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Transition-metal-catalyzed site-selective C7-functionalization of indoles: advancement and future prospects

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C7-Decorated indoles are important structural motifs present in a plethora of bioactive and pharmaceutical compounds. Early stage developments for C7 modifications were realized through directed metallation (DOM) and subsequent quenching with suitable electrophiles or by halogenation with Cu(II) halides. Direct C-7 functionalization of indoles is comparatively difficult compared to functionalization at C-2 and C-3 positions owing to the inherent reactivity of the pyrrole-type ring. However, recently transition-metal-catalyzed auxiliary assisted site-selective C-7 functionalization of indoles has emerged as an elegant synthetic tool for carbon–carbon and carbon–heteroatom bond formation to diversify the indoles. This article covers the advancement, application and mechanistic underpinnings of the evolved transformations of the otherwise inert C7–H bond up to October 2018.

1. Introduction

Transition-metal-catalyzed auxiliary assisted regioselective C–H bond functionalization[1] has emerged as a benchmark in mainstream synthetic enterprise to revolutionize the construction of bio-relevant scaffolds. Among them, indoles and their synthetic analogues epitomize a class of privileged substructures being present in more than twenty-four currently marketed pharmaceuticals and thus have become one of the most widely studied organic templates.[2] Due to their prevalence in many bio-active and functional molecules (Fig. 1),[3] the necessity for elegant techniques to enable site selective C–H functionalization is vast. As a progenitor, indole offers six distinctive C–H functionalization sites to fabricate its molecular topology in the disconnection of complex molecular architecture. Owing to the inherent reactivity of the pyrrole ring, commendable development has been witnessed for C2 and C3 C–H functionalization of the indole moiety. On these grounds, enabling site-selective C–H manipulations on the less reactive benzenoid ring has remained an inexplicable assignment. Until recently, graceful strategies have been constituted to access reactivity at the less activated positions: C4, C5, C6 and C7 *via* transition-metal-catalyzed C–H activation.[4] Though C2 and C3 functionalization has been covered extensively in a

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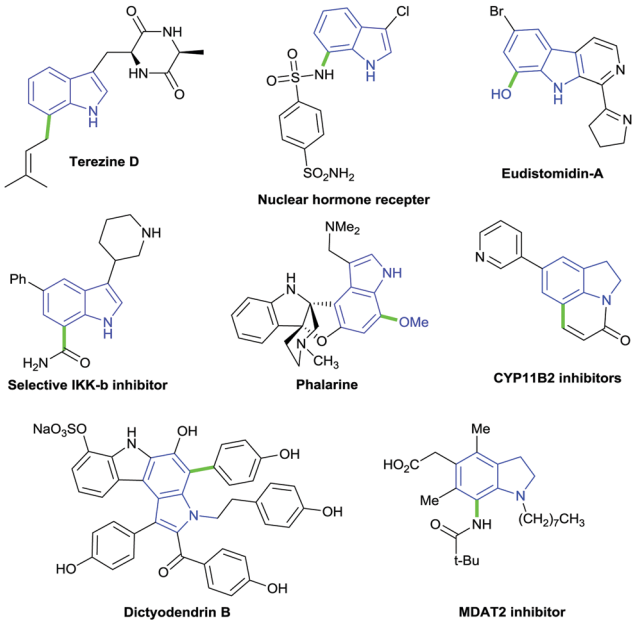
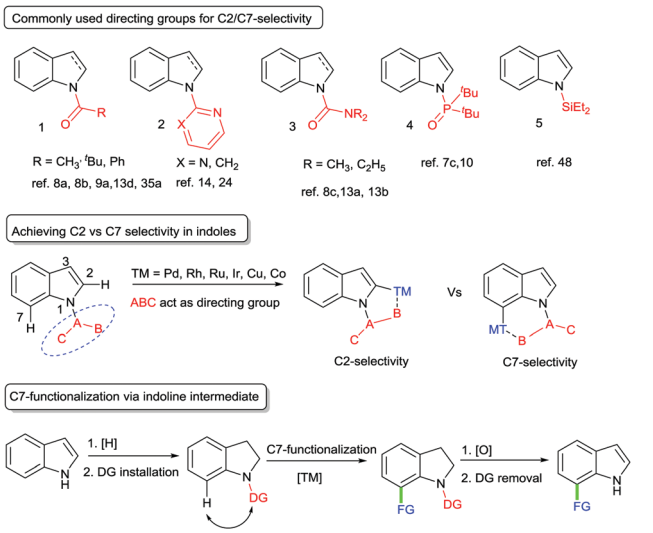


Fig. 1 Some examples of bio-relevant C7-decorated indole derivatives.



Scheme 1 Regioselective C–H activation of indoles/indolines.

review by Sandtorv,[5] the functionalization of benzenoid positions is barely explored. The latest reviews by the Ackermann[4e] and Shi[4f] groups cover the functionalization at the C4 position and regioselective arylation of the benzenoid moiety, respectively. In continuation of our studies on directed C–H functionalization[6] with an ardent eying on the transformation of the indole nucleus,[6b,c] we here present a feature article on transition-metal-catalyzed site-selective C7-functionalization of indoles. The innate reactivity of indoles indicates that metallation cum C–H activation would take place preferentially at the C3 position. To surmount this proclivity, various heteroatom containing groups (N, O, S, P, Si, *etc.*) are installed on the N-site of indole for assisting a huge selection of site-selective C–H functionalization of bio-relevant indoles. To this end, routinely used directing groups (DG), *viz.*, acetyl, pivaloyl, *N*,*N*-dimethylcarbamoyl and pyrimidyl groups, have been introduced to ensure C2 selectivity (Scheme 1), while more bulkier groups such as phosphinoyl and hydrosilyl alter the inherent selectivity more towards the C7 position. The sterically demanding groups such as di-*tert*-butyl substituents in **4** have a profound effect on selectivity in a way that they restrict the free N–P bond rotation and orient perfectly to allow C–H activation at the C7 position. However, pushing selectivity towards C7 contravening C2 selectivity imposes a significant challenge due to the preferable formation of a five membered metallacycle at the C2 position than the corresponding six membered metallacycle at the C7 position. Hence, the functionalization of the C7 position of indoles can be comprehended by (i) blocking the C2 position by substituents, (ii) using a bulkier and more

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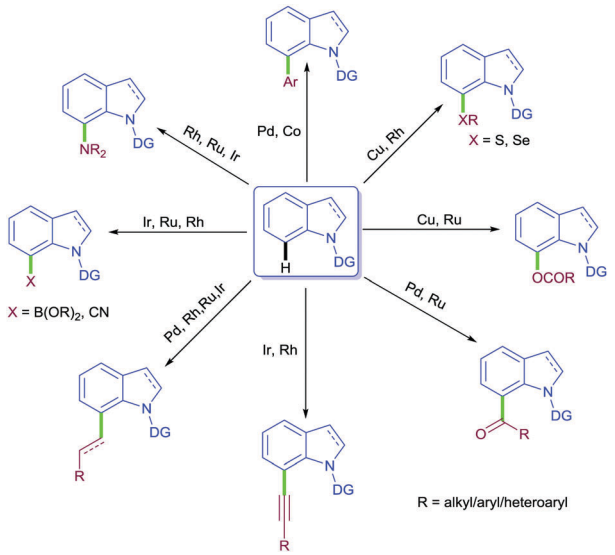
Tharmalingam Punniyamurthy

Tharmalingam Punniyamurthy received his PhD from Indian Institute of Technology Kanpur (Prof. J. Iqbal, 1995). After postdoctoral studies at North Dakota State University (Prof. M. P. Sibi, 1995–1996), Kyushu University (Prof. T. Katsuki, 1997–1999), and Montpellier University II (Prof. A. Vioux and Prof. J. J. E. Moreau, 2000–2001), he joined the Indian Institute of Technology Guwahati and became HAG Professor in 2015. He is an elected fellow of The Indian Academy of Sciences, The National Academy of Sciences and The Royal Society of Chemistry. His research interests include new reactions for sustainable synthetic methodologies for organic transformations.

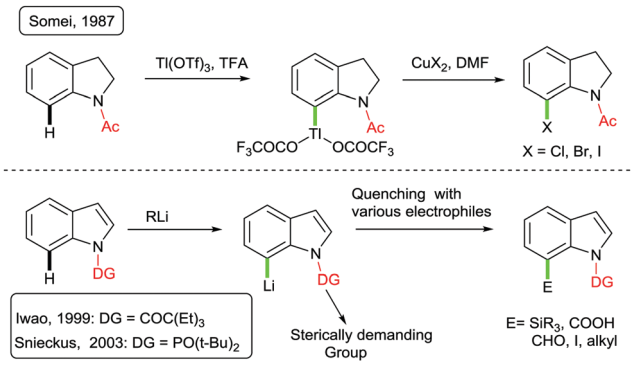


Scheme 2 Transition-metal-catalyzed C7-functionalization of indolines/indoles.

electron-withdrawing DG on the N-atom and (iii) the reduction of indoles to the corresponding indolines and subsequent regioselective C–H functionalization followed by oxidation. Certain pitfalls of the above ways (i and ii) are that the former has inadequate substrate scope and the latter suffers from absolute regioselectivity. Hence, C7 functionalization of indoles *via* reduced indolines and late stage oxidation has been realized as convenient to achieve complete C7 selectivity. Pertinently, general methods to have selectivity directly at the C7 position continue to be scarce. Despite this, a variety of elegant transition-metal-catalyzed methods have been developed. This article will focus on accessing reactivity at the less activated C7 position catalyzed by using transition-metals such as Pd, Rh, Ru, Ir, Cu and Co (Scheme 2).

2. C7 functionalization: the advent

Adaptation of the directed *ortho*-metallation (DOM) strategy has been a primitive asset in C–H functionalization. Taking advantage of such reactivity in 1987, Somei and co-workers attempted C7-thallation of acetylated indolines with stoichiometric $Tl(TFA)_3$, followed by C7-halogenation with Cu(II) halides.[7a] Later, in 1999, Iwao and co-workers[7b] reported C7 functionalization of indoles by employing the sterically demanding 2,2-diethylbutanoyl (DEB) directing group to access *ortho*-lithiation at the C7 position and subsequent quenching with various electrophiles such as CO_2, *N*,*N*-dimethylformamide, alkyl halides and chlorosilanes (Scheme 3). However, this protocol suffers from selectivity issues as besides C7, C2 byproducts were also observed. On improvisation, in 2003, Snieckus and co-workers achieved complete selectivity for C7, by employing a phosphonate directing group.[7c] With the coming of age, the synthetic fraternity ventured on more reliable and sustainable transition-metal-catalyzed C–H functionalization techniques to accomplish site-selective C–H functionalization



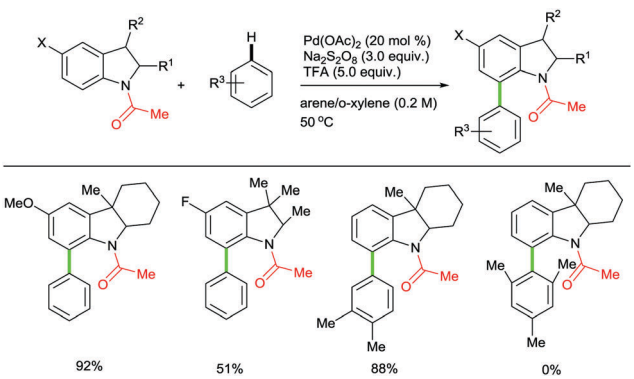
Scheme 3 C7-Functionalization of indoles *via* directed *ortho*-metallation.

of indole. In the earliest reports, research groups, *viz.*, Sanford (2005),[8a] Shi (2007)[8b] and Lipshutz (2010),[8c] implemented various directing groups to carry out Pd-catalyzed C7-arylation of indolines.

