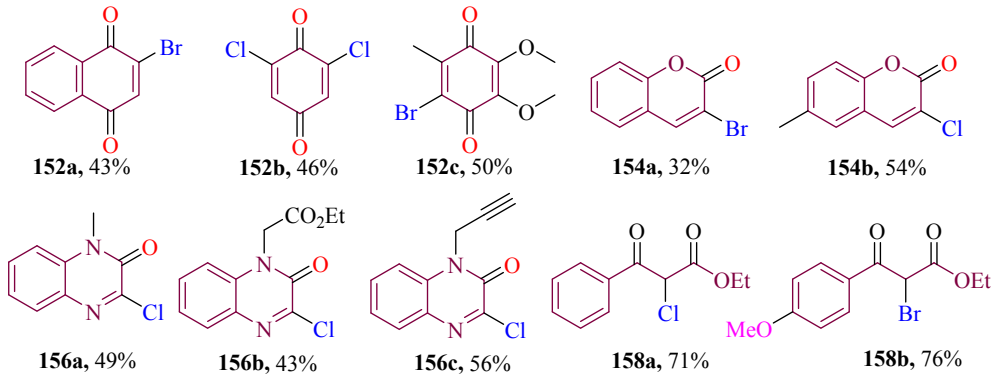

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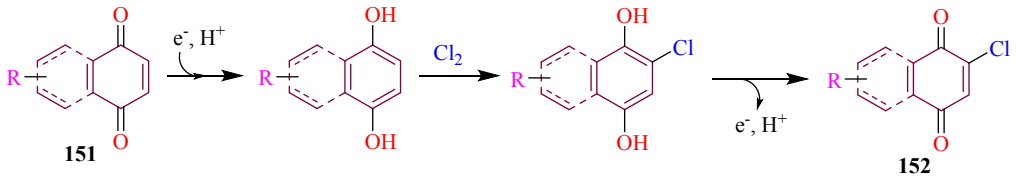
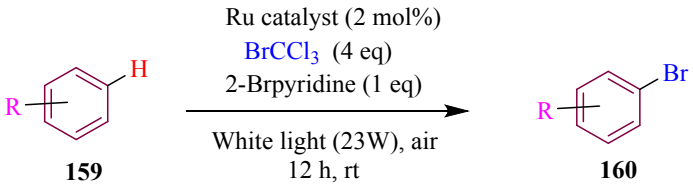


Scheme 60. Electrochemical chlorination and bromination of different heterocycles

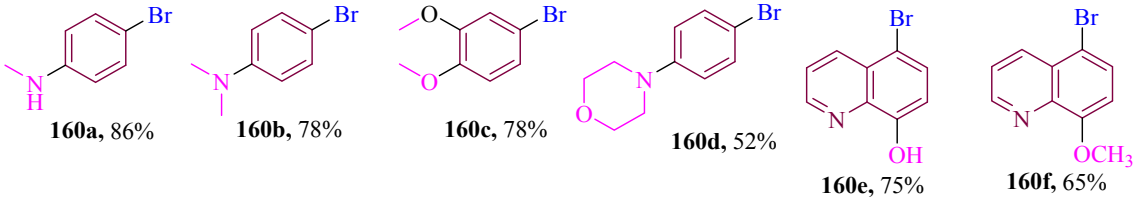
In 2021, Loh group reported an efficient method for visible-light-induced bromination of electron-rich arenes and heteroarenes. In this approach, substrate was treated with bromination reagent $BrCCl_3$ under 23 W white light irradiation, resulting in synthesis of C4-brominated compound (**Scheme 61**). Interestingly, unprotected 8-hydroxyquinoline demonstrated greater reactivity than methyl-protected 8-hydroxyquinoline, and both forms were significantly more reactive than 8-aminoquinoline. The photocatalyst Ru(II) was converted into excited Ru(II)* under visible light exposure. Then, Ru(II)* interacted with substrate (**159**), resulting in the formation of Ru(I) and the amino radical cation (**A**) *via* SET mechanism. Next, Ru(I) was oxidized by oxygen in air, regenerating the initial Ru(II) and

completing the photocatalytic cycle. Simultaneously, the intermediate **A** could undergo tautomerism to form a radical intermediate (**B**). Subsequently, the radical intermediate (**B**) reacted with $BrCCl_3$ through SET, forming a cationic intermediate (**C**). Finally, this cationic intermediate underwent deprotonation to yield the target product **160**.[116]

