有机化学 DOI: 10.6023/cjoc202205034 综述与进展
Chinese Journal of Organic Chemistry REVIEW

以 7-氮杂吲哚为内在导向基团的 *N*-芳基 C—H 官能化研究进展

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摘要 内在导向基团是底物中固有的官能团, 同时也是产物中的核心结构单元. 因此, 在 C—H 官能化反应中, 内在导向基团无需事先引入以及事后脱除. 在过渡金属催化的 *N*-芳基-7-氮杂吲哚的 *N*-芳基 C—H 官能化反应中, 7-氮杂吲哚往往作为内在的导向基团, 借助C—H官能化的反应策略, 在*N*-芳基的邻位引入各种官能团. 对过渡金属催化7-氮杂吲哚作为内在导向基的 *N*-芳基 C—H 官能化的最新研究进展进行了概述.
关键词 7-氮杂吲哚; 内在导向基; C—H 活化; 过渡金属催化

Recent Advances in the *N*-Aryl C—H Functionalization Using 7-Azaindole as Intrinsic Directing Group

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Abstract The intrinsic directing group is a functional group in the substrates and also serves as an essential component in products. Thus, the preinstallation and removal of directing groups are avoided. 7-Azaindole has been used as intrinsic directing group for the *N*-aryl-C—H functionalization of *N*-aryls under the catalysis of transition metals. Utilizing the C—H functionalization strategy, numerous functional groups were installed into the *ortho*-position of *N*-aryls of the corresponding *N*-aryl-7-azaindoles. In this review, the recent achievements on the transition-metal catalyzed *N*-aryl *ortho*-C—H functionalization directed by 7-azaindole are summarized.
Keywords 7-azaindole; intrinsic directing group; C—H activation; transition-metal catalyzed

In the past few decades, C—H functionalization has become one of the most popular hotspots of research due to its high efficiency, simple operation, high atom economy and environmentally benign nature.[1] In this field, directed C—H activation, which shows excellent site selectivity is one of the most powerful approaches for the construction of C—C and C—X bonds from inert C—H bonds.[2] However, there are various directing groups which cannot be removed or require some additional steps for their removal, thereby it limits the structural diversity of the products and lowers the step economy. These limitations are overcome by transient directing group strategy which coordinate themselves to any pre-existing moiety in the molecule and get released after reaction. The traceless directing group strategy features with functionalization of the substrates and removal of the directing groups in one pot is another wise choice. Moreover, intrinsic directing group strategy is also one efficient method to overcome such limitations, since the intrinsic directing group is a functional group that already existed in the substrates and serves as an essential component in products, thus there is no requirement for additional installation or removal steps. For example, sulfonamide, *β*-carboline amides, imidazole, purine, 2*H*-indazole were widely used as the intrinsic directing group for C—H functionalization.[3]

7-Azaindole, a bioisostere of indole, displays a wide range of biological activities, and has been found in a large number of drug molecules and candidate drugs.[4] With the tremendous progress in medicinal chemistry, a variety of 7-azaindole derivatives have been prepared and evaluated in clinical trials. For example, vemurafenib, GSK1070916, decernotinib and BMS378806 are currently on the market or under the clinical phase (Figure 1).[5] In addition, *N*-phenyl-7-azaindole derivatives also have a diverse bioactivity profile including anticancer, antiproliferative, antidiabetic, and NHE inhibitory activities (Figure 1).[6] Given the broad utilizations of 7-azaindoles in medicinal chemistry, there emerged many studies on the C—H functionali-

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Received May 20, 2022; revised June 29, 2022; published online August 10, 2022.
Project supported by the Qing Lan Project of Jiangsu Province.
江苏省高校青蓝工程资助项目.

zation of 7-azaindoles. For example, efficient functional group modifications at the C(2) or C(3) position of azaindoles under the catalysis of transition metals have been described.[7] Besides, 7-azaindole could be used as an intrinsic directing group to facilitate the functionalization of C(sp^2)—H in *N*-aryl moiety of *N*-aryl-7-azaindoles. In recent years, researches on the 7-azaindole-directed *N*-aryl C—H alkenylation, cyclization, amidation, amination, cyanation, alkynylation, nitration, *etc*. have been developed. The purpose of this review is to provide an essay on the advances of transition-metal catalyzed 7-azaindole-directed *N*-aryl C—H functionalizations (Figure 2).

2 Carbon-carbon bond formation by 7-azaindole-directed *N*-aryl C—H functionalization

2.1 *N*-Aryl C—H alkenylation of *N*-aryl-7-azaindoles

In 2016, Dong's group developed a rhodium(III)-catalyzed C—H alkenylation of *N*-aryl-7-azaindoles with electron-donating olefins (Scheme 1).[8] Variously substituted vinyl acetates and allyl acetates were used as coupling partners, providing the dehydrogenative Heck-type (DHR) products (**1-G**) and olefinated products (**1-H**).

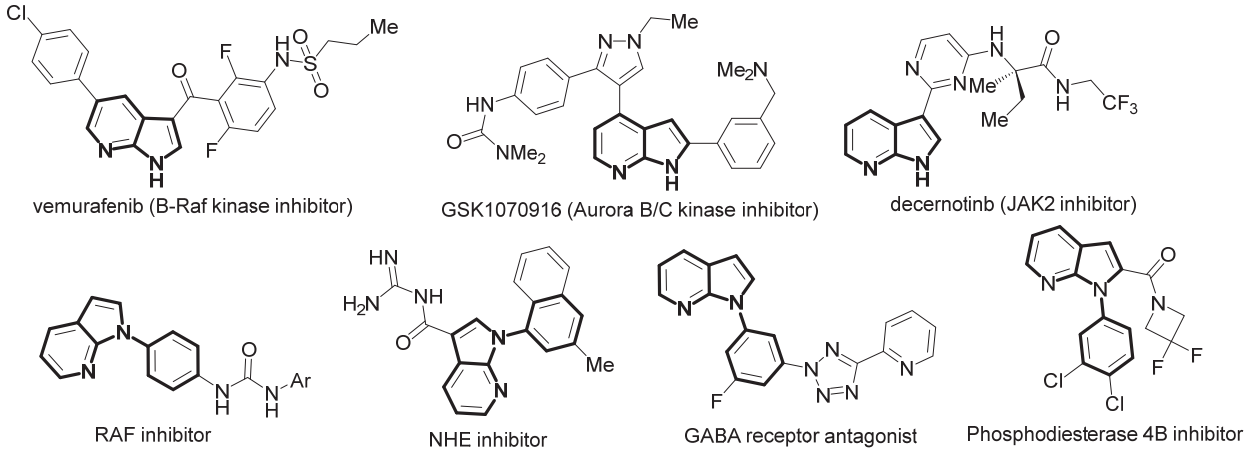


Figure 1 Pharmaceuticals containing 7-azaindole motif

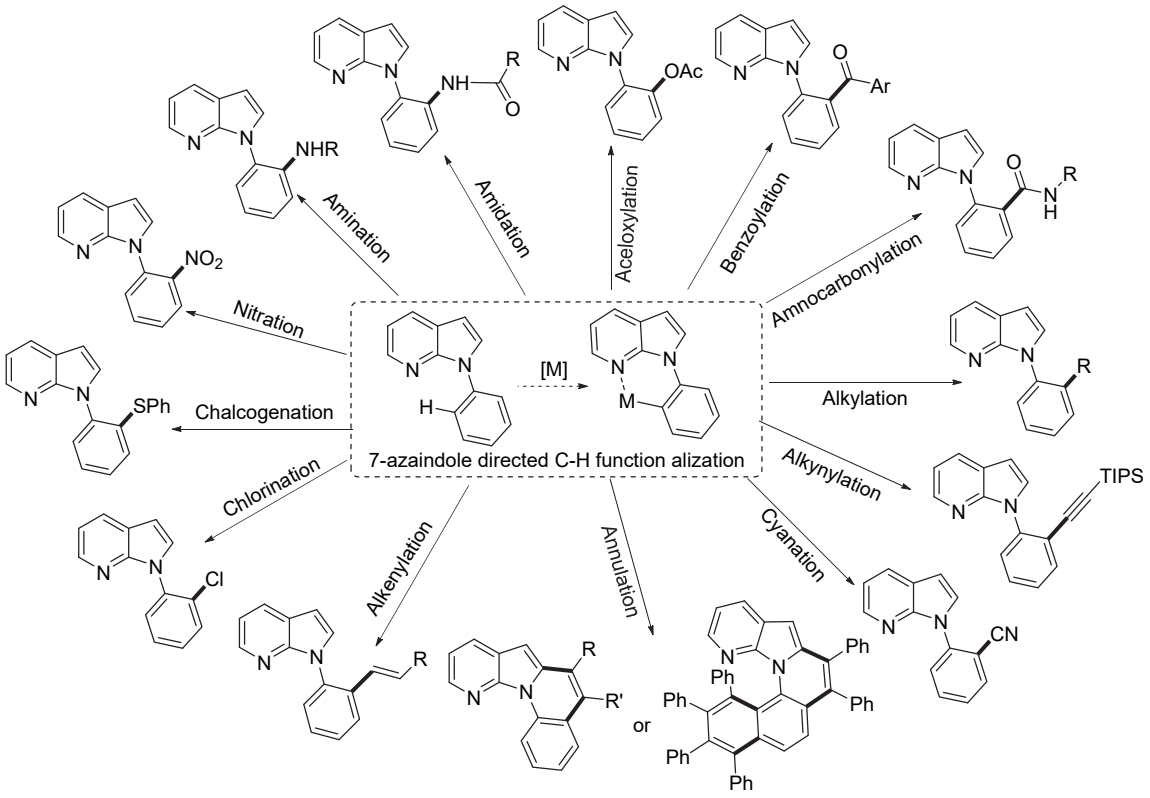
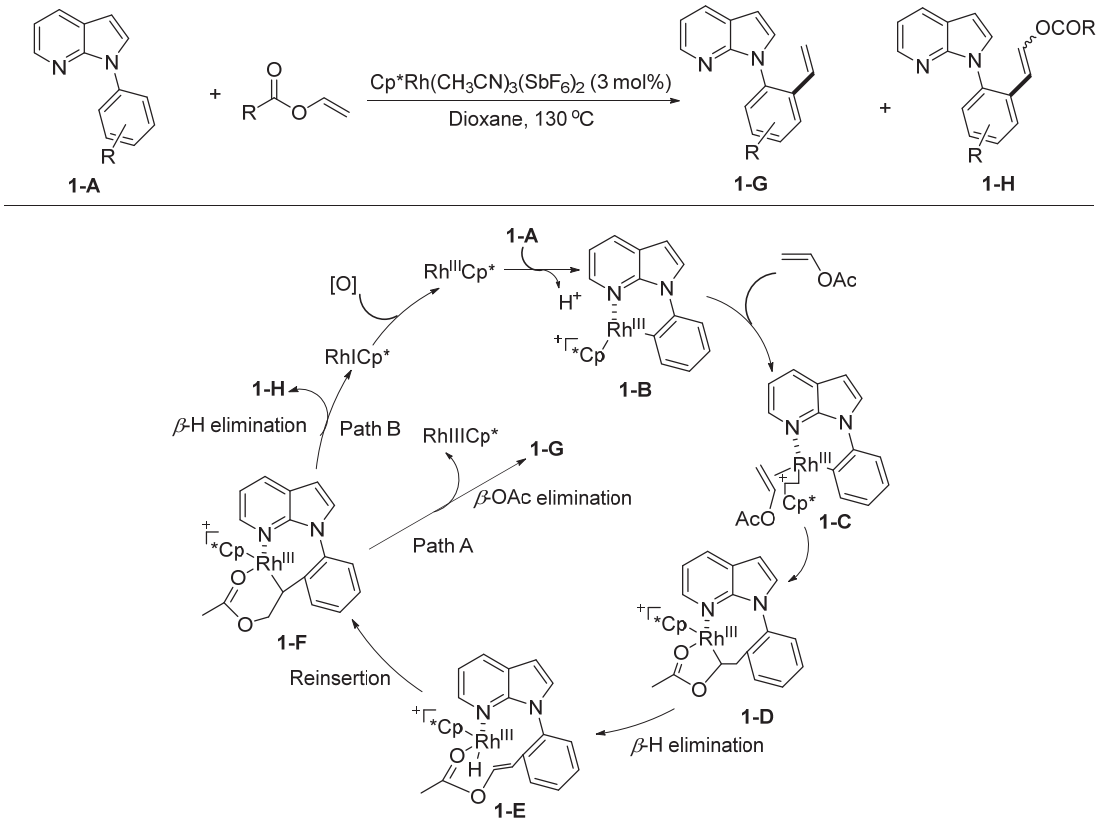