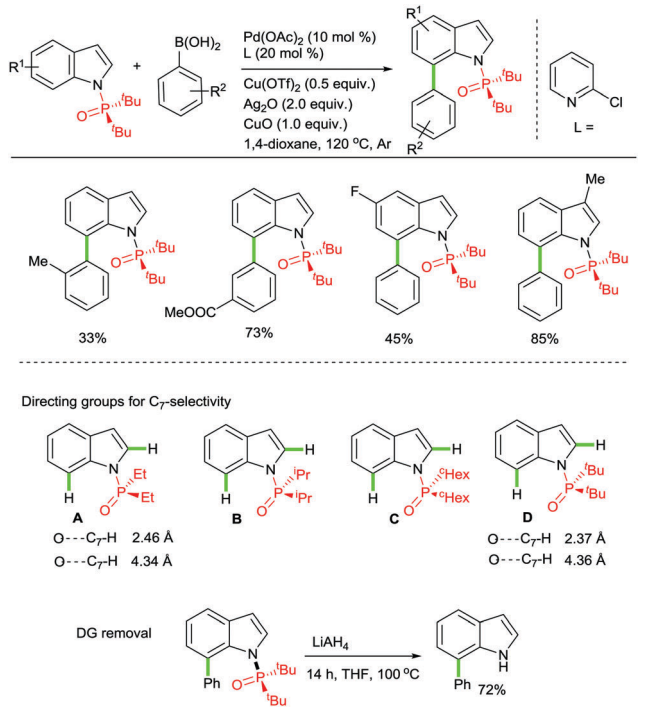
2.1. Arylation

In 2013, Oestreich and co-workers employed an acetyl group at the indoline nitrogen to promote C7 arylation with arenes *via* dehydrogenative coupling (Scheme 4).[9] This Pd(II)-based catalytic methodology requires TFA as an additive and $Na_2S_2O_8$ as an oxidant. Notably, a substituent at C2 was identified as a crucial factor for the selective arylation at C7. Later, the same group improved the arylation with a carbamoyl directing group on indoline utilizing either $Cu(OAc)_2$ in an open flask or molecular oxygen as an oxidant at ambient temperature. This prevented the *in situ* oxidation of indoline to indole and enabled the authors to use C2 and C3 unsubstituted indolines.

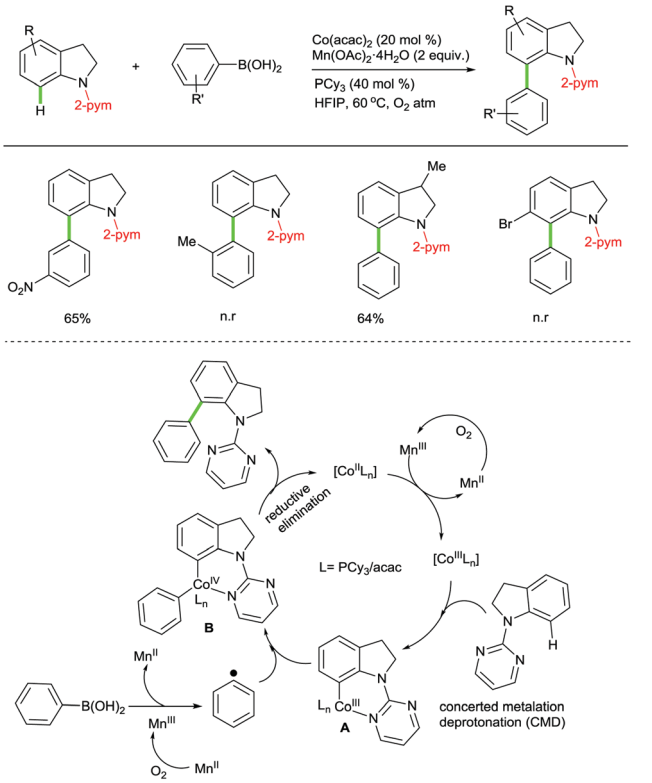
Later, Shi and co-workers developed a rationally designed di-*tert*-butylphosphine oxide (TBPO) directing-group enabled Pd(II)-catalyzed direct C7-arylation of indoles with arylboronic acids in the presence of pyridine as a ligand (Scheme 5).[10] In this method, competing C2 and C3 arylation was significantly suppressed, due to the synergistic effect of the ligand and the sterically hindered TBPO moiety. The authors studied a series of phosphinoyl based directing groups for the amplification of C7 selectivity. Single crystal X-ray diffraction studies of **A** and **D** revealed that the *O*-atom in both is impeccably oriented to



Scheme 4 Palladium-catalyzed dehydrogenative C–H/C–H arylation of indolines.



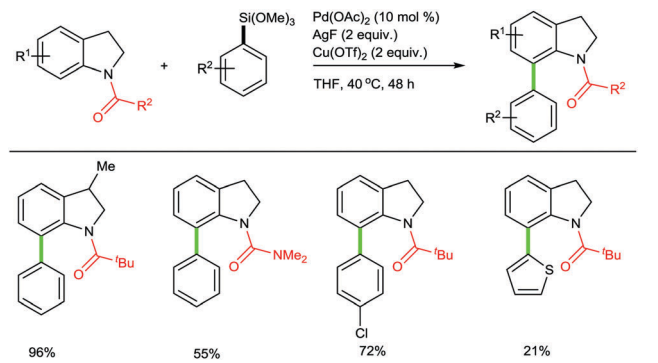
Scheme 5 Palladium-catalyzed direct C–H arylation of indoles with arylboronic acids.



Scheme 7 Cobalt-catalyzed C7-arylation of indolines with arylboronic acids.

assist C–H activation at the C7 position in the solid state as supported by the O–C7–H and O–C2–H bond lengths (Scheme 5). With directing groups having greater bulkiness such as **D**, the authors could obtain substantial selectivity for C7 arylation. Control and deuterium labelling experiments suggested that C–H activation at the C7 position of indole occurred reversibly with the sterically hindered TBPO directing group. The phosphonate DG could be removed by $LiAlH_4$ reduction to give C7-arylated indoles. Later, Wang and co-workers utilized arylsilanes as the coupling partners to carry out C7-functionalization of indolines under Pd(II)-catalysis.[11] Various carbonyl based directing groups were investigated; however, pivaloyl served as the best candidate (Scheme 6).

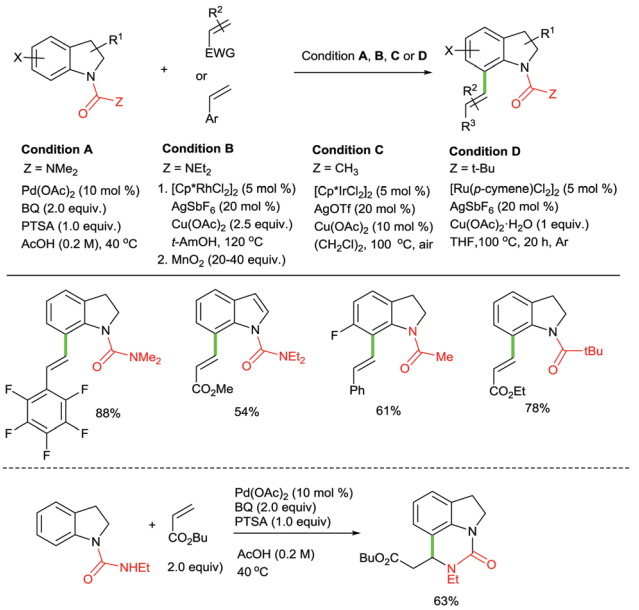
Recently, we successfully accomplished Co(II)-PCy_3-catalyzed site selective C7-arylation of indolines with arylboronic acids (Scheme 7).[12] The addition of the PCy_3 ligand and molecular oxygen had a profound effect on the product yield. The radical scavenger experiment bolstered that the reaction proceeded *via* a radical intermediate. The mechanism involves the formation of a cyclometalated Co(III) intermediate **A** *via* initial oxidation and concerted metallation-deprotonation (CMD). The aryl radical intermediate generated by the reaction of arylboronic acid and Mn(III) reacts with **A** to yield the Co(IV) species **B**. Subsequent reductive elimination of **B** delivers the C7-arylated indolines.



Scheme 6 Palladium-catalyzed C7-arylation of indolines with arylsilanes.

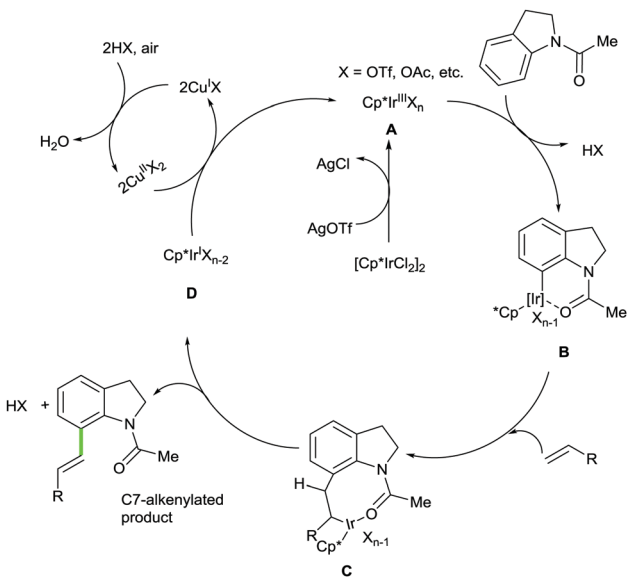
2.2. Alkenylation

The C7-alkenylation of indolines has been considerably studied with activated olefins using a carbonyl based directing group on the N-atom of indolines under varying conditions (Scheme 8).[13a–e] The Oestreich group utilized benzoquinone as an oxidant under Pd(II)-catalysis (condition A).[13a] The substrate scope with respect to both α,β-unsaturated acceptors and styrenes was well tolerated. Pertinently, C6 substituted indolines underwent C7 alkenylation with good yields and with a free NH group at the urea terminus, the authors obtained a six membered cyclized product as shown in Scheme 8. Antonchick and co-workers presented an atom-economic method for C7-alkenylation of indolines *via* Rh(III)-catalyzed oxidative cross-coupling (condition B).[13b] This versatile protocol offers simultaneous *in situ* oxidation of indoline to indoles in the presence of MnO_2 and provides broad substrate scope with regioselectivity. Subsequently, Shibata and co-workers reported Ir(III)-catalyzed C7-selective alkenylation of indolines in the presence of AgOTf and $Cu(OAc)_2$ (condition C).[13c] A carbonyl or carbamoyl group on the nitrogen atom of indoline as a