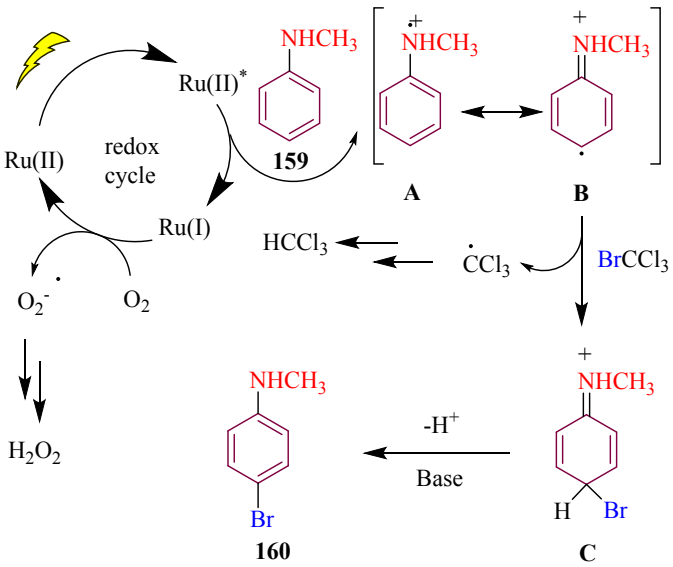
Visible-light-induced bromination



Representative examples



Proposed mechanism



Scheme 61. Visible-light induced regioselective bromination of arenes

Recently, Fu group incorporated regioselectively bromine and iodine at *N*-heteroarenes through FMO modulation strategy using *N*-benzyl azaarenium salts. In this strategy, dihalogenation was achieved in pyridines and quinolines while monohalogenation was formed in isoquinolines (**Scheme 62**). The optimized reaction conditions were explored on varied *N*-benzyl azaarenium salts for *meta*-bromination of *N*-heteroarenes, delivered products in good yields. Further, DFT studies were carried out to elucidate the reaction mechanism suggesting the electrophilic addition of bromine radical followed by deprotonation and finally the single

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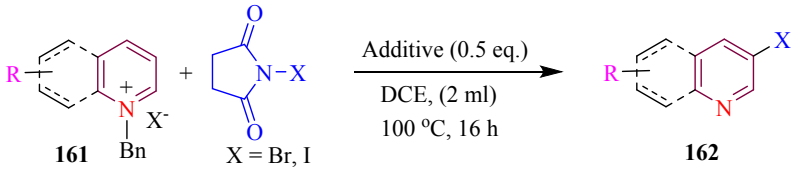
electron transfer to provide the final product.[117]

Regioselective bromination and iodination



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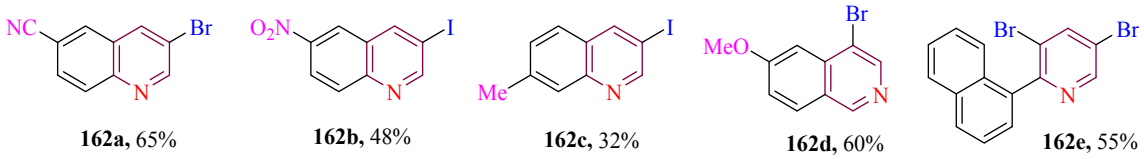