Figure 2 Transition-metal-catalyzed 7-azaindole-directed *N*-aryl C—H functionalization of *N*-aryl-7-azaindoles

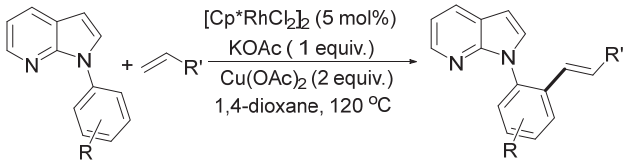


Scheme 1 *N*-Aryl C—H alkenylation of *N*-aryl-7-azaindoles with vinyl acetates

Interestingly, the selectivity of the coupling reaction is alkene-dependent: for vinyl acetate, DHR products were major products. If other alkenyl esters were used, the yields of olefinated products were relatively higher. Mechanistically, *N*-phenyl-7-azaindole coordinates with Rh to generate a six-membered rhodacycle species **1-B** through C—H activation. Afterwards, vinyl acetate coordinates to the rhodacycle species **1-B** to form intermediate **1-C**. The regioselective insertion of vinyl acetate into the Rh—C bond of intermediate **1-C** produces rhodacycle species **1-D**. Then, *β*-H elimination of **1-D** provides rhodium-hydride **1-E**, which undergoes reinsertion into the Rh-H bond to give a seven-membered metallacycle **1-F**. The styrene product **1-G** was obtained with the elimination of acetate (pathway A). Alternatively, intermediate **1-F** may undergo *β*-H elimination to give **1-H** (pathway B). Utilizing similar strategy, they developed an rhodium-catalyzed dehydrogenative Heck-type reaction between *N*-aryl-substituted 7-azaindoles and various alkenes through a H_2-releasing process.[9] The methodology broadens the scope of metal-catalyzed hydrogen-releasing reactions.

Almost at the same time, Ge and Li[10] described a similar Rh(III)-catalyzed C—H oxidative olefination of *N*-aryl-7-azaindoles with alkenes using $Cu(OAc)_2$ as oxidant (Scheme 2). Substituted alkenes such as styrenes and acrylates were all well tolerated.

In the same year, Miura and co-workers[11] disclosed a Rh-catalyzed regioselective alkenylation of *N*-aryl-7-azaindoles with 1 equiv. of alkenes using 2 equiv. of AgOAc as the oxidant. Notably, treating *N*-phenyl-7- azaindole with 5 equiv. of alkenes and 4 equiv. of AgOAc leads to the dialkenylated products (Scheme 3). Moreover, the synthesis of unsymmetrical dialkenylated benzene derivatives can also be achieved in a stepwise, one-pot procedure.

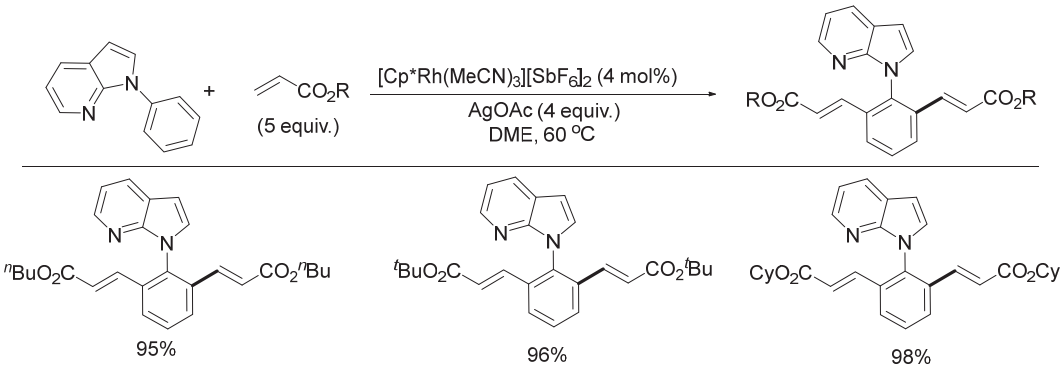


Scheme 2 *N*-Aryl *ortho*-olefination of *N*-aryl-7-azaindoles

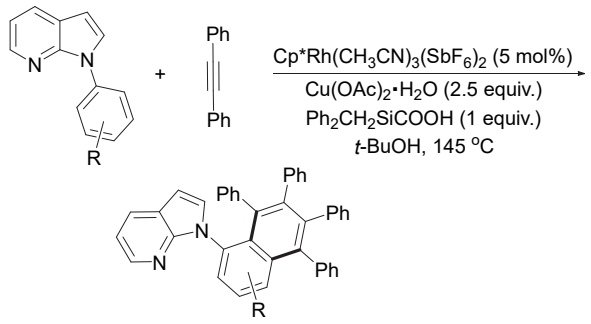
Later, Dong *et al*.[12] achieved a 7-azaindole directed *N*-aryl C—H alkenylation of *N*-aryl-7-azaindoles with styrene under the catalysis of $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ with $Cu(OAc)_2$ as the oxidant. If alkynes were used as substrates, dual C—H activation at the *N*-aryl was achieved to form *N*-naphthylazole derivatives (Scheme 4).

2.2 C—H alkynylation of *N*-aryl-7-azaindoles

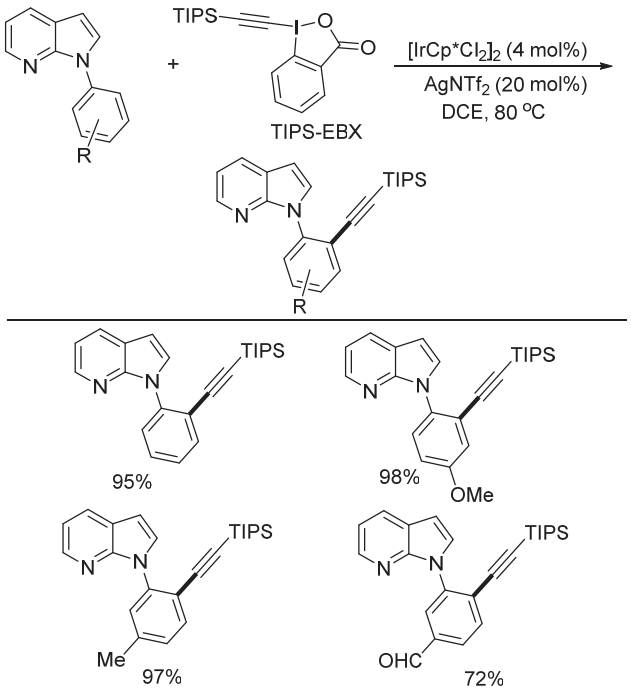
In 2016, Li's group[13] provided a general and straightforward route toward *N*-(2-ethynylaryl)-7-azaindoles through Ir(III)-catalyzed direct C—H alkynylation of *N*-aryl-7-azaindoles using 1-((triisopropylsilyl)ethynyl)-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX) as the alkynyl source (Scheme 5). A variety of *N*-aryl-7-azaindoles with different substituents were successfully transformed into the corresponding products in good yields.



Scheme 3 *N*-Aryl C—H alkenylation of *N*-aryl-7-azaindoles with alkenes



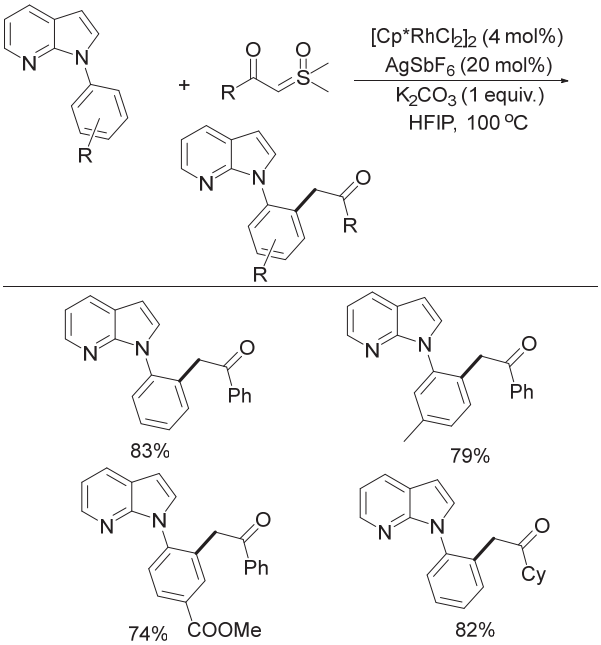
Scheme 4 *N*-Aryl C—H alkenylation and annulation of *N*-aryl-7-azaindoles



Scheme 5 *N*-Aryl C—H alkynylation of *N*-aryl-7-azaindoles with TIPS-EBX

2.3 C—H alkylation of *N*-aryl-7-azaindoles

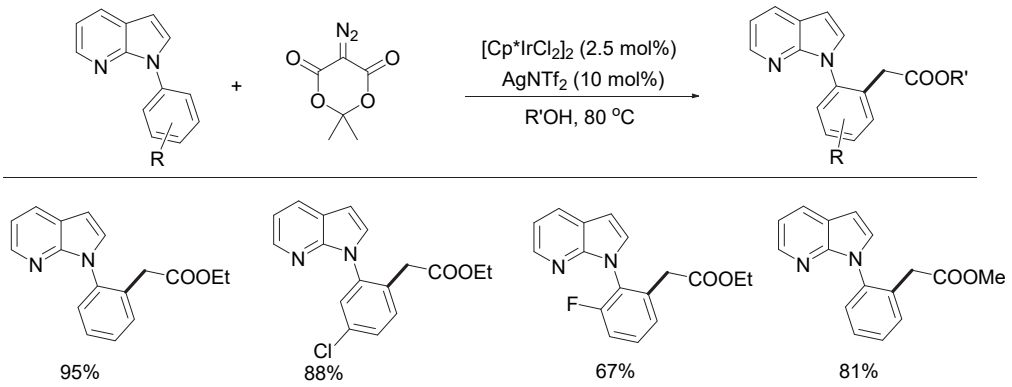
Sulfoxonium ylides, which are easily prepared, stable and safe, were developed and utilized in C—H functionalization reactions.[14] In 2020, Kong and Xu *et al.*[15] disclosed a rhodium-catalyzed C—H alkylation of *N*-(hetero) aryl-7-azaindoles with *α*-carbonyl sulfoxonium ylides via the formation of metal carbene species (Scheme 6). This transformation generates the ketone-decorated *N*-aryl-7-azaindoles in good yields with broad functional group tolerance, and does not require a sacrificial oxidizing reagent.