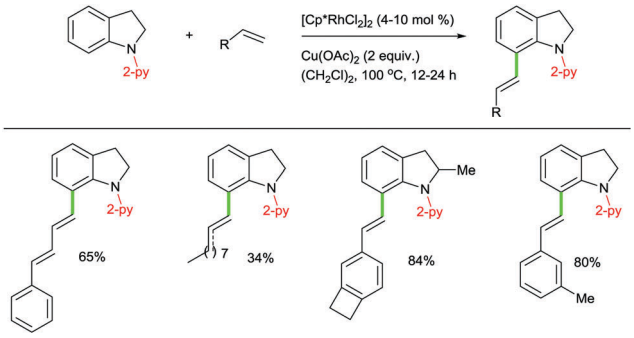


Scheme 8 Directed C7-alkenylation of indolines with activated olefins.

directing group was crucial for the transformation, and the synthesis of both 7-alkenylindoles and 7-alkylindoles has been accomplished. The mechanistic pathway involves an active cationic complex **A** generated by the reaction of $[Cp^*IrCl_2]_2$ and AgOTf (Scheme 9). Coordination of **A** to the carbonyl oxygen of the acetyl group and subsequent C–H activation gives aryliridium **B** *via* CMD. Alkene insertion into the carbon–iridium bond of **B** along with β-hydride elimination provides the desired product and Ir(I)-complex **D**. The latter is oxidized to active Ir(III)-complex **A** by Cu(II). Zhao and co-workers reported a similar type of transformation employing a pivaloyl directing group under inexpensive and stable Ru(II)-catalysis (condition D).[13d] Later, Loh and co-workers developed Rh(III)-catalyzed

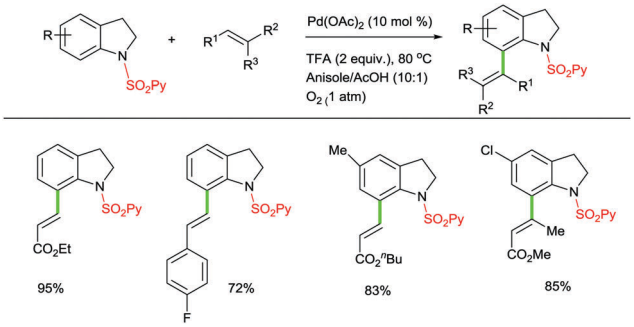


Scheme 9 Proposed mechanism.

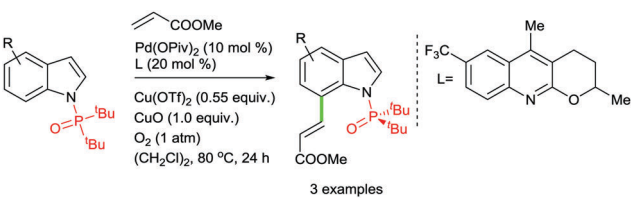


Scheme 10 Rhodium-catalyzed C7-alkenylation of indolines with olefins.

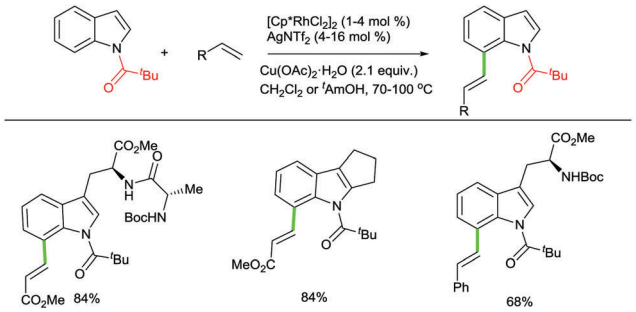
regioselective alkenylation of indolines using a removable pyridinyl group with aryl and alkyl olefins as coupling partners (Scheme 10).[14] Wang and co-workers reported Pd(II)-catalyzed intermolecular alkenylation of indolines using molecular oxygen as the sole oxidant (Scheme 11).[15] Compared to other oxidants such as 1,4-benzoquinone (BQ) and $Cu(OAc)_2$, oxygen offers attractive industrial prospects in terms of green and sustainable chemistry. Pertinently, C7 alkenylated products formed were exclusively *E*-isomers, thereby depicting that the protocol offers complete C7 regioselectivity and *E*-stereoselectivity. Shi and co-workers expanded their arylation methodology by oxidative Heck reaction to accomplish ligand accelerated C–H olefination with excellent regioselectivity, employing methyl acrylate as the coupling partner with indole in the presence of $Pd(OPiv)_2$ as the catalyst (Scheme 12).[10] Ma and co-workers reported unprecedented Rh(III)-catalyzed regioselective C7-olefination of indoles using *N*-pivaloyl as the directing group (Scheme 13).[16] Screening of various directing groups revealed that a bulkier acyl group enhances both C7 regioselectivity and conversion. The deuterium labelling experiment indicated that six membered metallacycle formation takes place during



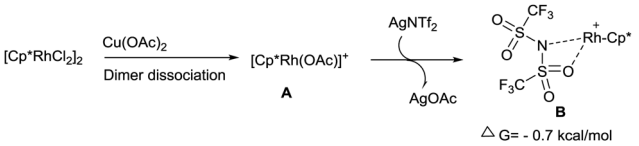
Scheme 11 Palladium-catalyzed C7-alkenylation of indolines with olefins.



Scheme 12 Palladium-catalyzed C7-alkenylation of indoles.



Scheme 13 Rhodium-catalyzed C7-alkenylation of *N*-pivaloylindoles.

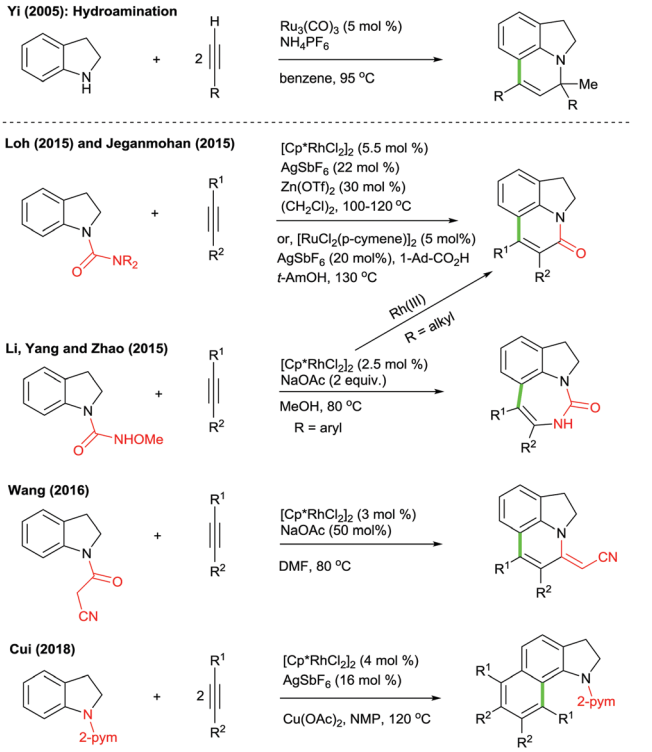


Scheme 14 Initialization of precatalyst.

C–H activation. The Liu group investigated the mechanistic aspects of this reaction employing the density functional theory (DFT) calculations.[4d] The authors addressed the key factors such as the role of $AgNTf_2$ as an additive, selectivity-determining steps and the origins of the substrate-controlled regioselectivity. The results suggest that $AgNTf_2$ not only removes the Cl^- from the catalyst like $AgSbF_6$, but also stabilizes the energetically favourable cationic species **B** (formed by the interaction of $AgNTf_2$ with species **A**) by 0.7 kcal mol^{-1} (Scheme 14). Moreover, with C6 unsubstituted *N*-acyl indoles, C7-olefination is preferred over C2-olefination due to the greater nucleophilicity of the C7 position, while in CF_3-substitued indoles C2 olefination is preferred over that of C7 due to strong steric effects in the transition-state.

Alkynes have been utilized for intermolecular annulation and homologation of indolines by various groups (Scheme 15). In 2005, Yi and co-workers reported the Ru-hydride complex-catalyzed C7-hydroamination of indolines with alkynes.[17] Later, in 2015, Loh and co-workers developed a Rh(III)-catalyzed alkenylation/annulation strategy for the construction of azatricyclic frameworks using internal alkynes.[18] The reaction involves sequential C7–H cleavage of indoline and the C–N bond of the urea motif to give bioactive pyrroloquinolinone scaffolds with high efficiency and selectivity. The feasibility of annulation was realized *via* the directing ability and the electrophilicity of the carbamoyl group. Later, Jeganmohan and co-workers unveiled pyrroloquinolinone synthesis *via* C7–H functionalization under Ru(II)-catalysis using *N*-carbamoyl indolines and alkynes as coupling partners.[19] Subsequently, Li, Yang and Zhou groups extended Rh(III)-catalysed C7 functionalization of indolines using *N*-methoxycarbamoyl indolines.[20]

In 2016, Wang and co-workers developed Rh(III)-catalyzed carbocyclization of indolines with alkynes and alkenes using oxopropanenitrile as the directing group (Scheme 15).[21a] In the same year, the authors reported Rh(III)-catalyzed C7 annulation of 3-(indolin-1-yl)-3-oxopropanenitriles with diazo compounds *via* tandem C–H activation, cyclization, and condensation to



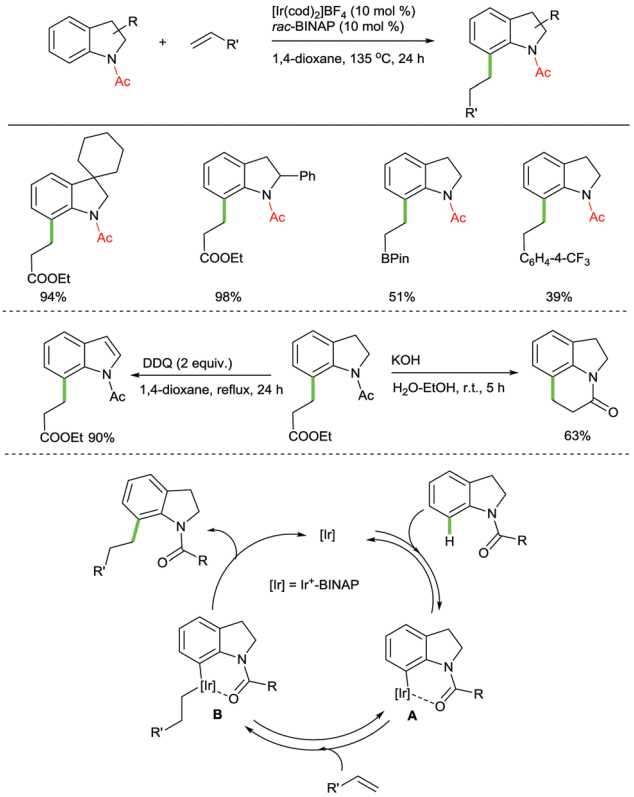
Scheme 15 Ruthenium and rhodium-catalyzed C7-alkenylation of indolines with alkynes.