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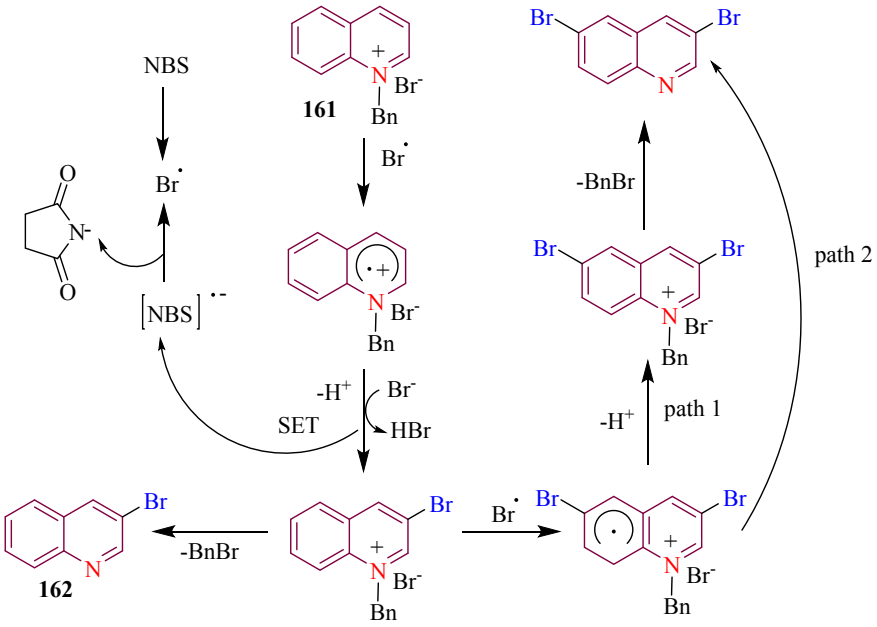
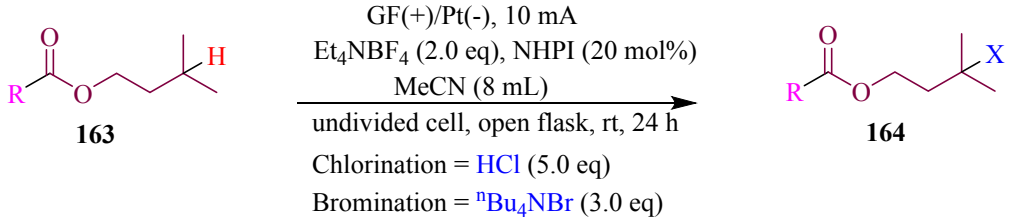


Scheme 62. *meta* C−H halogenation of azines

Recently, Liu group reported on electrochemical chlorination and bromination of minimally hindered tertiary and secondary benzylic C(sp^3)–H bonds (**Scheme 63**). Their method employed graphite felt (GF) as the anode and a platinum (Pt) sheet as the cathode, using tetraethylammonium tetrafluoroborate (Et_4NBF_4) as the electrolyte. For chlorination, hydrochloric acid (HCl) was used, while *n*-butyl tetraalkylammonium bromide ($^nBu_4NBr$) served as the brominating agent, with *N*-hydroxy phthalimide (NHPI) acting as a catalyst. This process was conducted under constant current in an undivided cell. The protocol demonstrated good tolerance for various substitutions, yielding the desired products in moderate to good yields. Mechanistic studies revealed the possible catalytic pathway involved the generation of chlorine radical, single-electron oxidation of NHPI and hydrogen atom transfer from alkane.[118]

Electrochemical chlorination and bromination



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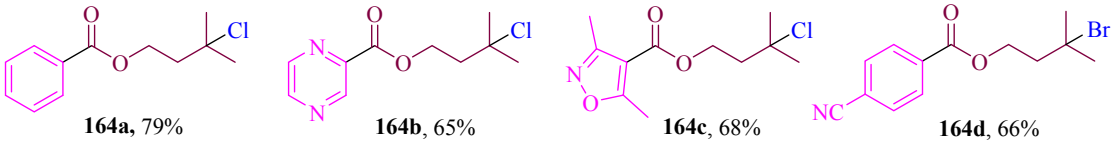
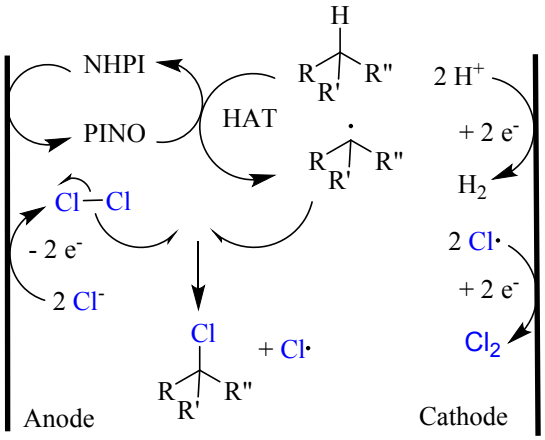