Scheme 6 *N*-Aryl C—H alkylation of *N*-aryl-7-azaindoles with *α*-carbonyl sulfoxonium ylides

Transition-metal catalyzed C—H bond functionalization with diazo compounds through the formation of metal carbene species has been proved as a powerful approach to construct complex structures.[16] In 2021, our group[17] developed an iridium-catalyzed selective *N*-aryl C—H carbenoid functionalization of *N*-aryl-7-azaindoles with *α*-diazotized Meldrum's acid (Scheme 7). This procedure was simple, mild with high regioselectivity and broad substrate scope, providing a series of 2-azaindolyl acetic esters in good to excellent yields. The obtained 2-azaindolyl acetic esters could be transformed into corresponding 2-(azaindolyl) acetic acids after hydrolysis in excellent yield.

In 2021, Liu's group[18] achieved the C—H alkylation of *N*-aryl-7-azaindoles with cyclopropanols through merging tandem C—H and C—C cleavage under the catalysis of Rh(III), giving *β*-arylated ketone derivatives in good yields



Scheme 7 *N*-Aryl C—H alkylation of *N*-aryl-7-azaindoles with *α*-diazotized Meldrum's acid

(Scheme 8). This transformation features with mild reaction conditions, broad substrate scope, high regioselectivity, and good functional group compatibility. In addition, the resulted *β*-aryl ketone derivatives can be readily transformed into 7-azaindole-containing π-extended polycyclic heteroarenes.

2.4 C—H aminocarbonylation of *N*-aryl-7-azaindoles

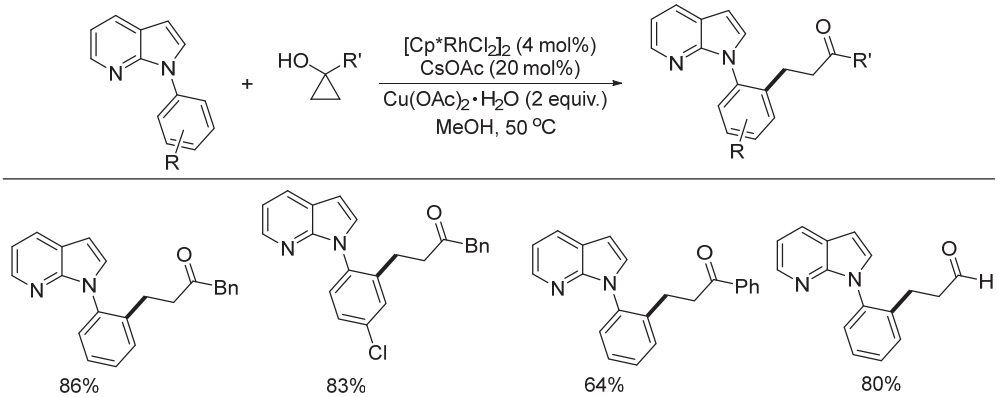
In 2018, Kim's group developed the reaction of *N*-aryl-7-azaindoles with a range of isocyanates to realize the site-selective C—H aminocarbonylation of 7-azaindoles under the catalysis of cheaper Ru(II) catalyst. A variety of amidated *N*-(hetero)aryl-7-azaindoles were formed in good yields (Scheme 9).[19] This transformation features with a wide range of substrates with excellent site- and chemoselectivity under mild conditions. It is worth noting that the *ortho*-amidated *N*-(hetero)aryl-7-azaindole can be further converted into corresponding carboxylic acid and alkylamine derivatives.

2.5 C—H benzoylation of *N*-aryl-7-azaindoles

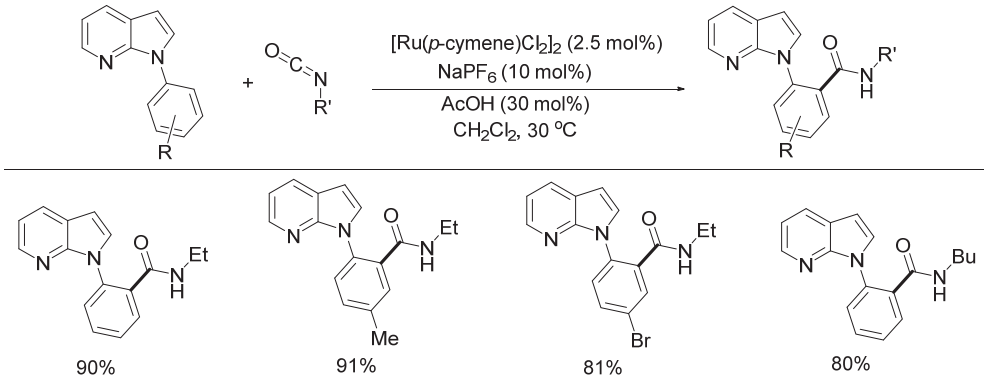
Recently, Jain's group[20] disclosed a protocol for the synthesis of benzoylated *N*-aryl-7-azaindoles under the assistance of Pd and photoredox dual catalysis (Scheme 10). They used *α*-keto acids as benzoyl radical precursors to realize the benzoylation of *N*-phenyl-7-azaindoles through radical decarboxylative coupling. The protocol has several advantages in terms of mild reaction conditions, utilization of oxygen as the oxidant, excellent regioselectivity, inexpensive organic dye as the photocatalyst and broad substrates scope. Mechanistically, this reaction is initiated by a visible light mediated single electron transfer between the excited state of photocatalyst (EY*) and *α*-keto acid to generate radical anion $(EY)^{\bullet-}$ and benzoyl radical **10-C** after following decarboxylation. At the same time, the Pd-catalytic cycle is initiated by the *ortho*-C—H activation of *N*-phenyl-7-azaindole to form palladacycle intermediate **10-D**, which reacts with **10-C** to provide Pd(III) intermediate **10-E**. The subsequent single electron oxidation generates Pd(IV) intermediate **10-F**, which undergoes reductive elimination to deliver the desired benzoylated product.

2.6 C—H cyanation of *N*-aryl-7-azaindoles

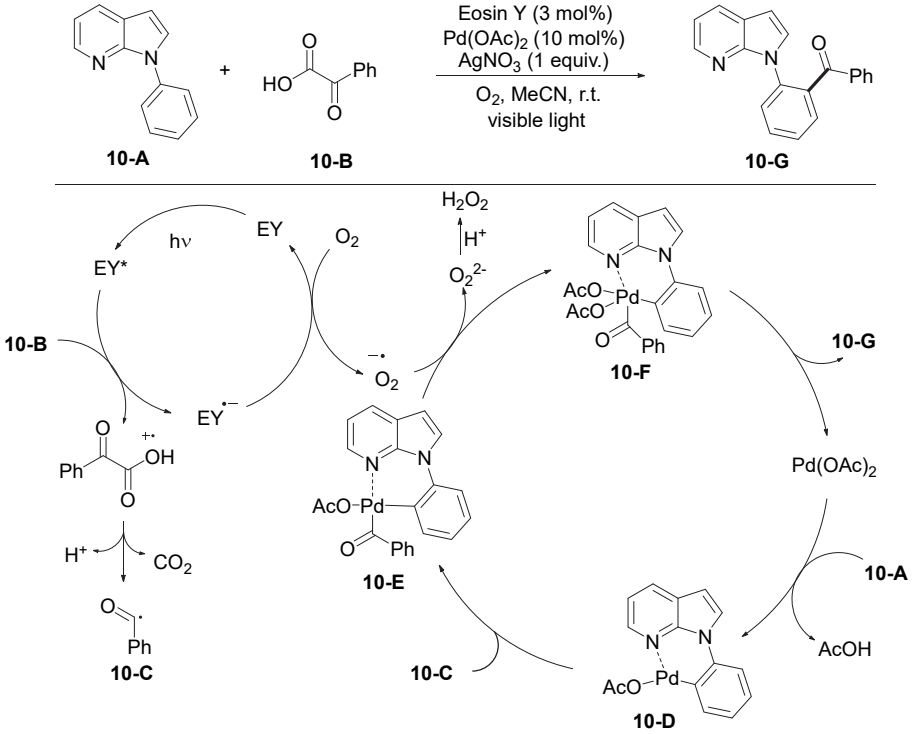
Cyano groups have important values in the fields of organic and medicinal chemistry.[21] They can be easily converted into many other important functional groups, such as amine, aldehyde, amide, ester, as well as heterocyclic scaffolds.[22] In 2016, Deb's group[23] employed the easily accessible *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) as the cyanating reagent to accomplish the C—H cyanation of *N*-aryl-7-azaindoles under the catalysis of cost-effective $[RuCl_2(p\text{-cymene})]_2$ (Scheme 11). A series of *N*-(2-cyanoaryl)-7-azaindoles were furnished with ample substrates scope and broad functional group tolerance in good to excellent yields. The cyano-bearing *N*-aryl-7-aza-



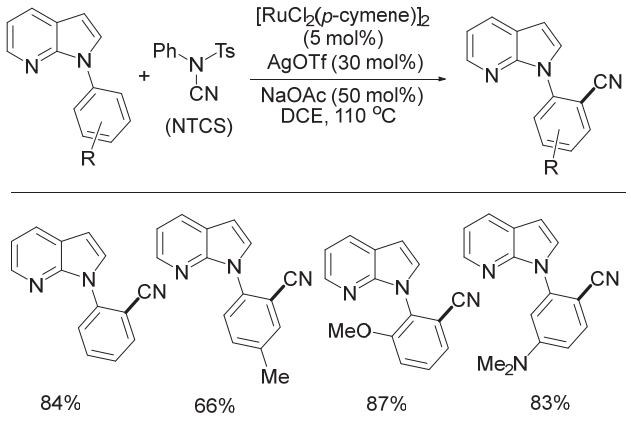
Scheme 8 *N*-Aryl C—H alkylation of *N*-aryl-7-azaindoles with cyclopropanols



Scheme 9 C—H aminocarbonylation of *N*-aryl-7-azaindole with isocyanates

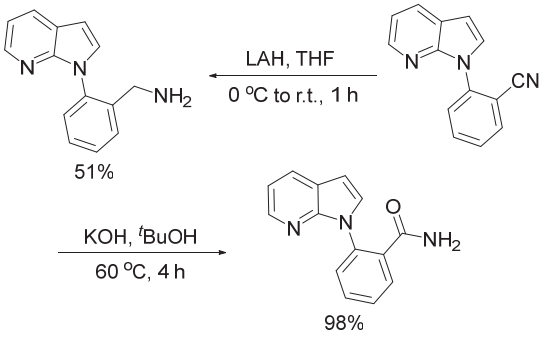


Scheme 10 *N*-Aryl C—H benzoylation of *N*-aryl-7-azaindole with *α*-keto acids



Scheme 11 *N*-Aryl C—H cyanation of *N*-aryl-7-azaindoles with NCTS

indole could be easily transformed into amine and amide, showing the applicability of such product as a synthetic intermediate (Scheme 12).



Scheme 12 Transformations of cyanated *N*-phenyl-7-azaindole

2.7 C—H annulation of *N*-aryl-7-azaindoles via multiple C—H activation

Besides the *N*-aryl C—H bond, the C(2)—H bond of *N*-aryl-7-azaindoles can also be activated under the transition-metal-catalyzed conditions as well to form cyclised structures. Dong's group made lots of contributions on the annulation of *N*-aryl-7-azaindole derivatives. In 2015, they reported the synthesis of cyclized 7-azaindole derivatives via dual C—H activation including *N*-directed *N*-aryl *ortho* C—H activation and subsequent roll-over C—H activation of the heterocyclic ring under the catalysis of Rh(III) (Scheme 13).[24] A broad scope of 7-azaindoles and internal alkynes has been demonstrated to form diverse ring-fused 7-azaindole derivatives in moderate to excellent yields.