form fused tetracyclic azepino[3,2,1-*hi*]indole scaffolds.[21b] More recently, Cui and co-workers developed pyrimidine directed Rh(III)-catalyzed dual (C6 and C7) C–H activation of indolines with alkynes.[22]

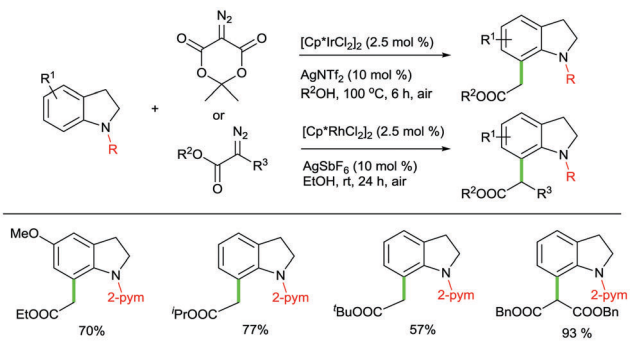
2.3. Alkylation

Several methods have been developed for the incorporation of alkyl groups at the C7 position, utilizing alkyl boron reagents,[23a] olefins, aliphatic acids, alcohols or α-diazocarbonyl compounds as coupling partners. In 2014, Shibata and co-workers reported the Ir(I)-catalyzed alkylation of indolines with alkenes as coupling partners (Scheme 16).[23b] This ligand (BINAP) accelerated protocol utilized BF_4 as a counter anion to Ir-catalyst and the yields were quite excellent. The authors were successful in transforming the C7 alkylated product to a tricyclic derivative by one step hydrolysis of the ester moiety (Scheme 16). The mechanism involves formation of a metallacycle **A** and subsequent hydroiridation to alkene to give species **B**. Finally, reductive elimination leads to the C7 alkylated product.

Later, Zhou and co-workers employed α-diazo carbonyl compounds for the C7 alkylation of indolines at ambient temperature under Rh(III) and Ir(III)-catalysis (Scheme 17).[24] Notably, their protocol was the first example of Ir(III)-catalyzed intermolecular insertion of α-diazocarbonyl compounds into indoline C–H bonds. The facile release of environmentally benign molecular N_2 as the sole byproduct under oxidant-free conditions with high functional-group tolerance makes this protocol an important advancement in C7 functionalization of indolines.



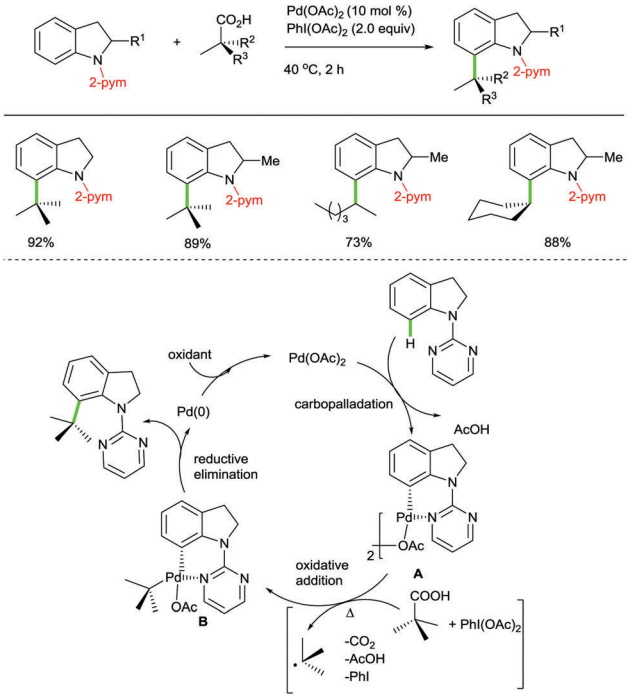
Scheme 16 Iridium-catalyzed C7-alkylation of indolines with olefins.



Scheme 17 Iridium-catalyzed C7-alkylation of indolines with diazocarbonyl compounds.

Jain and co-workers have made further advancement in the C7 alkylation using an unprecedented Pd(II)-catalyzed regioselective decarboxylative alkylation of indolines with inexpensive aliphatic carboxylic acids as the alkyl source (Scheme 18).[25] This report marked the Pd(II)-catalyzed alkylation of unactivated sp^2 C–H bonds using aliphatic carboxylic acids. The pyrimidine directed alkylation proceeded under solvent-free conditions with high functional group tolerance and involves oxidative addition of a pivaloyl radical (facilitated by thermal decomposition of $PhI(OAc)_2$) to palladacycle A, leading to the formation of intermediate B. Reductive elimination of B yields the final product.

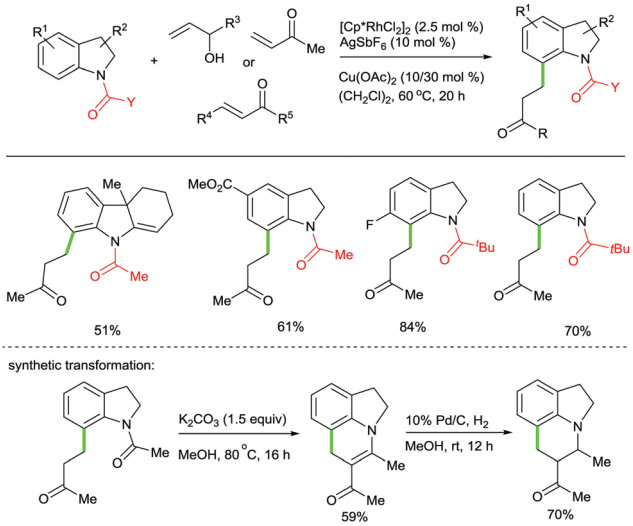
Kim and coworkers reported alkylation of indolines with allylic alcohols and α,β-unsaturated carbonyl compounds for the formation of β-indolinic carbonyl compounds using $[RhCp^*Cl_2]_2$



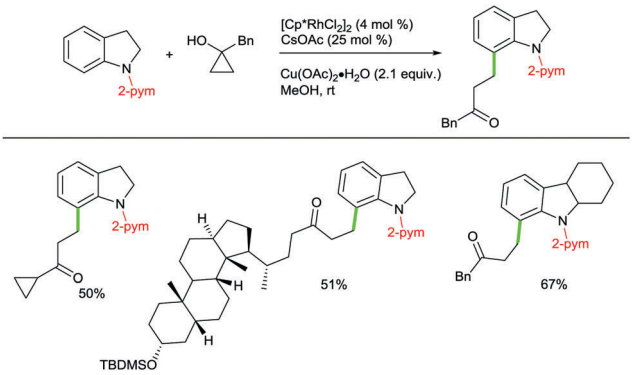
Scheme 18 Palladium-catalyzed C7-alkylation of indolines with aliphatic carboxylic acids.

and $AgSbF_6$ in 1,2-dichloroethane (DCE) (Scheme 19).[26a,b] The authors successfully carried out the synthetic transformation of indolinic carbonyl scaffolds *via* intramolecular aldol reaction followed by dehydration under basic conditions to afford tricyclic indolinic motifs, which were further subjected to catalytic dehydrogenation to give biologically active reduced tricyclic indolines.

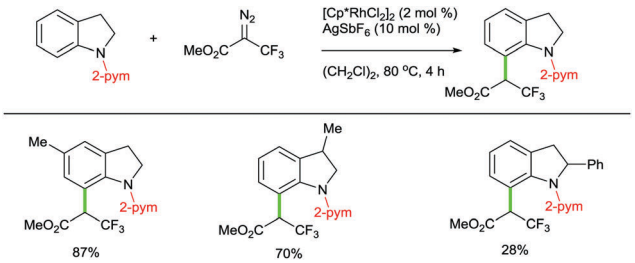
Li and co-workers explored alkylation using reactive/strained cyclopropanols as coupling partners with indolines under mild conditions (Scheme 20).[27] The reaction proceeded *via* the sequence of C–H activation and ring opening in the presence of



Scheme 19 Rhodium-catalyzed C7-alkylation of indolines with allylic alcohols and α,β-unsaturated carbonyl compounds.



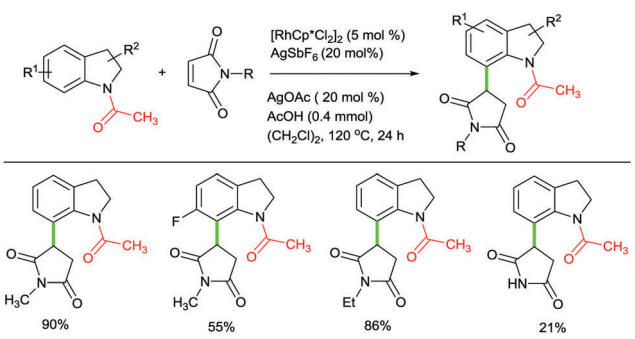
Scheme 20 Rhodium-catalyzed C7-alkylation of indolines with cyclopropanols.



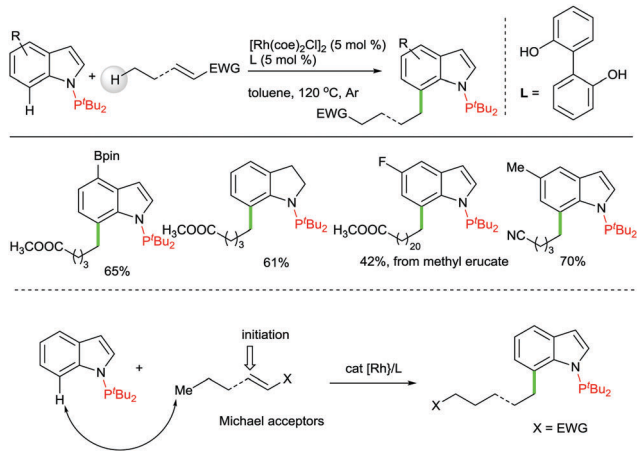
Scheme 21 Rhodium-catalyzed C7-alkylation of indolines with diazo compounds.

Rh(III)-catalyst to give β-aryl ketones. Osipov and co-workers reported pyrimidine directed Rh(III)-catalyzed C7-alkylation of indolines utilizing CF_3-carbenoid C–H functionalization. The chelation assisted strategy used methyl-3,3,3-trifluoro-2-diazopropionate as a carbene source (Scheme 21).[28] Yu and co-workers incorporated maleimides at the C7 position of indolines under Rh(III)-catalysis using $AgSbF_6$/AgOAc as an additive in the presence of acetic acid at elevated temperatures (Scheme 22).[29]

Recently, Shi and co-workers showed a remarkable advancement in C7 alkylation of indoles employing the sterically hindered *N*-P*t*Bu_2 directing group under Rh(I)-catalysis (Scheme 23).[30] With conjugate active olefins as coupling partners, they could easily override the electronic biases at the indole C3-position. This unique functionalization proceeds *via* long range deconjugative



Scheme 22 Rhodium-catalyzed C7-alkylation of indolines with maleimides.