Proposed mechanism



Scheme 63. Electrochemical chlorination and bromination of benzylic C(sp^3)–H bonds

4. Conclusion and future outlook

This review aims to provide a comprehensive overview of recent advancements in directing group-assisted synthesis of organohalides, including aryl, vinyl, alkyl, and heteroaryl halides. Halogen bonds are vital in organic and inorganic compounds, making them essential in material science, molecular recognition, crystal engineering, catalysis and rational drug design. Additionally, the significance of organohalides as fundamental building blocks for further transformations is emphasized, showcasing how C–H activation strategies with directing groups create a solid mechanistic foundation for future innovations in synthetic chemistry. This review emphasizes the utilization of various types of directing groups to achieve regioselective C–H halogenation (fluorination, chlorination, bromination, and iodination) through various mechanistic pathways involved, including photocatalysis, visible-light-induced methods, transition-metal catalysis, and electrochemical approach, which offer efficient alternatives to conventional lengthy synthetic routes and harsh reaction conditions.

Besides various advantages, the approach is also associated with various shortcomings, like the requirement of additional steps, additives, and high stoichiometric oxidants, leading to reduced overall efficiency and atom economy. Some directing groups add complexity to the process, generating waste and acting highly substrate-specific, limiting their general applicability. Current research shows much potential for this approach, but we have only tapped into a small part. To make these methods more useful, future studies should focus on creating techniques that can handle various functional groups, such as amines, nitro, carbonyl, thioether, hydroxyl, and oxime groups. Moreover, directing groups can be designed to increase their efficiency, such as replacing 8-aminoquinoline with 8-quinolinamide and quinoline N-oxide, converting amide to Weinreb amide, which acts as a weakly coordinating group with transition metal, leads to a more selective C−H activation and enhancing the ability of aldehyde, ketone through transient group strategy where imine generated *in situ* acts as directing group that increases the overall efficiency of the process. Advances in catalyst design, sustainability, and reaction efficiency shape its future outlook. Future research will also likely focus on DGs that can be easily removed or naturally degraded after functionalization to enhance the efficiency of synthetic routes. Using recyclable DGs that can be regenerated and reused will improve cost-effectiveness and sustainability. As medicinal chemistry and late-stage functionalization grow, DGs compatible with biomolecules will become crucial for pharmaceutical applications.

Moreover, significantly less research has focused on fluorination in halogenation despite its increasing demand in drug discovery and agrochemicals, which will catalyze innovation in mild and site-selective fluorination methods. Developing techniques for the selective introduction of chlorine, bromine and iodine will broaden applications in cross-coupling reactions and late-stage functionalization. Adopting metal-free approaches that employ organic catalysts and light-driven halogenation strategies could mitigate toxicity, reduce environmental impact, offer more sustainable and selective alternatives. Employing computational strategy for better understanding of reaction pathways will facilitate the design of more efficient halogenation processes. Prioritizing the development of catalytic systems that utilize stable, non-toxic and minimal halogen sources which maximize atom economy and make these methods more practical for industrial applications. Thus, by integrating computational tools, greener catalysts, and innovative directing group strategies, the utility of this approach in organic synthesis, pharmaceuticals, and material sciences can be further expanded. Therefore, ongoing research into C–H halogenation with directing groups presents a valuable opportunity to unlock new reactivity, develop creative synthetic pathways, and

achieve transformations with enhanced regio- and stereo-selectivity, sustainability and improved step and atom economy.

Associated content

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Author Contributions

P. S.: conceptualization, and drafting. V. L.: visualization, and editing. K. P.: visualization, investigation, supervision and editing.

Notes

The authors declare no competing financial interest.

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Data Availability Statement

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.