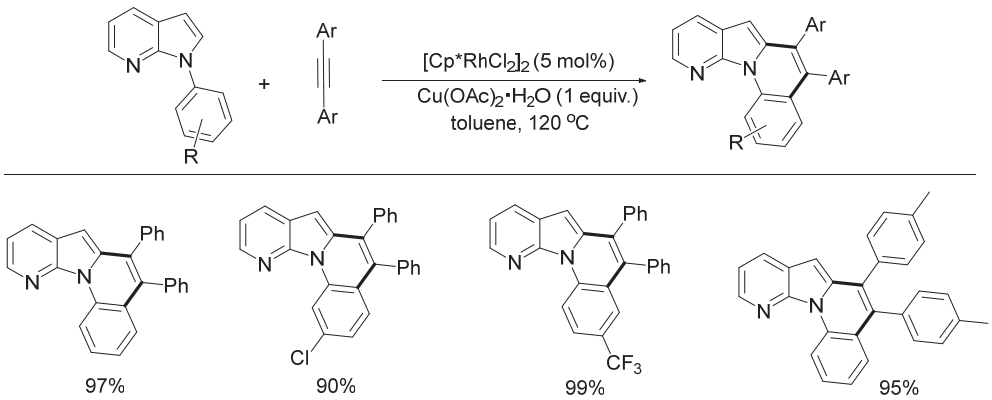
Two years later, they achieved the synthesis of unique [5]azahelicenes by Rh-catalyzed cascade reaction of 7-azaindoles with alkynes via multiple C—H bond activations (Scheme 14).[25] A variety of electronically and sterically diverse aryl substituted 7-azaindoles were examined to deliver the corresponding products in moderate to good yields. These screw-shaped helicene derivatives showed interesting photophysical properties. For example, **14-A** was successfully utilized in the selective detection of mercury ions.

In 2016, Dong's group[26] demonstrated a tandem annulation utilizing 7-azaindole as the directing group under the catalysis of Rh(III) (Scheme 15). *N*-Aryl-7-azaindoles and electron-deficient olefins were used as substrates to deliver the corresponding products via a sequence of olefination and Michael-type cyclization.

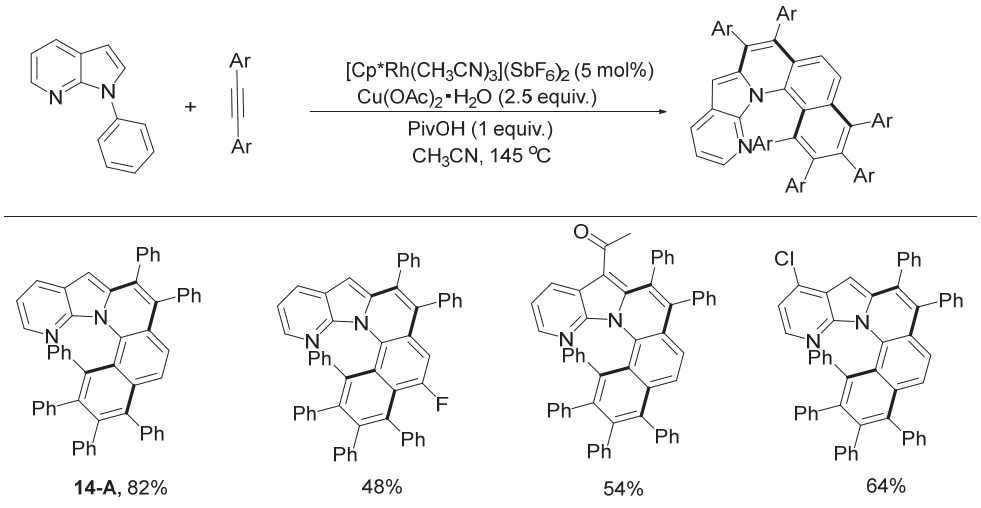
Subsequently, the same group reported a rhodium-catalyzed cyclization of *N*-aryl-7-azaindoles with alkenyl esters to access complex π-conjugated 7-azaindole derivatives (Scheme 16).[27] Notably, no oxidant was required in this transformation.

Shortly afterwards, *α*,*β*-unsaturated ketones were used as coupling partners to form π-conjugated acylated 7-azaindoles catalyzed by $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ with HOAc as the additive in toluene (Scheme 17).[28] This transformation proceeded through rhodium(III)-catalyzed C—H functionalization and the following copper-catalyzed annulation-aromatization processed to afford the cyclized products.

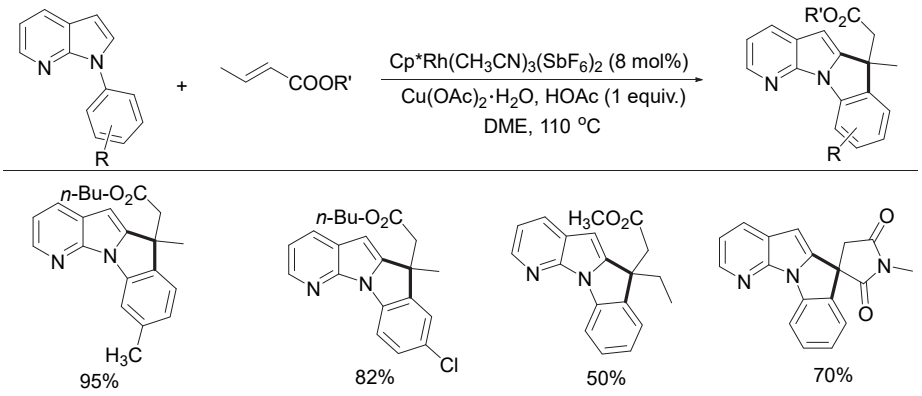
In 2017, using diazo compounds as coupling partners, Dong's group realized the synthesis of π-conjugated 7-azaindole derivatives (Scheme 18). A series of 7-azain-



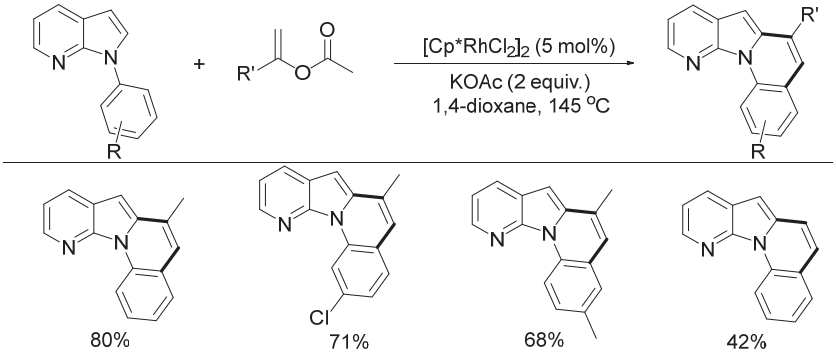
Scheme 13 C—H annulation of *N*-aryl-7-azaindoles with internal alkynes



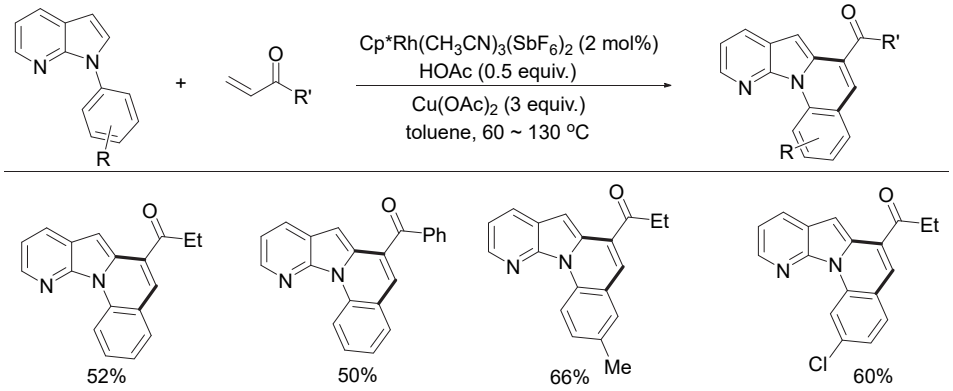
Scheme 14 Annulation of *N*-aryl-7-azaindoles



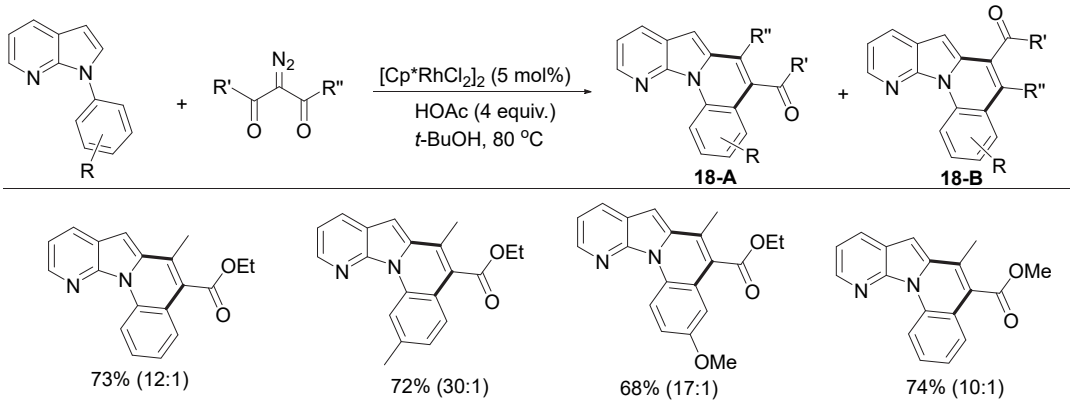
Scheme 15 Annulation of *N*-aryl-7-azaindoles with electron-deficient olefins



Scheme 16 C—H annulation of *N*-aryl-7-azaindoles with alkenyl esters



Scheme 17 C—H alkylation and annulation of *N*-aryl-7-azaindoles with *α*,*β*-unsaturated ketones



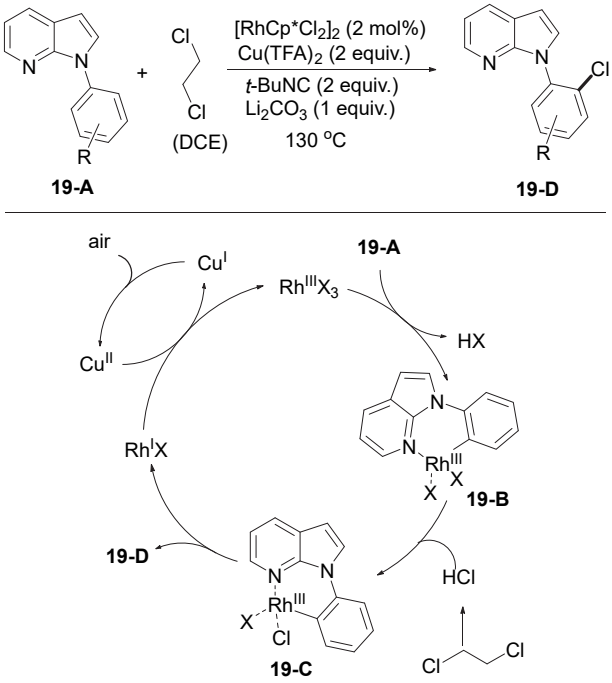
Scheme 18 C—H annulation of *N*-aryl-7-azaindoles with diazo compounds

doles bearing either electron-donating or electron-withdrawing groups were well tolerated, delivering the products **18-A**/**18-B** in moderate to high yields.[29] This one-pot procedure undergoes *ortho* C—H activation, carbene insertion, and intramolecular dehydration processes.