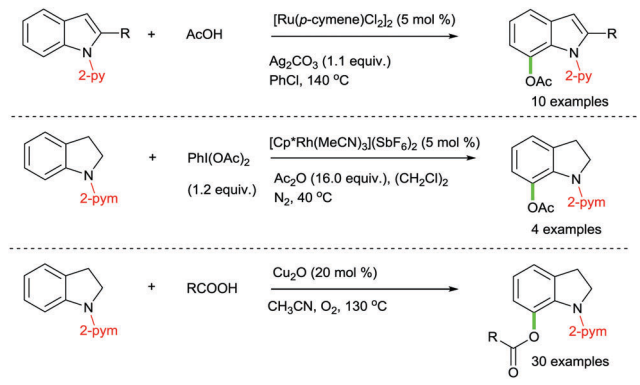


Scheme 23 Rhodium-catalyzed C7-alkylation of indolines with activated olefins.

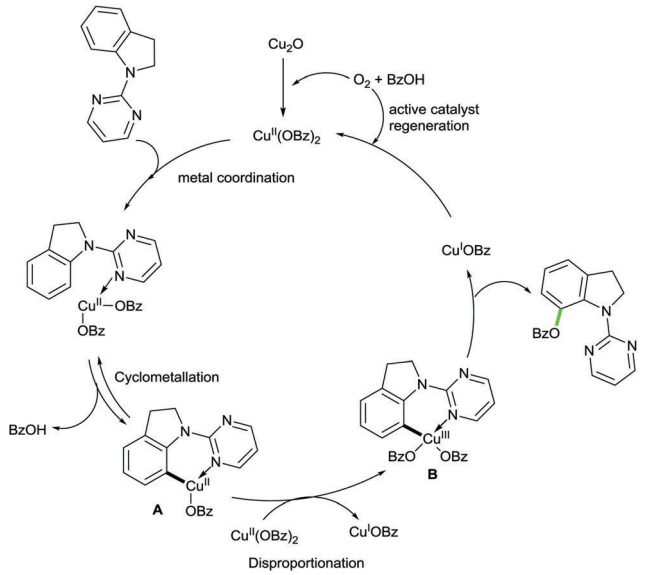
isomerisation triggered by hydrometalation rather than traditional Michael addition.

2.4. Acyloxylation

Efforts have been paid to the direct acyloxylation of indolines using carboxylic acids because of their easy accessibility and versatility. In 2016, Miura and co-workers reported C7-acetoxylation of indoles using acetic acid as the coupling partner under ruthenium catalysis (Scheme 24).[31] Soon after, Deb and co-workers reported pyrimidine directed Rh(III)-catalyzed C7-acetoxylation of indoline derivatives utilizing PIDA as an acetoxylation source.[32] The method is highly selective and requires acetic anhydride as the additive. Later, Koley and co-workers reported Cu-catalyzed C7-acyloxylation of indolines using Cu_2O (20 mol%) under an oxygen atmosphere at elevated temperature (Scheme 24).[33] The authors were successful in carrying out C7-hydroxylation and intramolecular Heck-reaction through Pd-catalysis to afford indoloisochromenones. The radical scavenger experiment using TEMPO suggested a non-radical pathway. The mechanism involves the formation of cyclometalated Cu(II) **A**, followed by disproportionation of the Cu(II) ion to produce highly active Cu(III) intermediate **B** (Scheme 25). Reductive elimination affords the product and Cu(I)OBz. Subsequently, oxidation of Cu(I)OBz using oxygen regenerates the active catalyst.

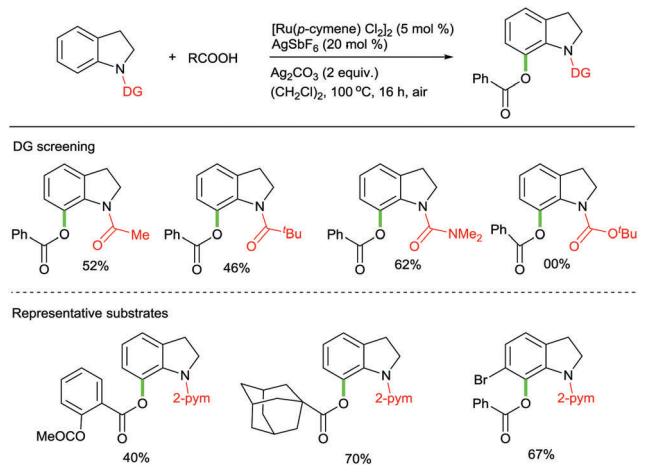


Scheme 24 C7-Acyloxylation of indolines with PIDA or carboxylic acids.

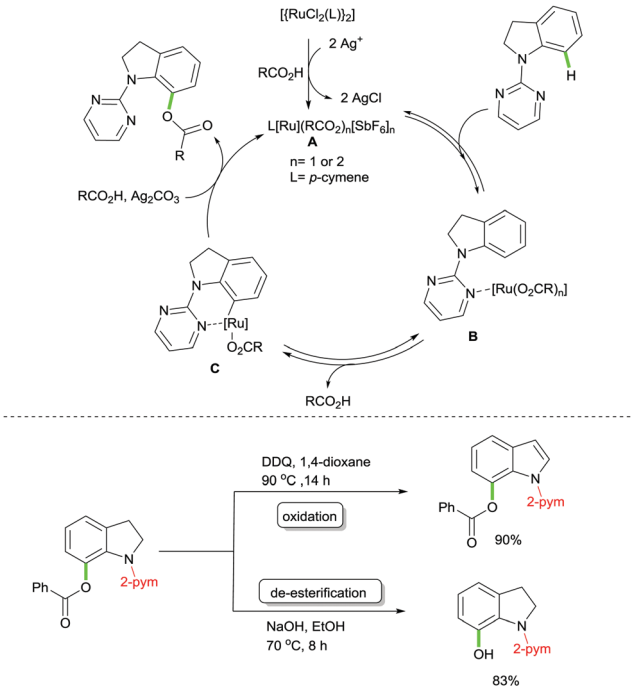


Scheme 25 Proposed mechanism.

Our group reported a Ru(II)-catalyzed C7-acyloxylation of indolines with carboxylic acids. Oxidation of these functionalized scaffolds using DDQ furnishes C7-oxygenated indoles (Scheme 26).[34] The optimized conditions involve the combination of [Ru(*p*-cymene)Cl_2]$_2$ and $AgSbF_6$ in the presence of Ag_2CO_3 as an oxidant. The protocol afforded ample substrate scope as aryl, alkyl, heterocyclic and α,β-unsaturated carboxylic acids were tolerated. Intermolecular competition experiments disclosed that electron-deficient aromatic carboxylic acids react at a faster rate than electron donating ones. H/D scrambling and isotope exchange experiments revealed reversible C–H activation and C–H bond cleavage as the rate determining step at the C7 position of indolines, respectively. On the basis of mechanistic investigations as discussed above, the catalytic cycle was proposed (Scheme 27). The active Ru(II)-catalyst **A** generated by the silver salt coordinates with pyrimidyl-nitrogen to give intermediate **B** along



Scheme 26 Ruthenium-catalyzed C7-acyloxylation of indolines with carboxylic acids.

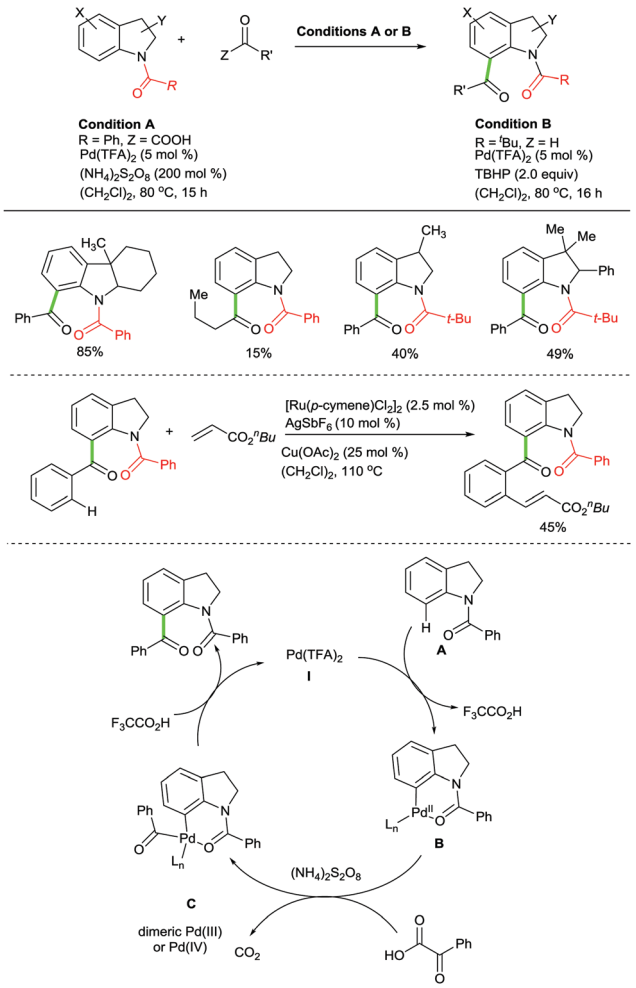


Scheme 27 Proposed mechanism and late-stage modification.

with the elimination of RCOOH. Six membered ruthenacycle **C** formed by metallation and subsequent reductive elimination completes the catalytic cycle by affording the desired product. The catalytically active Ru-species **A** is regenerated upon oxidation with Ag(I) to complete the catalytic cycle.

