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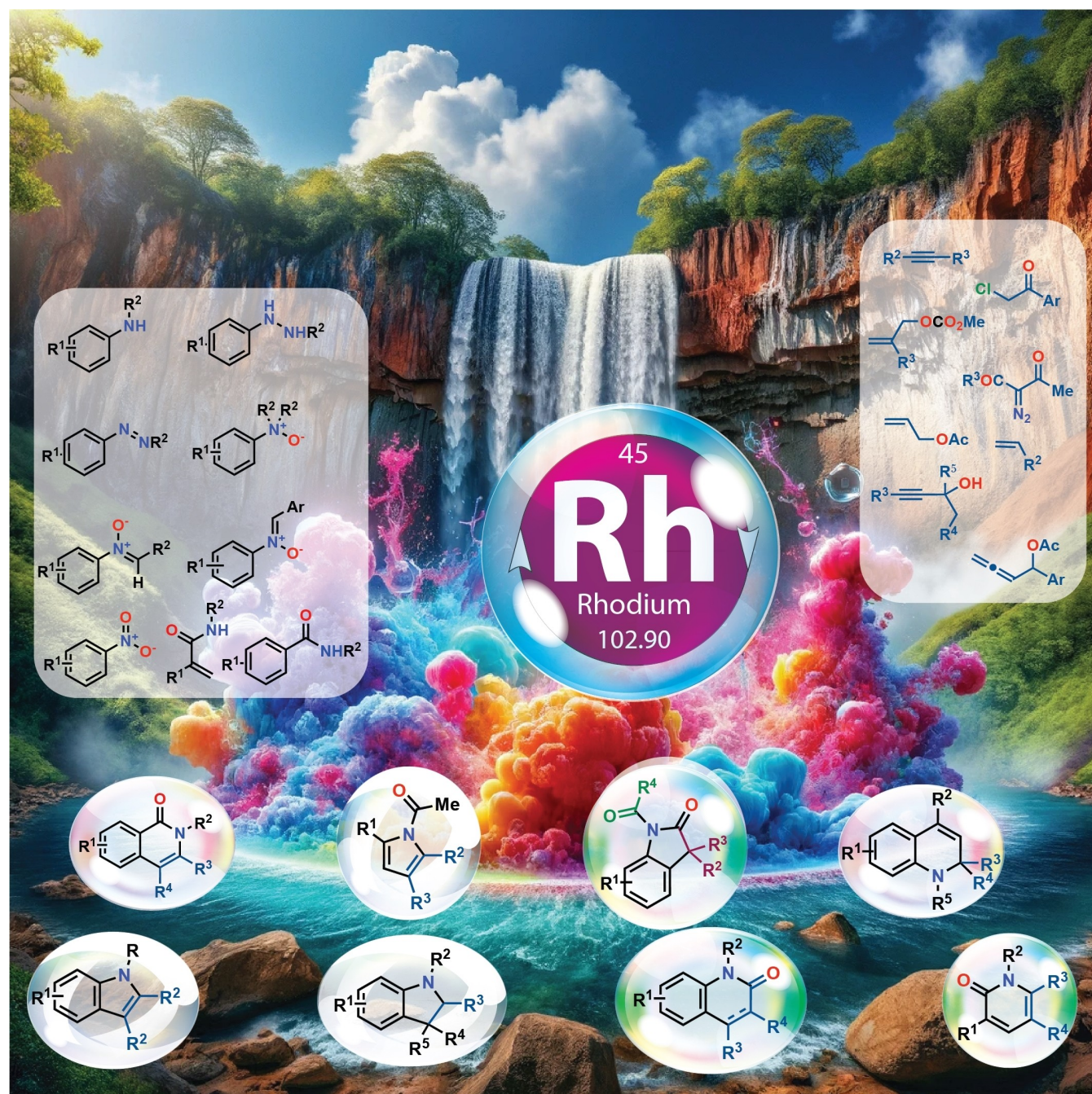
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Rhodium-Catalyzed C–H Bond Annulation for the Synthesis of 5- and 6-Membered *N*-Heterocyclic Building Blocks

Marie Peng,^[a] Henri Doucet,^[a] and Jean-François Soulé*^[b]