3 Carbon-heteroatom bond formation by 7-azaindole-directed *N*-aryl C—H functionalization

3.1 C—H chlorination of *N*-aryl-7-azaindoles

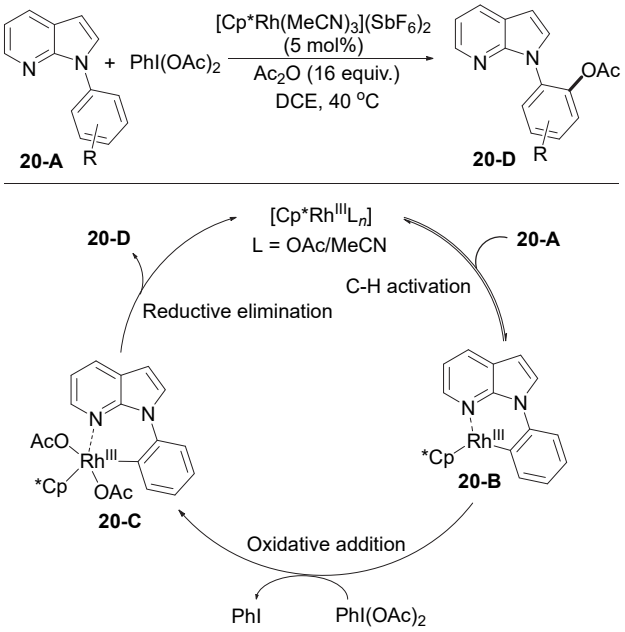
In 2014, Xu and co-workers[30] reported a rhodium-catalyzed regioselective C—H cyanation of arenes to afford (hetero)aryl and cycloalkenyl nitriles in the presence of *tert*-butyl isocyanide. However, when they expanded this protocol to *N*-phenyl-7-azaindole, an unexpected *N*-aryl C—H bond chlorination occurred. Based on this study, they used easily available 1,2-dichloroethane (DCE) as a "Cl" source and 7-azaindole as the directing group to realize the regioselective C—H chlorination of *N*-aryl-7-azaindoles under the catalysis of rhodium.[31] This protocol provides an efficient access to chlorinated 7-azaindoles with operational simplicity, good functional group tolerance, and a wide substrate scope (Scheme 19). Mechanistically, intermediate **19-B** is furnished with the formation of a C—Rh bond, which may reacts with hydrogen chloride generated *in situ* from 1,2-dichloroethane to afford rhodium complex **19**—**C**. Intermediate **19-C** gives the final product through reductive elimination, and the rhodium catalyst can be regenerated with the oxidation of Cu(II) and atmospheric oxygen. The installation of chloride to the *N*-aryl motif provides much potentials for further derivation reactions.



Scheme 19 *N*-Aryl C—H chlorination of *N*-aryl-7-azaindoles with DCE

3.2 C—H acetoxylation of *N*-aryl-7-azaindoles

In 2017, Deb's group demonstrated a rhodium-catalyzed highly efficient *ortho*-acetoxylation of *N*-aryl-7-azaindoles employing iodobenzene diacetate (PIDA) as a nonmetallic acetoxy source under mild conditions (Scheme 20).[32] The method is highly selective, efficient, and scalable with diverse functional group tolerance. In addition, this method also enables C—H acetoxylation of *N*-arylazaindolines. Mechanistically, the reversible C—H bond activation of *N*-phenyl-7-azaindole with complex [Cp*RhL$_n$] produces a rhodacycle intermediate **20-B**. The following oxidative addition in the presence of PIDA forms rhodium(V) complex **20-C**. Subsequent reductive elimination of **20-C** affords the desired product **20-D**.

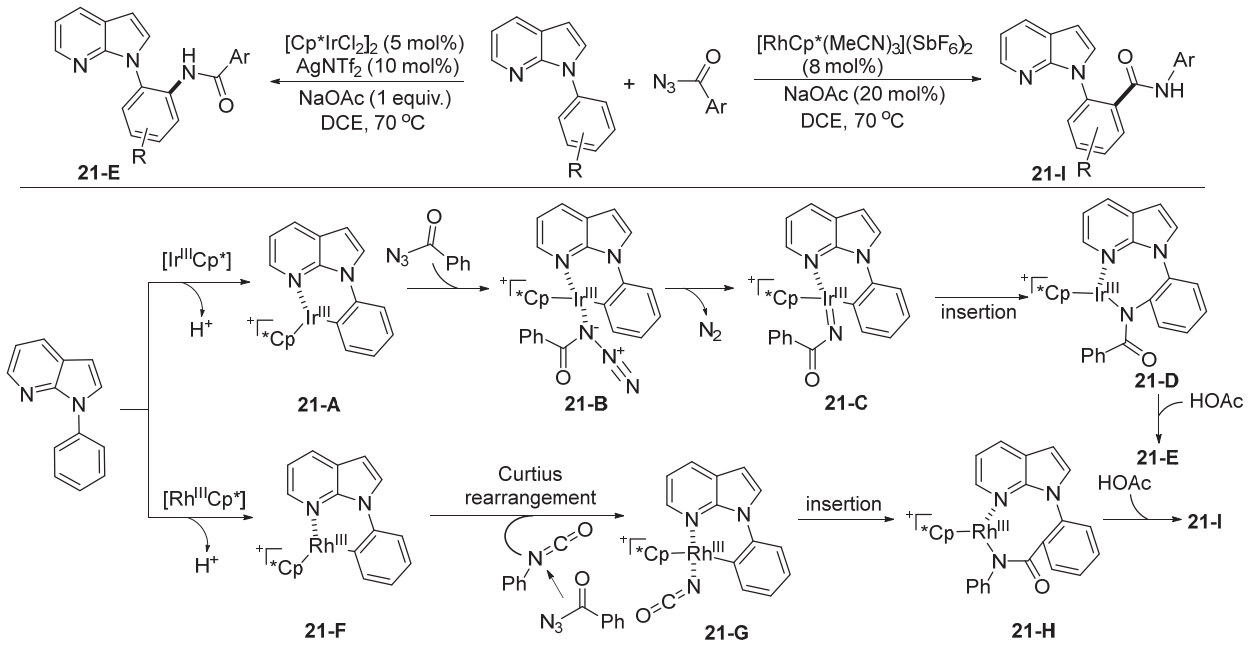


Scheme 20 *N*-Aryl C—H acetoxylation of *N*-aryl-7-azaindoles with PhI(OAc)$_2$

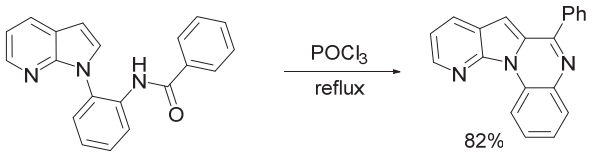
3.3 C—H amidation/amination of *N*-aryl-7-azaindoles

In 2017, Dong *et al.*[33] disclosed a novel protocol for the synthesis of C—N or C—C amidated 7-azaindole derivatives through C—H amidation of *N*-aryl-7-azaindoles with acyl azides (Scheme 21). In this transformation, acyl azides performed a dual reactivity function as amino or carbon sources. The catalyst system of the reaction plays a key role in the selectivity of the reaction: C—N amidation with acyl azides is occurred under the catalysis of Ir(III), while C—C amidation with isocyanates generated *in situ* from acyl azides is promoted by Rh(III). The amidated product can be transformed into polycyclic heteroarenes if treated by $POCl_3$ (Scheme 22).

Mechanistically, the direct C—H bond activation of *N*-phenyl-7-azaindole with iridium catalyst generates an iridium complex intermediate **21-A**. Subsequently, benzoyl azide coordinates to the iridium metal center gives inter-



Scheme 21 *N*-Aryl C—H amidation of *N*-aryl-7-azaindoles with acyl azides

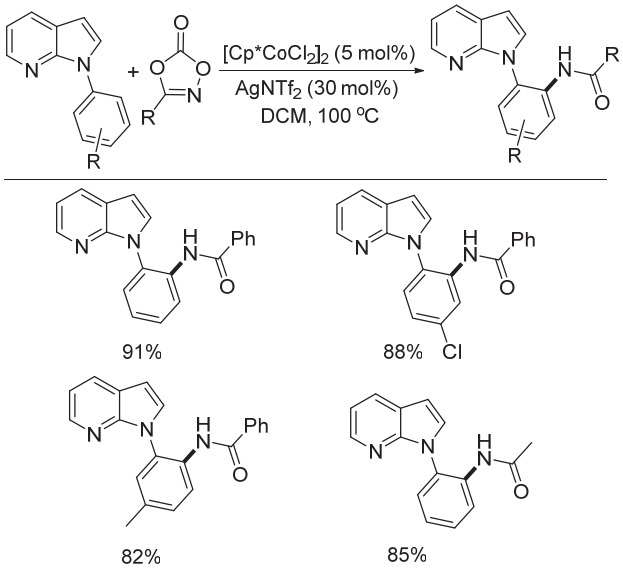


Scheme 22 Transformation of the amidated product into polycyclic heteroarenes

mediate **21-B** with the release of N_2. The following insertion of imido group into the Ir—C bond of **21-C** delivers an iridium amido intermediate **21-D**. Finally, the C—N amidated product **21-E** is generated via the protonolysis of **21-D**. While, under the Rh-catalyzed system, the coordination of isocyanate to rhodacycle **21-F** forms intermediate **21-G**. Then, insertion occurs to access intermediate **21-H**. At last, the desired C—C amidated product **21-I** is released via protonation.

In the same year, Dong described an efficient and convenient amidation of *N*-aryl 7-azaindoles using dioxazolones as the amidating reagents under the catalysis of cobalt (Scheme 23).[34] This is the first example of cobalt-catalyzed amidation of 7-azaindoles, which is more cost-effective. The reaction can proceed well without the requirement of external oxidants and have a wide range of substrates scope and good functional group tolerance. It's worth noting that the *N*-alkenyl-substituted 7-azaindoles could also undergo such C(sp^2)—H amidation by adding 0.5 equiv. of PivOH.

Phosphoramidates are important structural units that exist in many biologically active compounds.[35] The phosphoramidates can also be utilized in the synthesis of nitrogen containing heterocyclic structures.[36] In 2018, our group[37] achieved the synthesis of 7-azaindole phenylphosphoramidates using phosphoryl azides under the catalysis of iridium (Scheme 24). This reaction has a wide

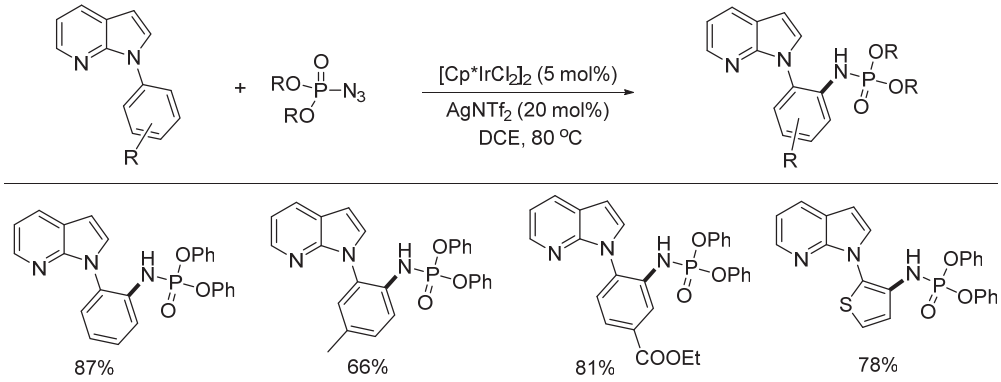


Scheme 23 *N*-Aryl C—H amidation of *N*-aryl-7-azaindoles with dioxazolones

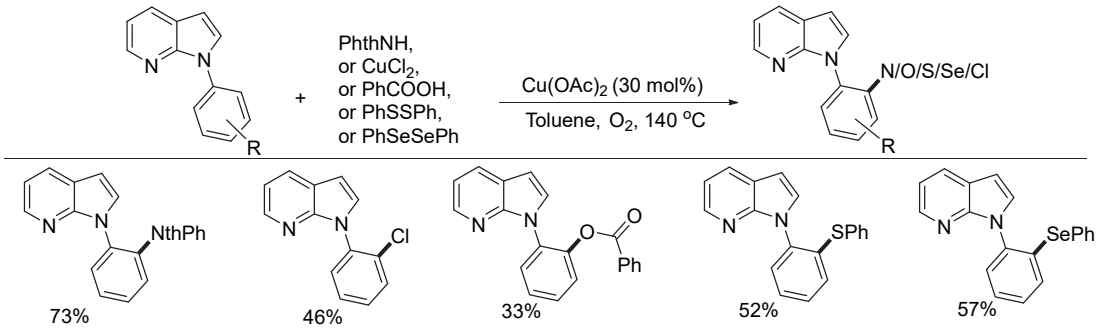
substrates scope with good functional group tolerance.