2.5. Acylation

Kim and co-workers reported functionalization of indolines at the C7 position with α-keto acids to afford C7-aroylated/carbonylated indolines under Pd(II) catalysis (Scheme 28).[35a] The benzoyl group directed Pd(II) to the C7 site in the presence of $(NH_4)_2S_2O_8$ as an oxidant to afford the desired product (condition A). Directing groups such as pivaloyl, *N*,*N*-dimethylcarbamoyl or pyrimidyl were found to be less effective. The scope of the protocol revealed excellent functional group tolerance and *N*-benzoyl protection could be removed under hydrolysis to give free-(NH)-indoline. Further, treating the C7-aroylated product with *n*-butyl acrylate under Ru(II)-catalysis produced the olefinated product. Later, the authors reported Pd(II)-catalyzed oxidative acylation of indolines at C7-position with aldehydes or alcohols (condition B).[35b] Mechanistic investigations revealed the formation of six-membered palladacycle **B** by coordination of Pd(II)-catalyst to **A** and subsequent reaction of **B** with α-keto acid to afford dimeric Pd(III) or Pd(IV) intermediate **C** along with decarboxylation. Reductive elimination completes the catalytic cycle to afford the C7 acylated product (Scheme 28). During their optimization studies in coupling indolines with ethyl glyoxalate in the presence of $Cu(OAc)_2$ as an additive, they surprisingly got C7-indolinyl ketoesters rather than alcohols. This prompted them to extend their work to Ru(II)-catalysis for the site selective C7 acylation of indolines using a removable pyrimidyl group (Scheme 29).[35c] Pertinently, in this case C–H activation

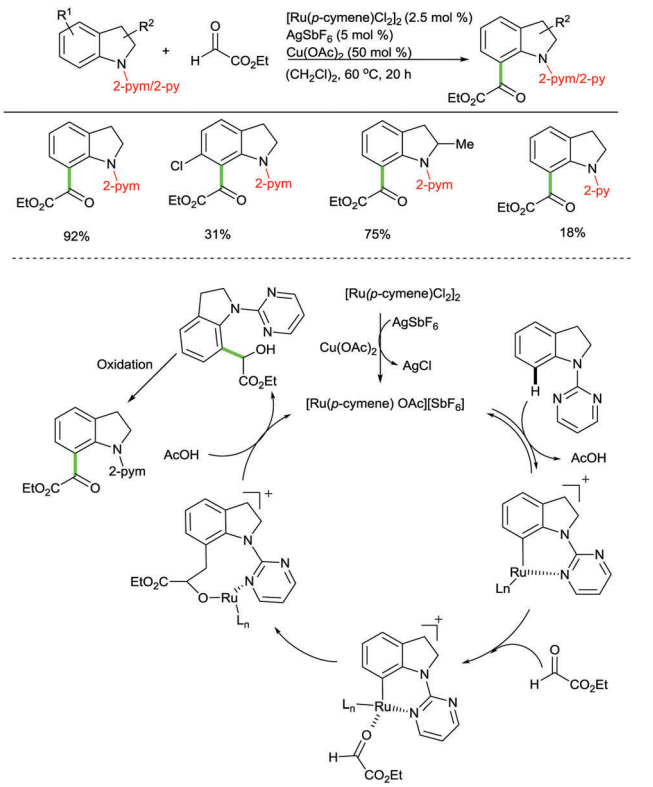


Scheme 28 Palladium-catalyzed C7-acylation of indolines with α-keto acids and aldehydes.

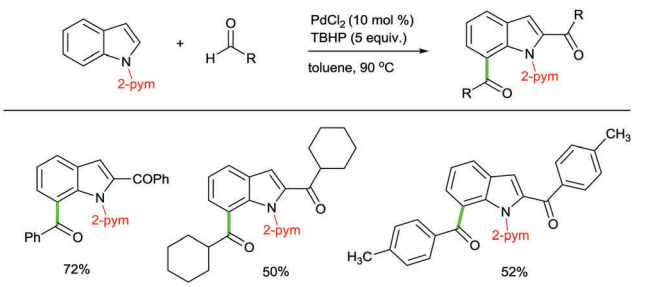
is subsequently followed by glyoxalate insertion to give C7-functionalized alcohol which subsequently undergoes oxidation to give the final product. In 2015, Sekar and co-workers reported pyrimidine directed diacylation of indoles employing an excess amount (3.0 equiv.) of aldehydes as coupling partners under Pd(II)-catalysis using TBHP as an oxidant (Scheme 30).[36] They could obtain a symmetric C2 and C7-diacylated product through double functionalization of C2 and C7 C–H bonds.

2.6. Allylation

In 2015, Kim and co-workers pioneered the developments in C7-allylation of indolines *via* the use of a meticulously designed carbamoyl directing group (–NH^{n}Bu) (Scheme 31).[37] The cationic Rh(III)-complex, formed from $[Cp^*RhCl_2]_2$ and $AgSbF_6$, was found to effectively catalyze the coupling of *N*-butylindoline-1-carboxamide with allyl methyl carbonate/vinyldioxolanone in the presence of $Cu(OAc)_2$ as an additive. Using –NH^{n}Bu, as the directing group, the C7-allylated products were formed as a regioisomeric mixture with high terminal selectivity and yield. However, other directing groups displayed low levels of reactivity and selectivity. The authors could couple indoline with 2-vinyloxirane *via* olefin



Scheme 29 Ruthenium-catalyzed C7-alkylation of indolines with ethyl glyoxalate.

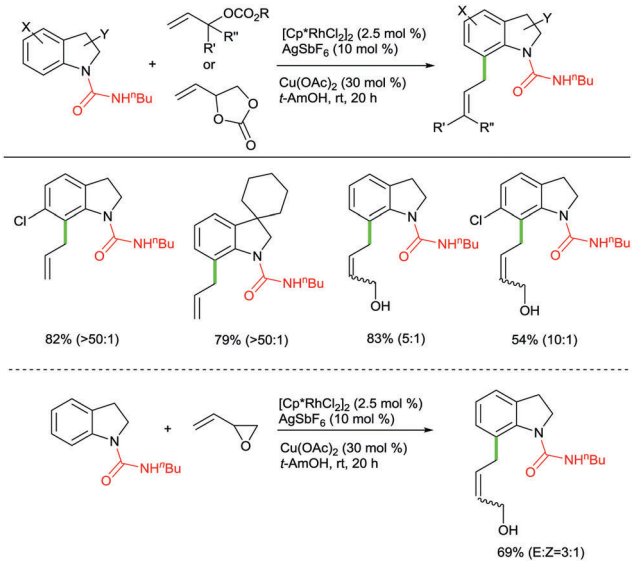


Scheme 30 Ruthenium-catalyzed C7-alkylation of indolines with aldehydes.

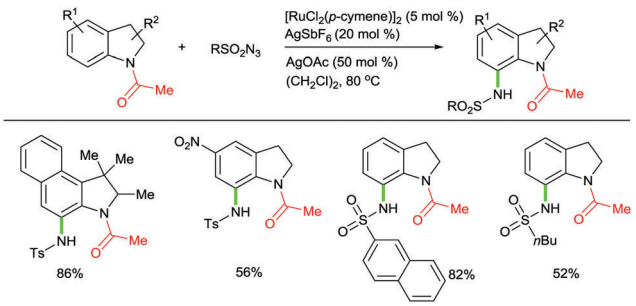
insertion and epoxide ring-opening to give allylic alcohol in good yield.

2.7. Amidation

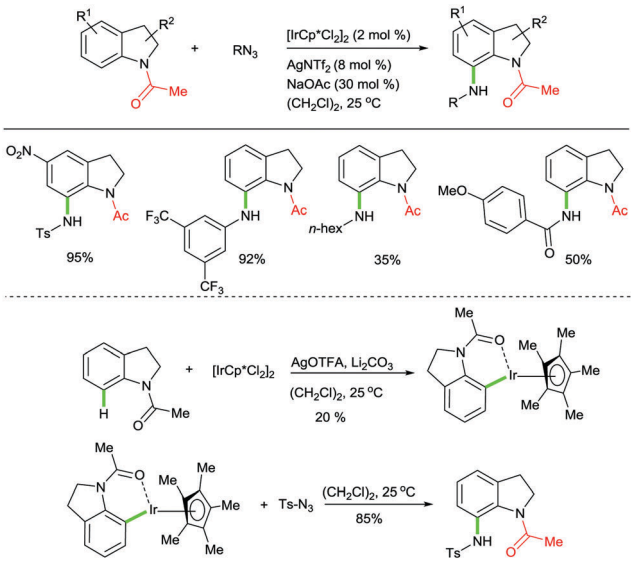
In 2014, Zhu and co-workers reported C7 amidation of indolines, wherein they utilized sulfonyl azides as coupling partners under ruthenium catalysis (Scheme 32).[38] The effect of solvent was vital for amidation, as among the various solvents screened, only DCE provided the best yield. The presence of AgOAc as an additive enhanced the yield to 76%. Within a span of next three years, many groups, *viz.*, Chang,[39] Li,[40] Antonchick[41] and Ma,[42] utilized organic azides for carrying out the amidation at the C7 position under iridium catalysis (Schemes 33 and 34). To understand the mechanistic aspects of amidation, Chang and co-workers showed a cyclometalated iridacyclic intermediate in



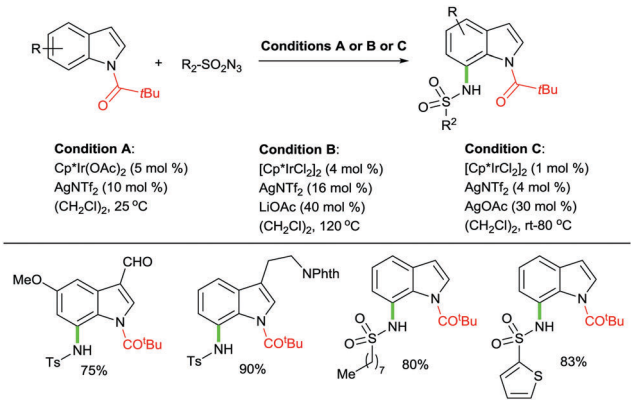
Scheme 31 Rhodium-catalyzed C7-allylation of indolines with allylic carbonates and dioxolanone.



Scheme 32 Ruthenium-catalyzed C7-amidation of indolines with sulfonyl azides.



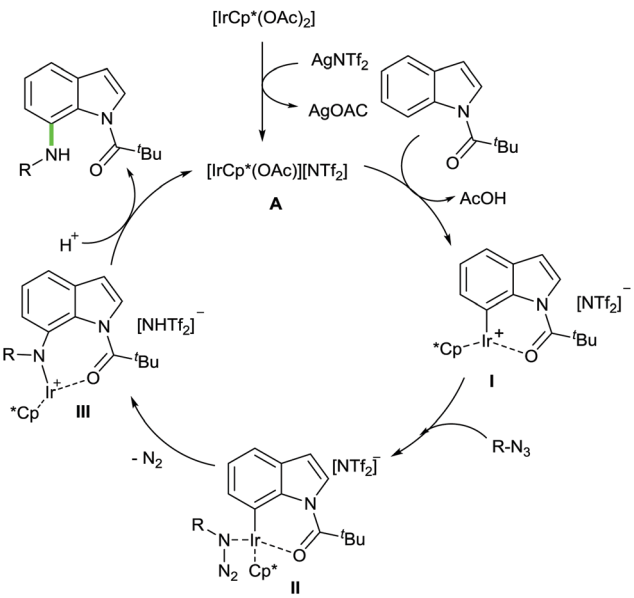
Scheme 33 Iridium-catalyzed C7-amidation of indolines with organic azides.