The sustainable preparation of *N*-heterocycles is one of the most active research areas owing to their predominance as synthetic building blocks with extensive applications in organic, pharmaceutical, and material chemistry fields. Among the various catalytic protocols, the C–H bond functionalization with the concomitant C–N bond formation, so-called C–H bond annulation, has become one of the most sustainable routes to access *N*-heterocycles because it starts from low-functionalized materials and generates a limited amount of waste, all respecting the concept of atom economy. Rhodium complexes often catalyze these reactions. This review focuses on the

synthesis of 5- and 6-membered ring *N*-containing heterocycles such as indoles, pyrroles, indolines, (iso)quinolinones, dihydroquinolines, and pyrrolidones from readily available starting materials, with an emphasis on the novel C–H bond cascade synthetic methodologies *via* C–N/C–C bond formation, as well as on the mechanisms of these reactions, especially the oxidation steps. We hope this review will help researchers looking to prepare *N*-heterocycles in a minimum of steps and those who want to develop new methodologies based on C–H bond activation/functionalizations.

1. Introduction

N-heterocycles are key structural units embedded in many active pharmaceutical ingredients (APIs), biologically exciting molecules, natural products, and functional materials.^[1] Therefore, developing novel synthetic routes of *N*-heterocycles, respecting some of the 12 principles of green chemistry, has gained increased attention in academia and industry. The development of novel catalytic transformations can unlock the preparation of unprecedented *N*-heterocycles with further potential applications in medicinal or material sciences. Over the past decades, many metal-catalyzed C–N bond formation methodologies, such as Buchwald-Hartwig cross-coupling and Ullmann reaction, have been widely applied to prepare *N*-heterocycles with high efficiencies.^[2] However, these approaches required pre-functionalized starting materials, limiting the exploration of *N*-heterocycle structures to target-oriented rather than diversity-oriented synthesis. To avoid the generation of wastes, intramolecular C–H bond amination has been applied to the synthesis of *N*-heterocycles,^[3] but once again, specific substrates must be designed.

Thanks to the deep investigation of C–H bond functionalizations,^[4] more and more complex transformations have flourished, notably, the C–H bond functionalization with the concomitant C–N bond formation, so-called C–H bond annulation, which furnishes diverse nitrogen-containing heterocycles in a single step.^[5] This rapid construction of diverse and functional nitrogen-containing heterocycles from simple building blocks entirely fits with the idea of suitable synthesis in terms of atom economy. In most cases, the *N*-atom present on the starting materials (e.g., anilines, amides, triazenes, imidamides, *N*-arylhydrazine, and others) serves to direct the C–H bond functionalization at the *ortho*-position and then, reacts

intramolecularly to create the C–N bond under oxidative conditions. Among the diverse metal catalysts, rhodium has been predominant in achieving these *ortho*-directed C–H bond annulations. However, the use of an external oxidant to regenerate the catalyst, mainly Cu(OAc)₂, could misrepresent the sustainability of the C–H bond annulation reaction. Alternatively, oxidizing directing groups can replace the external conditions, resulting in milder reaction conditions.^[6] Oxidizing directing groups are generally composed of N–O or N–N bonds, which can reoxidize the metal catalyst at the end of the catalytic cycles through an oxidative addition step of the N–X bond. During these last 15 years, these two strategies for Rh(III)-catalyzed C–H bond annulation have been applied to the construction of diverse heterocycles depending on the choice of the starting materials.

In this review, we would like to summarize the different *N*-heterocycles than can be prepared by this method, *asides (iso)quinolines, because their preparations have been widely covered by precedent reviews including other metals than rhodium.*^[7] The contents were categorized by the type of *N*-heterocycles: indoles, pyrroles, indolines, (iso)quinolinones, dihydroquinolines, and pyrrolidones. We will focus on 1) reaction design, including catalyst choice and substrate design, and 2) mechanistic insights of cascade C–H bond functionalizations. Finally, the challenges and future developments in this research field will be also discussed.