In 2021, Koley *et al.*[38] disclosed a copper-catalyzed *N*-aryl C—H imidation of *N*-aryl-7-azaindoles with phthalimides. This protocol used earth-abundant copper salt as catalyst and molecular oxygen as oxidant. Moreover, aryloxylation, chlorination and chalcogenation of *N*-aryl-7-azaindoles were also achieved under standard conditions (Scheme 25). The formed phthalimide derivative could be transformed into amine, amide and hemiaminal derivative after simple procedures (Scheme 26).

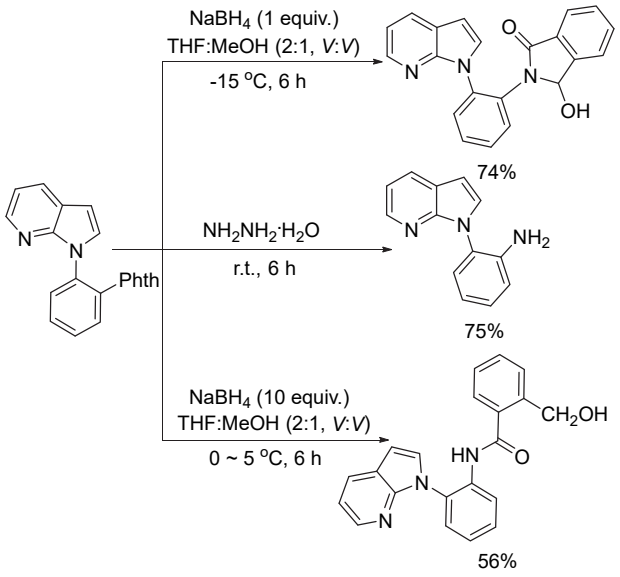
Very recently, Liu *et al.*[39] demonstrated a dual catalytic system to achieve the *N*-aryl C—H amidation of *N*-aryl-7-azaindoles (Scheme 27). In this reaction, *N*-aroyloxycarbomates were used as amino precursors under Ir/ionic



Scheme 24 *N*-Aryl C—H phosphoramidation of *N*-aryl-7-azaindoles with phosphoryl azides



Scheme 25 C—N, C—O, C—Cl, C—S and C—Se bonds formation directed by 7-azaindole

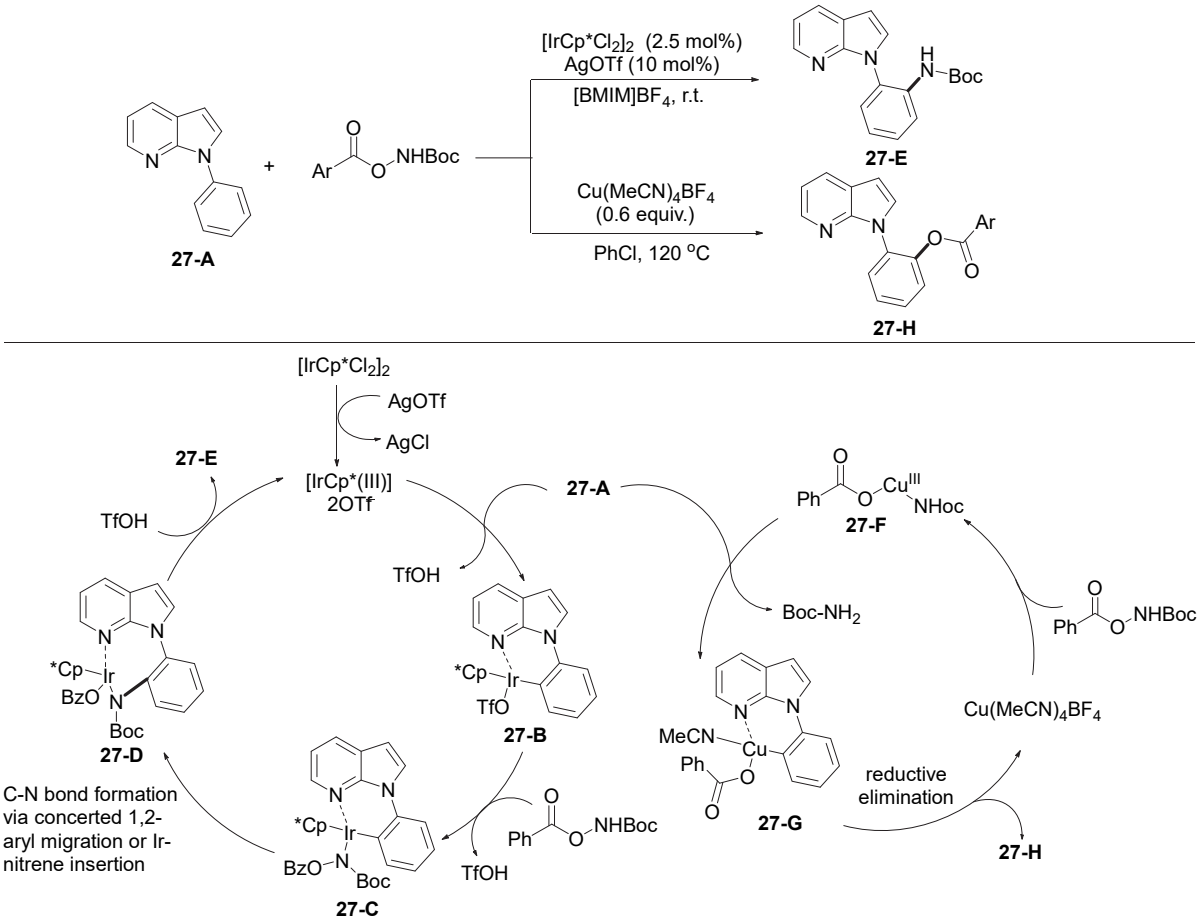


Scheme 26 Synthetic applications of the imidated product

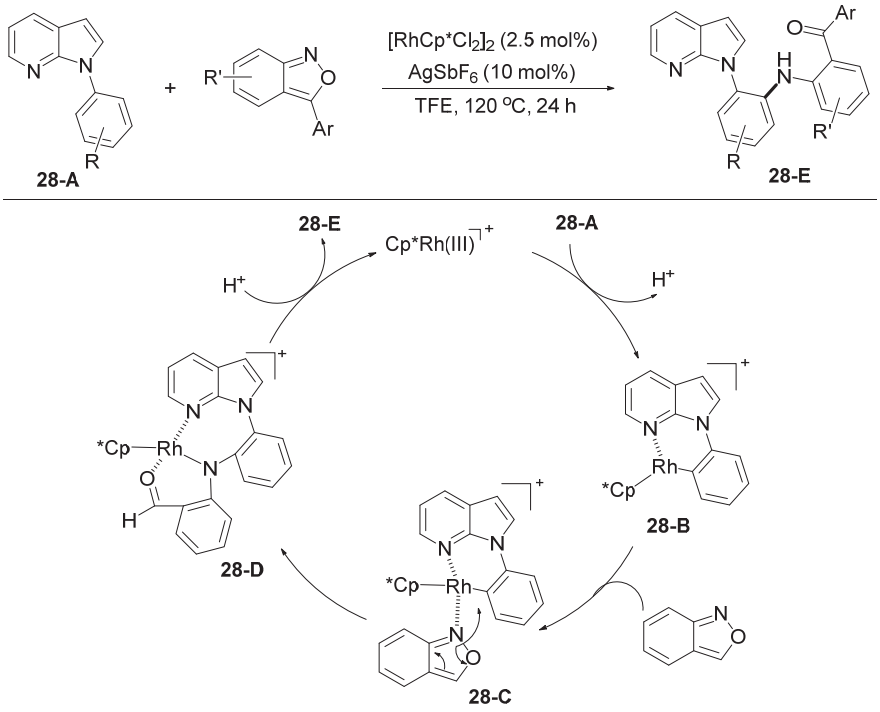
liquid catalytic system. However, if $Cu(MeCN)_4BF_4$ was used as catalyst, C—H aryoloxylation was achieved with *N*-aroyloxycarbomate as an oxygen source via the removal of a nitrogen fragment. Mechanistically, the reaction is initiated by the formation of active Ir(III) species under the assistance of AgOTf. Then, the following C—H metalation of Ir(III) catalyst with *N*-phenyl-7-azaindole **27-A** provides an iridacycle intermediare **27-B** together with the elimination of HOTf. Then, the coordination of nitrogen atom on carbamate to iridacycle **27-B** produces complex **27-C**. The migratory insertion or alternative nitrene insertion gives iridium amido complex **27-D**, which undergoes protonation to deliver the *ortho*-amidated azaindole **27-E**. In copper-catalyzed system, the oxidative addition of N—O bond to Cu(I) produces copper(III) species **27-F**. Then, species **27-F** dissociates an amide to trigger C—H activation of **27-A** to form complex **27-G**. Afterwards, complex **27-G** undergoes reductive elimination to give the aroyloxylated product **27-H**.

In 2017, Kim *et al.*[40] disclosed a rhodium(III)-catalyzed C—H amination of 7-azaindoles with anthranils (Scheme 28). This transformation has been applied to a broad scope of substrates, and featured with excellent site-selectivity as well as high functional group tolerance. The resulted *ortho*-aminated 7-azaindoles can be easily converted into biologically relevant heterocycles such as azaindoloacridine, azaindoloacridone, and bis-indoles. Mechanistically, the coordination of *N*-phenyl-7-azaindole to active Cp*Rh(III) complex *in situ* formed from $[RhCp^*Cl_2]_2$ in the presence of $AgSbF_6$ affords the six-membered cyclorhodated complex **28-B**. Then, the coordination of anthranil and subsequent migratory insertion produce a Rh(III)-amino species **28-D**, which delivers the *ortho*-aminated azaindole **28-E** after protonation along with the regeneration of active Rh(III) species.