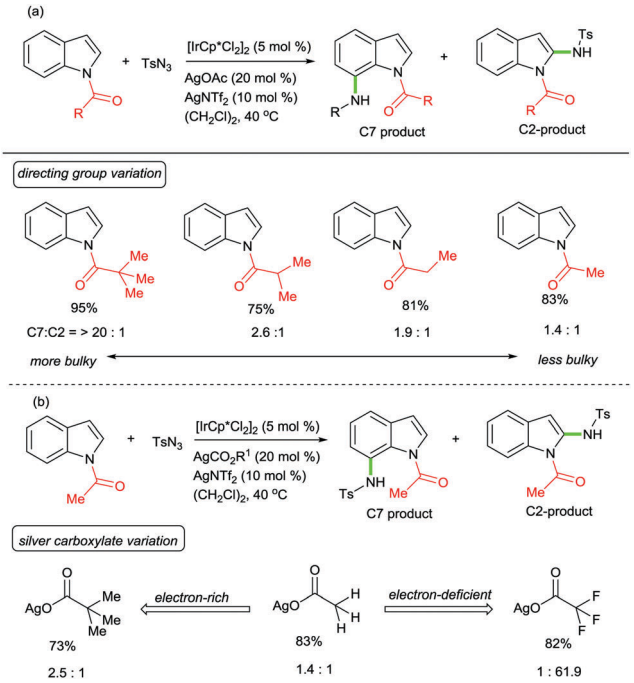
Scheme 34 Iridium-catalyzed C7-sulfonamidation of indoles with sulfonyl azides.

the catalytic cycle, and for that they isolated and subjected their corresponding iridacycle to amidation. The mechanisms of these iridium-catalyzed methods are more or less similar, involving generation of an active cationic species **A**, by the reaction of $[Cp^*IrCl_2]_2$ with silver salt and the acetate anion (Scheme 35). Coordination of carbonyl oxygen of the directing group with active iridium species followed by C–H activation delivers the metallocycle **I**. Azide coordination to **I** produces intermediate **II**, and subsequent migratory insertion of the amido group affords intermediate **III** with the concomitant release of N_2. Finally, protolysis affords the final product and the active catalyst.

Chang and co-workers recently described a substrate-guided and base-controlled approach to invert site selectivity in Ir(III)-catalyzed C–H amidation of *N*-acylindoles (Scheme 36). The mechanisms associated with factors controlling C2 and C7 selectivity were studied with DFT-based transition state analysis.[39c] The authors observed that the site-selectivity was highly dependent on *N*-acyl groups, as C7 amidation was observed exclusively with *N*-pivaloylindole (Scheme 36a). On the other hand, directing groups with a smaller alkyl chain, *viz.*, isobutyrylindole, produced C2 and C7-amidation products in 21% and 54% yield, respectively.



Scheme 35 Proposed mechanism.

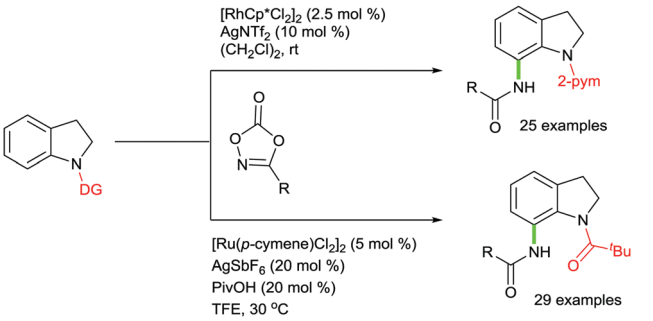


Scheme 36 Effect of reaction parameters on the site selectivity of iridium-catalyzed amidation of indoles with azides.

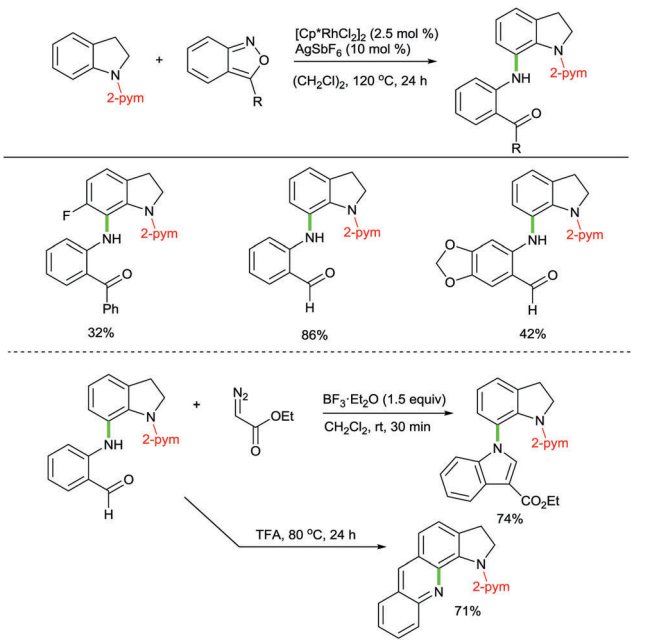
Further reduction in the size of *N*-substituent enhanced the C2 products and with *N*-acetylindoles the two regioisomeric products were obtained in the ratio of 1.4 : 1 (C7/C2). The effect of additives on selectivity revealed that the nature of carboxylates directly affects the relative energy differences between selectivity-determining transition states (Scheme 36b). With the more basic silver pivalate, C7 selectivity increased and by employing silver trifluoroacetate as the additive, the authors observed suppression in C7 functionalization and enhancement in C2-amidation. Following the above mentioned reports, Kim and co-workers described C7 amidation of indolines utilizing dioxazolone as an amidating reagent (Scheme 37).[43] For this transformation the authors used Rh(III)-catalyst along with $AgNTf_2$ as an additive in DCE at ambient temperature. One of the synthesized compounds was shown to possess cytotoxic efficiency. The methodology offers ample substrate scope. Soon after, Prabhu and co-workers disclosed a similar type of amidation using the comparatively cost-effective Ru(II)-catalyst in combination with $AgSbF_6$, assisted by the easily removable pivaloyl directing group at ambient temperature (Scheme 37).[44] The synthetic methodology offers broad substrate scope with excellent yields and selectivity.

2.8. Amination

Kim and co-workers showed amination of indolines under Rh(III) catalysis by utilizing anthranils as amination sources (Scheme 38).[45] A wide range of C7 amination substrates could be synthesized with excellent site-selectivity and high functional group tolerance. The C7-amination products containing both amino and carbonyl moiety could be easily transformed into biologically significant 1,7-bisindoline and pyrroloacridine



Scheme 37 Rhodium-catalyzed C7-amidation of indolines with organic dioxazolones.

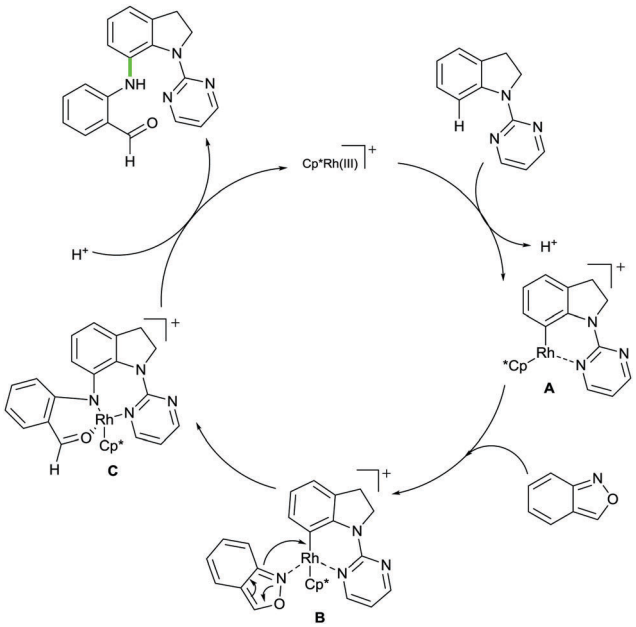


Scheme 38 Rhodium-catalyzed C7-amination of indolines with anthranils.

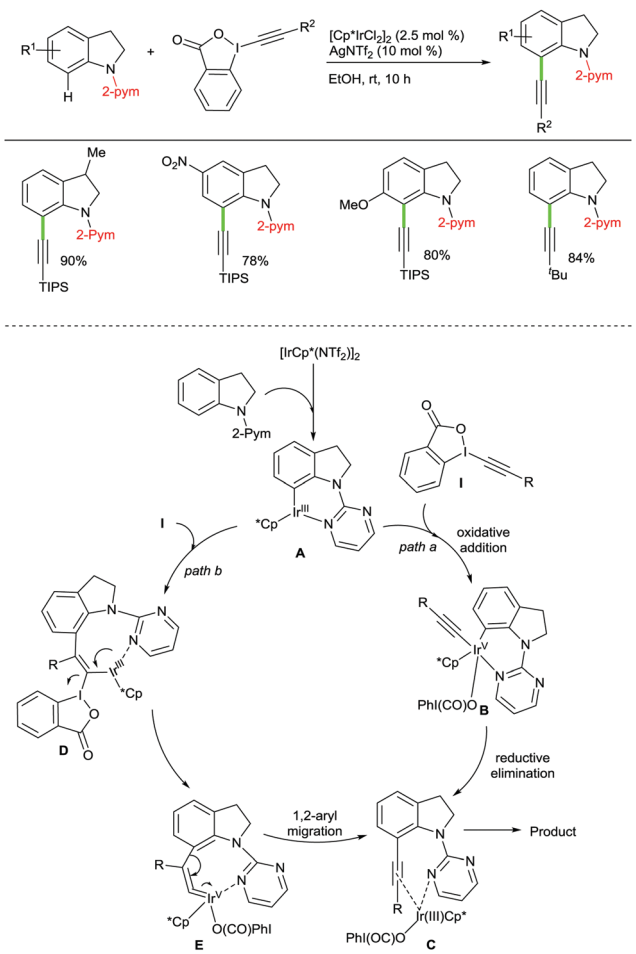
derivatives. The mechanism involves formation of a cationic Rh(III)-complex **A** from indolines and $[RhCp^*Cl_2]_2$ in the presence of $AgSbF_6$. Migratory insertion after anthranil ligation provides species **C**, which undergoes protonation to give C7-aminated indoline, along with subsequent generation of active Rh(III) species (Scheme 39). Chang,[39a] and Zhou and Li[40] groups showed C7-amination of indolines using alkyl/aryl azides as an amination source in their seminal work.

2.9. Alkynylation

In 2015, Li and co-workers reported alkynylation of indolines employing hypervalent iodine (TIPS-EBX), assisted by a pyrimidyl directing group.[46] For this functionalization, the optimized conditions utilized the 2.5 mol% Ir(III) catalyst in the presence of $AgNTf_2$ (10 mol%) in ethanol (Scheme 40). The protocol offers broad substrate scope with easily removable directing group. On the basis of deuterium labeling, competitive experiments and single crystal X-ray diffraction analysis, the authors proposed two mechanistic paths for the catalytic cycle (Scheme 40). Path 'a'



Scheme 39 Proposed mechanism.



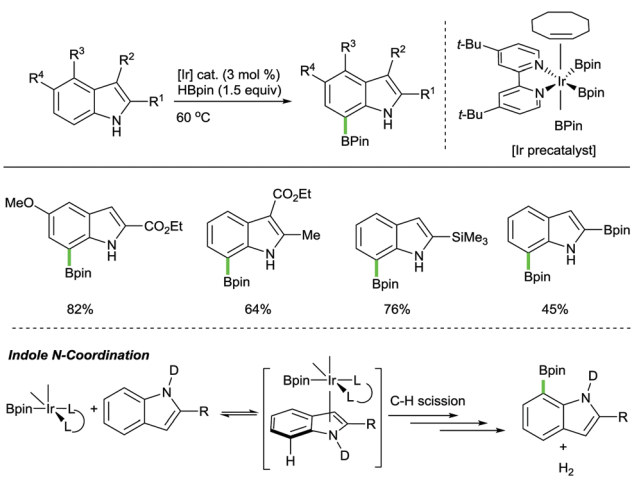
Scheme 40 Iridium-catalyzed C7-alkynylation of indolines with a hypervalent iodine reagent (TIPS-EBX).

proceeds *via* formation of a metallacycle **A**, followed by oxidative addition to the hypervalent iodine to give intermediate **B**, which undergoes reductive elimination to form intermediate **C**. Alternatively, Path "b" may also offer intermediate **C** by migratory insertion of alkyne, α-elimination and aryl migration. Alkyne dissociation from intermediate **C** gives the C7 alkynylated indolines. In the same year, Loh and co-workers have also employed hypervalent iodine reagents (EBX) as alkynylating agents under Rh(III)-catalysis.[14]

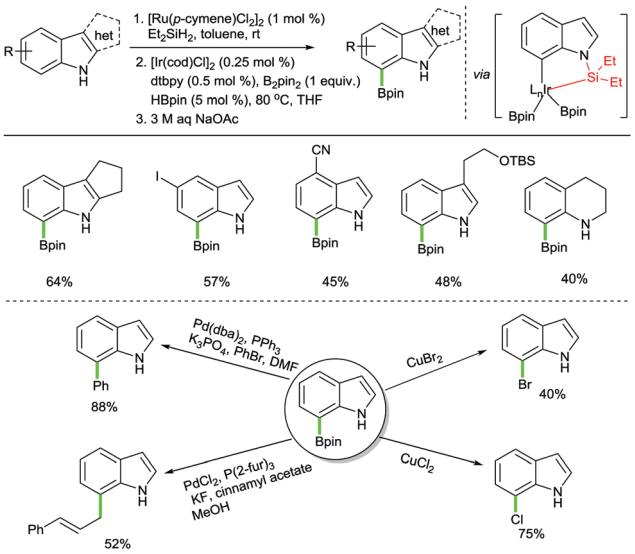
2.10. Borylation

In 2003, Snieckus and co-workers developed a directed metalation approach for functionalizing 2-substituted indoles.[7c] However, the methodology requires *N*-protection and late-stage deprotection. To address the direct functionalization of unprotected 2-substituted indoles at C7, Smith and co-workers reported nitrogen-directed Ir-catalyzed borylation with pinacolborane (HBPin) at elevated temperature (Scheme 41).[47] The authors improved the yield by employing bipyridine as a ligand. Pertinently, substrates that were unsubstituted at C2 afforded diborylated products. A remarkable example in Smith's study was 2-trimethylsilyl indole, which was boronated in 76% yield, with subsequent desilylation affording 7-boroindole in 88% yield. By various synthetic transformations, the authors proposed the mechanism which involves "*N*-chelation to Ir" assisted borylation that proceeded *via* C–H insertion.

Following this, Hartwig's group reported silyl-directed C7 borylation of indoles devoid of any substituent at the 2-position under Ir-catalysis (Scheme 42).[48] Their three-step methodology utilized the N1-appended silane directing group on indole to facilitate regioselective boronation to 7-boroindole. The directing group had a profound role in overriding the intrinsic site selectivity for the borylation of indoles at the C2-position, as the products were obtained with complete selectivity using *bis*(pinacolato)-diboron (B_2pin_2) in the presence of $[Ir(cod)Cl]_2$ and 4,4′-di-*tert*-butylbipyridine (dtbpy). The authors could easily further functionalize 7-borylindole under varying conditions as shown in Scheme 43.

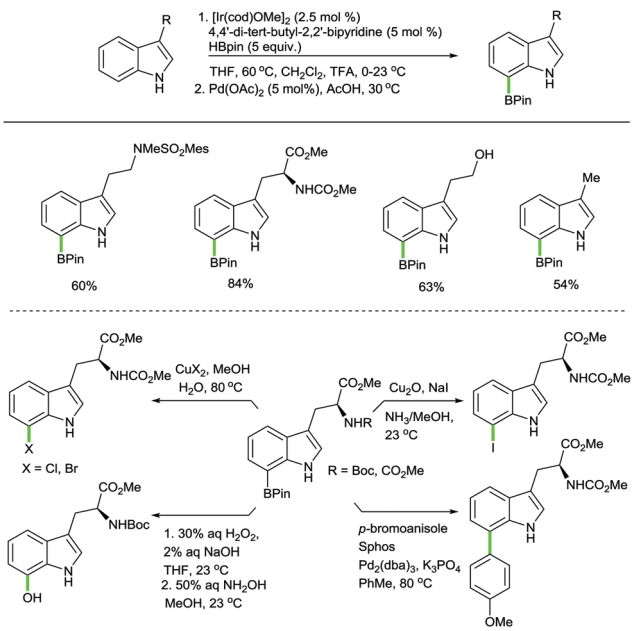


Scheme 41 Iridium-catalyzed C7-borylation of indoles with pinacolborane (HBPin).



Scheme 42 Iridium-catalyzed C7-borylation of indoles with bis(pinacolato)-diboron (B_2pin_2).

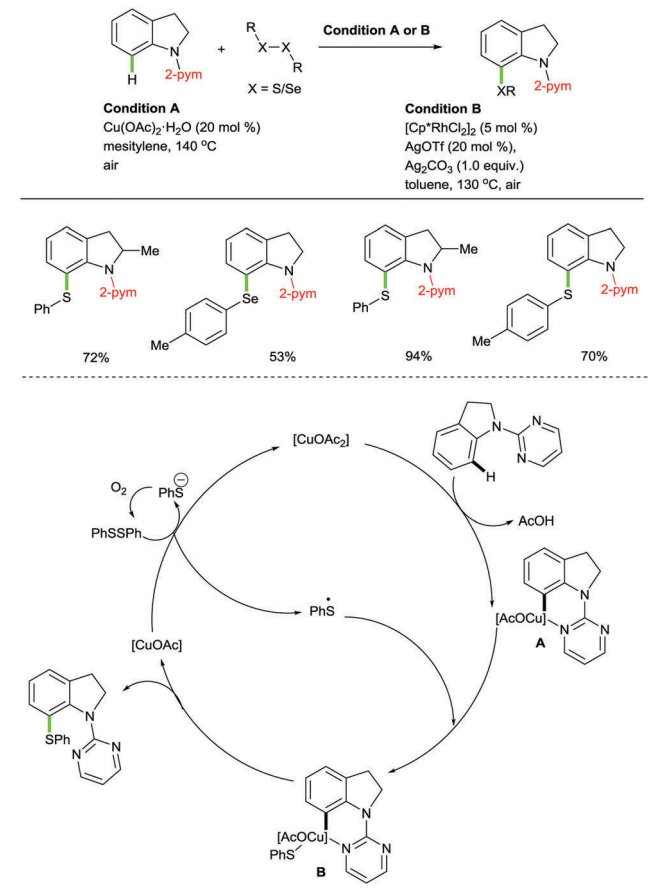
Inspired by Smith's and Hartwig's studies, Movassaghi and co-workers developed a more rationalized method for direct conversion of tryptamines and tryptophans to the corresponding C7-boronated indoles (Scheme 43).[49] This two-step, one-pot Ir-catalyzed functionalization involved C2/C7-diboronation followed by *in situ* Pd-catalyzed C2-protodeboronation to afford C7-boroindoles, which in turn enabled further C7-derivatization. The authors were successful to extend further transformation of 7-borotryptophan to the corresponding 7-chloro, 7-bromo and 7-iodotryptophan derivatives using Cu-catalysis. Similarly, employing Suzuki–Miyaura coupling and peroxide-mediated oxidation of 7-borotryptophan, C7-arylated and the corresponding phenol derivatives were obtained, respectively.



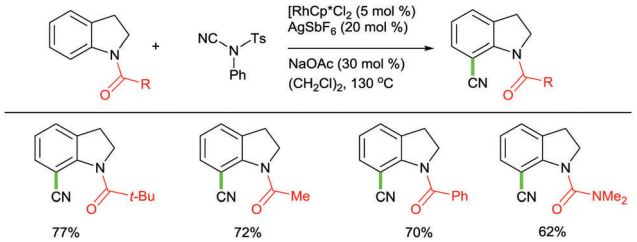
Scheme 43 Iridium-catalyzed C7-borylation of indoles with HB_{pin}.

2.11. Chalcogenation

In 2016, Wang and co-workers reported C7-thiolation and selenation of indolines under Rh(III)-catalysis utilizing a removable pyrimidyl directing group (Scheme 44, condition A).[50] Disulphides and diselenides served as the coupling partners and a wide range of substrates could be functionalized. Deuterium exchange experiments indicated that the C–H activation is reversible. Selective oxidation of the C7 thiolated product with *m*-CPBA produced sulphonyl indolines in good yield. The Ackermann group made a remarkable advancement in the area of C7 functionalization of indolines utilizing the cost-effective copper catalyst (condition B).[51] The authors achieved C7-thiolation/selenation of indolines with diphenylsulphides/selenides using 20 mol% $Cu(OAc)_2{\cdot}H_2O$ in mesitylene as the solvent. The methodology offers notable features in terms of aerobic conditions and being additive-free. Mechanistic studies indicated a facile C–H activation and SET-type mechanism being operative. The catalytic cycle involves facile chelation-assisted C–H cleavage to produce metallacycle A, followed by its reaction with sulfonyl radical to form Cu(III) species B (Scheme 44). Reductive elimination of B yields the desired product with the simultaneous release of Cu(I). Finally, the active Cu(II) is rejuvenated by the action of disulfide and oxygen.



Scheme 44 Copper and rhodium-catalyzed C7-chalcogenation of indolines with disulphides/diselenides.



Scheme 45 Rhodium-catalyzed C7-cyanation of indolines with the NCTS reagent.

2.12. Cyanation

Kim and co-workers reported C7-cyanation of indolines using *N*-cyano-*N*-phenyl-*para*-methylbenzenesulfonamide (NCTS) as a user-friendly cyanation precursor instead of commonly used metal cyanide salts under Rh(III)-catalysis (Scheme 45).[52] The authors have examined various *O*-coordinating directing groups and surprisingly all the directing groups led to the formation of C7-cyanated indolines. Mechanistic studies revealed that the reversible C–H activation step might be involved in the rate determining step.

3. Conclusions and outlook

In view of the omnipresence of indole moieties in plentiful organic candidates, exemplary efficient synthetic arsenals for practical site-selective C–H functionalization of indoles have emerged thoroughly. Overriding the inherent C2 and C3 reactivity, a number of competing approaches to perform selective functionalization on the less activated benzenoid ring have been achieved. The current precedent encompasses the development of transition-metal-catalyzed C7 functionalization of indoles by means of an indoline intermediate, with judicious selection of catalytic systems and coupling partners. So far, reported set-ups hinge on the use of noble transition-metal catalysts (Rh, Ir, Ru, Pd) and inevitable DG installation and amputation steps, which questions step-economy and sustainability. Considering this synthetic space, discovery of streamlined strategies such as traceless directing groups, the merger of electro-catalysis or photocatalysis or non-covalent interactions with first-row transition-metals will adorn the synthetic landscape in contemporary organometallic research. Undeniably, these early methods will bestow a platform to uncover new facets for both the synthetic and material chemists.

Conflicts of interest

There are no conflicts to declare.

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