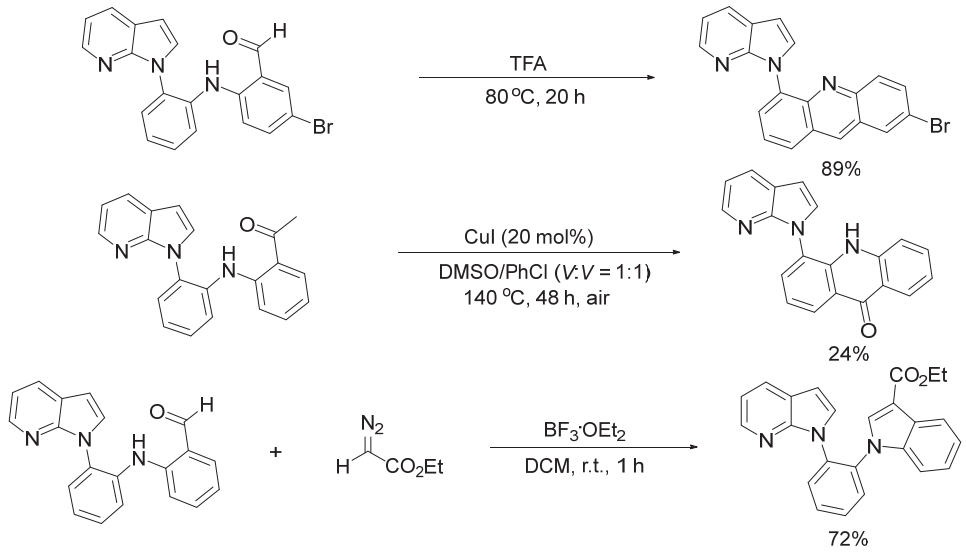
The *ortho*-aminated azaindoles have plenty of applications (Scheme 29). For example, azaindoloacridine could be formed when treated by TFA through the dehydrative Friedel-Crafts cyclization, azaindoloacridone was obtained by the Cu(I)-catalyzed oxidative C—C bond cleavage and



Scheme 27 *N*-Aryl amidation and aryoloxylation of *N*-aryl-7-azaindoles with *N*-aroyloxycarbomates



Scheme 28 *N*-Aryl C—H amination of *N*-aryl-7-azaindoles with anthranils



Scheme 29 Synthetic utility of *ortho*-aminated azaindoles

intramolecular cyclization. Moreover, the intermolecular coupling reaction with ethyl 2-diazoacetate led to the corresponding biindole derivatives via the 1,2-aryl shift pathway.

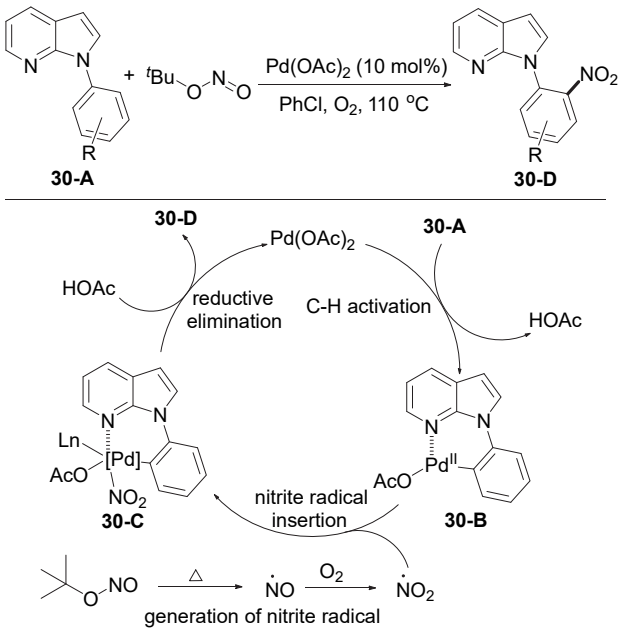
3.4 C—H nitration of *N*-aryl-7-azaindoles

The traditional C—H nitration of aromatic compounds usually employs expensive $AgNO_2$ and $AgNO_3$ as nitro sources, and requires the addition of stoichiometric oxidants such as peroxides, hypervalent iodine oxidants and toxic metal salts.[41] In 2018, Kim and co-workers[42] disclosed a Pd-catalyzed *N*-aryl C—H nitration of *N*-aryl-7-azaindoles to access nitrated *N*-aryl-7-azaindoles (Scheme 30). In this transformation, *t*-$BuNO_2$ was used as nitro sources and O_2 as external oxidant. This reaction has the advantages of excellent site-selectivity and functional group compatibility. Furthermore, under palladium-catalyzed hydrogenation conditions, the resulted 7-azaindole derivatives can be easily converted into 7-azaindole-containing anilines. Mechanistically, NO_2 radical species is generated from the decomposition of ^{t}$BuNO_2$ in the presence of O_2 followed by aerobic oxidation. The palladacycle complex **30-B** is delivered via C—H palladation with *N*-phenyl-7-azaindole under the catalysis of Pd(II). The oxidative insertion of NO_2 radical to **30-B** provides Pd(III) or Pd(IV) intermediate **30-C**, which affords the desired product **30-D** after reductive elimination.

3.5 C—H chalcogenation of *N*-aryl-7-azaindoles

C—S bond is widespread in numerous bioactive natural products and drug molecules.[43] In 2018, Deb *et al.*[44] realized a *N*-aryl C—H thiolation of *N*-aryl-7-azaindoles with diphenyldisulfides under the catalysis of $[Cp^*RhCl_2]_2$ (Scheme 31). This strategy is efficient, highly regioselective and scalable. In addition, this method can also be applied to the *N*-aryl C—H selenylation of *N*-arylazaindoles/indolines.

In 2021, Xiong and Duan *et al.*[45] achieved the direct

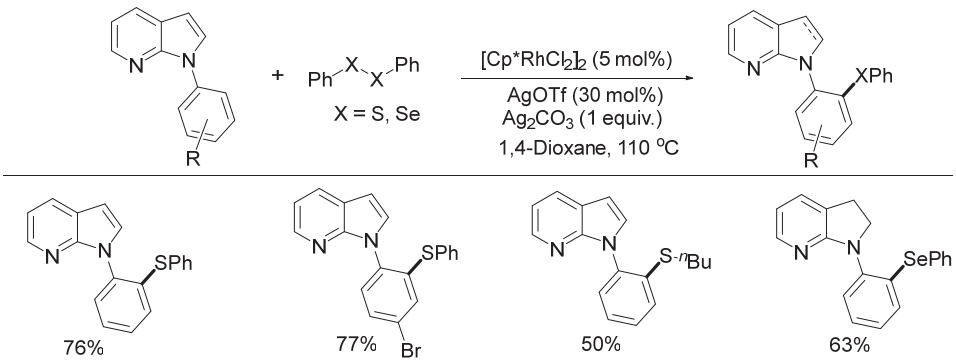


Scheme 30 *N*-Aryl C—H nitration of *N*-aryl-7-azaindoles with *t*-butyl nitrite.

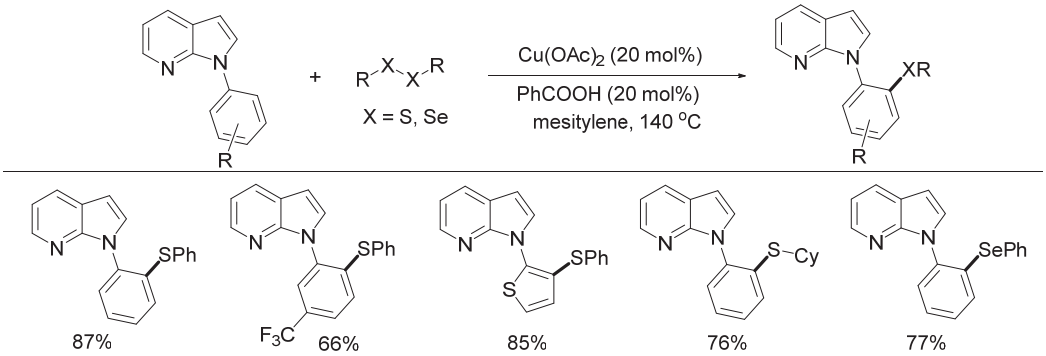
N-aryl C—H chalcogenation of *N*-aryl-azaindoles with disulfides using $Cu(OAc)_2$ as catalyst and air as a terminal oxidant (Scheme 32). Compared with Deb's work,[43] this reaction is more economical. Diphenyl diselenides were also suitable reaction partners to deliver the desired selenylated products.

4 Conclusions and outlooks

N-Phenyl-7-azaindole motif is a privileged framework presented in various pharmaceutical molecules and drug candidates. Organic chemists have devoted many contributions on the installation of functional groups into the *ortho* position of *N*-aryl in *N*-aryl-7-azaindole derivatives by C—H functionalization strategy. In those reactions, 7-aza-



Scheme 31 Rh(III)-catalyzed *N*-aryl C—H chalcogenation of *N*-aryl-7-azaindoles



Scheme 32 Cu(II)-catalyzed *N*-aryl C—H chalcogenation of *N*-aryl-7-azaindoles

indole was used as intrinsic directing group for the late-stage functionalization of the *N*-arylazaindole moiety under the catalysis of transition-metals. For example, Rh-catalyzed C—H alkenylation reactions, Rh-catalyzed annulation reactions, Ru-catalyzed C—H cyanation reaction, Ir-catalyzed C—H alkynylation reaction, Rh- or Ir-catalyzed C—H alkylation reactions, Rh-catalyzed C—H chlorination reaction, Ir-, Ru- or Co-catalyzed C—H amidation reactions, Rh-, Ir-catalyzed amination reactions, Rh-catalyzed C—H acetoxylation reaction, Pd-catalyzed C—H nitration reaction, and Rh- or Cu-catalyzed C—H chalcogenation reactions were developed.

Despite these achievements, there still have some drawbacks. For example, some reactions required high temperatures to achieve satisfactory yields. Noble transition metals (Rh, Ir, Ru, Pd) were used in most of those reactions. Cost-effective metals such as Co and Cu were rarely applied in those reactions. Exploring low-cost and earth-abundant metals is the key to reduce costs. Besides, the reaction types were still limited. Because of the steric hindrance of those mono-functionalized *N*-aryl-7-azaindoles, the formation of difunctionalized products was unrealizable in most of the cases discussed above. Developing efficient methods to achieve multiple C—H functionalizations on the *N*-aryl motif of *N*-aryl-7-azaindoles was highly demanded. Overall, the development of more green, economical, efficient and mild methods for C—H functionalization of *N*-aryl-7-azaindole using 7-azaindole as the intrinsic directing group should be further investigated.

References

[1] (a) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. *Chem. Rev.* **2017**, *117*, 8754.
(b) Yang, Y.; Lan, J.; You, J. *Chem. Rev.* **2017**, *117*, 8787.
(c) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. *Chem. Rev.* **2017**, *117*, 9016.
(d) Yuan, S.; Chang, J.; Yu, B. *Top. Curr. Chem.* **2020**, *378*, 23.
(e) Yang, Z.; Yu, J.-T.; Pan, C. *Org. Biomol. Chem.* **2021**, *19*, 8442.
(f) Liu, B.; Romine, A. M.; Rubel, C. Z.; Engle, K. M.; Shi, B.-F. *Chem. Rev.* **2021**, *121*, 14957.
(g) Xie, J.; Pan, C.; Abdukader, A.; Zhu, C. *Chem. Soc. Rev.* **2014**, *43*, 5245.

[2] (a) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. *Chem. Soc. Rev.* **2018**, *47*, 6603.
(b) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107.

[3] (a) Dai, H.-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222.
(b) Viart, H. M.-F.; Bachmann, A.; Kayitare, W.; Sarpong, R. *J. Am. Chem. Soc.* **2017**, *139*, 1325.
(c) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019.
(d) Lakshman, M. K.; Deb, A. C.; Chamala, R. R.; Pradhan, P.; Pratap, R. *Angew. Chem., Int. Ed.* **2011**, 50, 11400.
(e) Kumar, S. V.; Ellairaja, S.; Satheesh, V.; Vasantha, V. S.; Punniyamurthy, T. *Org. Chem. Front.* **2018**, *5*, 2630.

[4] (a) Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120.
(b) Mérour, J.-Y.; Buron, F.; Plé, K.; Bonnet, P.; Routier, S. *Molecules* **2014**, *19*, 19935.

[5] (a) Wang, T.; Zhang, Z.; Wallace, O. B.; Deshpande, M.; Fang, H.; Yang, Z.; Zadjura, L. M.; Tweedie, D. L.; Huang, S.; Zhao, F.; Ranadive, S.; Robinson, B. S.; Gong, Y.-F.; Ricarrdi, K.; Spicer, T.

P.; Deminie, C.; Rose, R.; Wang, H.-G. H.; Blair, W. S.; Shi, P.-Y.; Lin, P.-F.; Colonno, R. J.; Meanwell, N. A. *J. Med. Chem*. **2003**, *46*, 4236.
(b) Hardwicke, M. A.; Oleykowski, C. A.; Plant, R.; Wang, J.; Liao, Q.; Moss, K.; Newlander, K.; Adams, J. L.; Dhanak, D.; Yang, J.; Lai, Z.; Sutton, D.; Patrick, D. *Mol. Cancer Ther.* **2009**, *8*, 1808.
(c) Mullard, A. *Nat. Rev. Drug Discovery* **2012**, *11*, 91.
[6] (a) Smith, N. D.; Cosford, N. D. P.; Reger, T. R.; Roppe, J. R.; Poon, S. F.; Huang, D.; Chen, C.; Eastman, B. W. *WO 2003077918*, **2003**.
(b) Carry, J. C.; Mignani, S.; Evers, M.; Doerflinger, G.; Genevois, B. A.; Brun, A. Le.; Martin, J. P.; Desmazeau, P.; Kleemann, H. W. *FR 2856062*, **2004**.
(c) Popowycz, F.; Routier, S.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2007**, *63*, 1031.
(d) Mérour, J.-Y.; Buron, F.; Plé, K.; Bonnet, P.; Routier, S. *Molecules* **2014**, *19*, 19935.
(e) Vadukoot, A. K.; Sharma, S.; Aretz, C. D.; Kumar, S.; Gautam, N.; Alnouti, Y.; Aldrich, A. L.; Heim, C. E.; Kielian, T. Hopkins, C. R. *ACS Med. Chem. Lett.* **2020**, *11*, 1848.
[7] (a) Chen, Y.; Guo, S.; Li, K.; Qu, J.; Yuan, H.; Hua, Q.; Chen, B. *Adv. Synth. Catal.* **2013**, *355*, 711.
(b) Kannaboina, P.; Anilkumar, K.; Aravinda, S.; Vishwakarma, R. A.; Das, P. *Org. Lett.* **2013**, *15*, 5718.
(c) Kannaboina, P.; Kumar, K. A.; Das, P. *Org. Lett.* **2016**, *18*, 900.
(d) Urvashi, Dar, M. O.; Bharatam, P. V.; Das, P.; Kukreti, S.; Tandon, V. *Tetrahedron* **2020**, *76*, 131337.
(e) Hu, J.; X. Ji, Hao, S.; Zhao, M.; Lai, M.; Ren, T.; Xi, G.; Wang, E.; Wang, J.; Wu, Z. *RSC Adv.* **2020**, *10*, 31819.
(f) Kannaboina, P.; Raina, G.; Kumara, K. A.; Das, P. *Chem. Commun.* **2017**, *53*, 9446.
(g) Laha, J. K.; Bhimpuria, R. A.; Prajapati, D. V.; Dayal, N.; Sharma, S. *Chem. Commun.* **2016**, *52*, 4329.
[8] Li, S.-S.; Wang, C.-Q.; Lin, H.; Zhang, X.-M.; Dong, L. *Org. Biomol. Chem.* **2016**, *14*, 229.
[9] Li, W.-H.; Wu, L.; Li, S.-S.; Liu, C.-F.; Zhang, G.-T.; Dong, L. *Chem.-Eur. J.* **2016**, *22*, 17926.
[10] Liu, B.; Li, R.; Zhan, W.; Wang, X.; Ge, Z.; Li, R. *RSC Adv.* **2016**, *6*, 48205.
[11] Morioka, R.; Satoh, T.; Miura, M. *Chem. Lett.* **2016**, *45*, 682.
[12] Li, S.-S.; Wang, C.-Q.; Li, W.-H.; Zhang, X.-M.; Dong, L. *Tetrahedron* **2016**, *72*, 2581.
[13] Liu, B.; Wang, X.; Ge, Z.-M.; Li, R.-T. *Org. Biomol. Chem.* **2016**, *14*, 2944.
[14] (a) Wu, X.; Sun, S.; Yu, J.-T.; Cheng, J. *Synlett* **2019**, *30*, 21.
(b) Kumar, A.; Sharanappa, M. S.; Hanchate, V.; Prabhu, K. R. *Tetrahedron* **2021**, *101*, 132478.
[15] Tian, Y.; Kong, X.-Q.; Niu, J.; Huang, Y.-O.; Wu, Z.-H.; Xu, B. *Tetrahedron Lett.* **2020**, *61*, 151627.
[16] (a) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704.
(b) Kumar, S.; Nunewar, S.; Oluguttula, S.; Nanduri, S.; Kanchupalli, V. *Org. Biomol. Chem.* **2021**, *19*, 1438.
[17] Yu, J.-T.; Shan, Y.-J.; Yuan, C.; Pan, C. *Tetrahedron Lett.* **2021**, *62*, 152703.
[18] Liu, J.-D.; Jiang, J.-Y.; Yang, Z.-K.; Zeng, Q.-H.; Zheng, J.-Y.; Zhang, S.-Y.; Zheng, L.-Y.; Zhang, S.-S.; Liu, Z.-Q. *Org. Biomol. Chem.* **2021**, *19*, 993.
[19] Jeong, T.; Lee, S. H.; Chun, R.; Han, S.; Han, S. H.; Jeon, Y. U.; Park, J.; Yoshimitsu, T.; Mishra, N. K.; Kim, I. S. *J. Org. Chem.* **2018**, *83*, 4641.
[20] Rajput, S.; Kaur, R.; Jain, N. *Org. Biomol. Chem.* **2022**, *20*, 1453.
[21] (a) Miller, J. S.; Manson, J. L. *Acc. Chem. Res.* **2001**, *34*, 563.
(b) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902.
[22] Fatiadi, A. J.; Patai, S.; Rappoport, Z. *Preparation and Synthetic Applications of Cyano Compounds*, Wiley-VCH, New York, **1983**.
[23] Mishra, A.; Vats, T. K.; Deb, I. *J. Org. Chem.* **2016**, *81*, 6525.
[24] Li, S.-S.; Wang, C.-Q.; Lin, H.; Zhang, X.-M.; Dong, L. *Org. Lett.* **2015**, *17*, 3018.
[25] Li, S.-S.; Liu, C.-F.; Zhang, G.-T.; Xia, Y.-Q.; Li, W.-H.; Dong, L. *Chem. Asian J.* **2017**, *12*, 415.
[26] Li, S.-S.; Lin, H.; Liu, C.-F.; Xia, Y.-Q.; Zhang, X.-M.; Dong, L. *Adv. Synth. Catal.* **2016**, *358*, 1595.
[27] Li, S.-S.; Liu, C.-F.; Xia, Y.-Q.; Li, W.-H.; Zhang, G.-T.; Zhang, X.-M.; Dong, L. *Org. Biomol. Chem.* **2016**, *14*, 5214.
[28] Li, S.-S.; Li, W.-H.; Zhang, G.-T.; Xia, Y.-Q.; Liu, C.-F.; Su, F.; Zhang, X.-M.; Dong, L. *Org. Biomol. Chem.* **2016**, *14*, 7859.
[29] Liu, C.-F.; Zhang, G.-T.; Sun, J.-S.; Dong, L. *Org. Biomol. Chem.* **2017**, *15*, 2902.
[30] Hong, X.-H.; Wang, H.; Qian, G.-Y.; Tan, Q.-T.; Xu, B. *J. Org. Chem.* **2014**, *79*, 3228.
[31] Qian, G.-Y.; Hong, X.-H.; Liu, B.-X.; Mao, H.; Xu, B. *Org. Lett.* **2014**, *16*, 5294.
[32] Mishra, A.; Vats, T. K.; Nair, M. P.; Das, A.; Deb, I. *J. Org. Chem.* **2017**, *82*, 12406.
[33] Li, W.-H.; Dong, L. *Adv. Synth. Catal.* **2018**, *360*, 1104.
[34] Sun, J.-S.; Liu, M.; Zhang, J.; Dong, L. *J. Org. Chem.* **2018**, *83*, 10555.
[35] (a) Duquesne, S.; Destoumieux-Garzón, D.; Peduzzi, J.; Rebuffat, S. *Nat. Prod. Rep.* **2007**, *24*, 708.
(b) Phillips, D. R.; Uramoto, M.; Isono, K.; McCloskey, J. A. *J. Org. Chem.* **1993**, *58*, 854.
(c) Wagner, S. R. V.; Iyer, V.; McIntee, E. J. *Med. Res. Rev.* **2000**, *20*, 417.
[36] (a) Yadav, L. D. S.; Rai, A.; Rai, V. K.; Awasthi, C. *Tetrahedron Lett.* **2008**, *49*, 687.
(b) Yadav, L. D. S.; Srivastava, V. P.; Patel, R. *Tetrahedron Lett.* **2008**, *49*, 5652.
(c) Yadav, L. D. S.; Awasthi, C.; Rai, V. K.; Rai, A. *Tetrahedron Lett.* **2007**, *48*, 8037.
[37] Pan, C.; Wang, Y.; Wu, C.; Yu, J.-T. *Org. Biomol. Chem.* **2018**, *16*, 3711.
[38] Kumar, M.; Raziullah, Ahmad, A.; Dutta, H. S.; Khan, A. A.; Rastogi, A.; Kant, R.; Koley, D. *J. Org. Chem.* **2021**, *86*, 15185.
[39] Liu, S.-S.; Zhang, Y.-Y.; Zhao, C.; Zhou, X.-Y.; Liang, J.-H.; Zhang, P.-J.; Jiao, L.-Y.; Yang, X.-F.; Ma, Y.-M. *Org. Chem. Front.* **2022**, *9*, 2093.
[40] Jeon, M.; Park, J.; Dey, P.; Oh, Y.; Oh, H.; Han, S.; Um, S. H.; Kim, H. S.; Mishra, N. K.; Kim, I. S. *Adv. Synth. Catal.* **2017**, *359*, 3471.
[41] (a) Liu, Y.-K.; Lou, S.-J.; Xu, D.-Q.; Xu, Z.-Y. *Chem.-Eur. J.* **2010**, *16*, 13590.
(b) Zhang, L.; Liu, Z.; Li, H.; Fang, G.; Barry, B.-D.; Belay, T. A.; Bi, X.; Liu, Q. *Org. Lett.* **2011**, *13*, 6536.
(c) Fan, Z.; Li, J.; Lu, H.; Wang, D.-Y.; Wang, C.; Uchiyama, M.; Zhang, A. *Org. Lett.* **2017**, *19*, 3199.
(d) Pawar, G. G.; Brahmanandan, A.; Kapur, M. *Org. Lett.* **2016**, *18*, 448.
[42] Chun, R.; Kim, S.; Han, S. H.; Pandey, A. K.; Mishra, N. K.; Kim, I. S. *Tetrahedron Lett.* **2020**, *59*, 3848.
[43] (a) Liu, N.-W.; Liang, S.; Manolikakes, G. *Synthesis* **2016**, *48*, 1939.
(b) Shaaban, S.; Liang, S.; Liu, N.-W.; Manolikakes, G. *Org. Biomol. Chem.* **2017**, *15*, 1947.
[44] Vats, T. K.; Mishra, A.; Deb, I. *Adv. Synth. Catal.* **2018**, *360*, 2291.
[45] Jian, Y.-R.; Yan, Z.-C.; Xiang, Z.; Xiong, Y.-S.; Duan, X.-M. *Org. Biomol. Chem.* **2021**, *19*, 2901.

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