2. Preparation of Indoles and Related 5-Membered Ring Scaffolds

2.1. C–H Bond Functionalization under Oxidative Conditions

In 2008, Fagnou and co-workers reported the first synthesis of indoles starting from readily available *N*-acetyl anilines and alkynes as starting materials through Rh(III)-catalyzed C–H bond annulation reaction (Scheme 1A).^[8] Initially, the conditions employed [Cp*₂RhCl₂]₂ in conjunction with a stoichiometric amount of Cu(OAc)₂ as oxidant at 120 °C. Both electron-rich and -deficient acetanilides were efficiently coupled with internal alkynes. The reaction is fully regioselective with aryl-alkyl di-substituted alkynes, while mixtures of regioisomers were obtained using unsymmetrical alkynes with two different alkyl

[a] Dr. M. Peng, Dr. H. Doucet
Univ Rennes, CNRS, ISCR UMR 6226, F-35000 Rennes, France

[b] Prof. Dr. J.-F. Soulé
Chimie ParisTech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences, 75005 Paris, France
E-mail: jean-francois.soule@chimieparistech.psl.eu

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groups. This regioselectivity arises from the alkyne insertion event owing to the electronic factors. In 2010, Fagnou and co-workers upgraded the reaction conditions by using a catalytic amount of $\text{Cu}(\text{OAc})_2$ in the presence of atmospheric oxygen as the terminal oxidant at a lower temperature of 60°C (Scheme 1B).^[9] The substrate scope was enlarged to 35 examples demonstrating a high functional group tolerance, including sensitive ones such as benzyl, silyl, (protected)c alcohols, cyclopropyl, and ester groups. This Rh(III)-catalyzed formation of indole scaffold was also applied to the preparation of Paullone, a complex synthetic product, known for its utility as a kinase inhibitor in cancer research. (Scheme 1C).^[9] The authors conducted a deep mechanistic study using kinetics and deuterium-labeling experiments, enabling them to propose the catalytic cycle depicted in Scheme 1D. Cationic Rh complex I is formed (by halogen abstraction using silver salts) in the presence of 1 equivalent of acetate. [A deactivation pathway was revealed in the presence of alkyne to form nonproductive coordination complexes.] After the coordination of acetanilides through the Lewis basic amide oxygen, C–H bond cleavage occurs to form rhodacycle II in an irreversible and rate-determining step. Alkyne may then coordinate II, followed by carbo-rhodation to yield III. C–N bond reductive elimination extrudes the desired indole product along with $\text{Cp}^*\text{Rh}(\text{I})$. The reduced catalyst is then oxidized back to the active species via catalytic copper(II) acetate [which is then reoxidized by the combination of molecular oxygen and acetic acid (generated in the reaction) in the case of conditions 2.]

In 2010, Li and co-workers reported a similar formation of indoles, but they used pyridine as directing group instead of amide (Scheme 2, top).^[10] From *N*-aryl-2-aminopyridines and symmetrical alkynes, the corresponding *N*-pyridinyl-substituted

indoles were obtained in good yields using $[\text{Cp}^*\text{RhCl}_2]_2$ in the presence of a stoichiometric amount of $\text{Cu}(\text{OAc})_2$ as oxidant at 120°C in DMF. The reaction proceeded through a similar catalytic cycle to the one proposed by Fagnou (Scheme 1D).^[8] The reaction exhibited poor functional group tolerance as only substrates bearing Me, MeO, F, and Cl substituents were employed. Later, the same group showed that this indole synthesis is also applicable to *trans*-crotylamide, albeit using a cationic Cp^*Rh catalyst (Scheme 2, bottom).^[11]

In 2011, after the unfortunate death of Keith Fagnou, his group reported the preparation of unsymmetrical 2,3-substituted indoles through rhodium(III)-catalyzed oxidative C–H bond annulation of *N*-aryleurea with enynes (Scheme 3).^[12] Similarly to aryl-alkyl di-substituted alkynes,^[8–9] the alkyne insertion reaction was highly regioselective, leading to the production of C2-vinyl-substituted indoles. Nevertheless, acetamide (–NHAc as directing group) was not a suitable partner for this transformation, and *N*-aryleurea (–NHCONMe₂ as directing group) had to be employed. Several functional groups were compatible with the optimized conditions on the aniline unit, such as trifluoromethyl, methoxy, chloro, and methyl. α,β -unsaturated esters could also be employed, including those containing functional groups such as *tert*-butylcarbamate-protected amines and triphenylmethyl ethers. Notably, olefin isomerization was observed with (*Z*)-alkenes, and 2,2-disubstituted alkenes were also tolerated. An allylic alcohol, protected as the *tert*-butyldimethylsilyl ether, was also installed alongside another indolyl ring. The authors demonstrated that these C2-vinyl-substituted indoles could serve as building blocks for the preparation of unsymmetrical 2,3-aliphatic-substituted indoles through hydrogenation using Pd/C as catalyst. Notably, such compounds are not directly accessible by this rhodium syn-



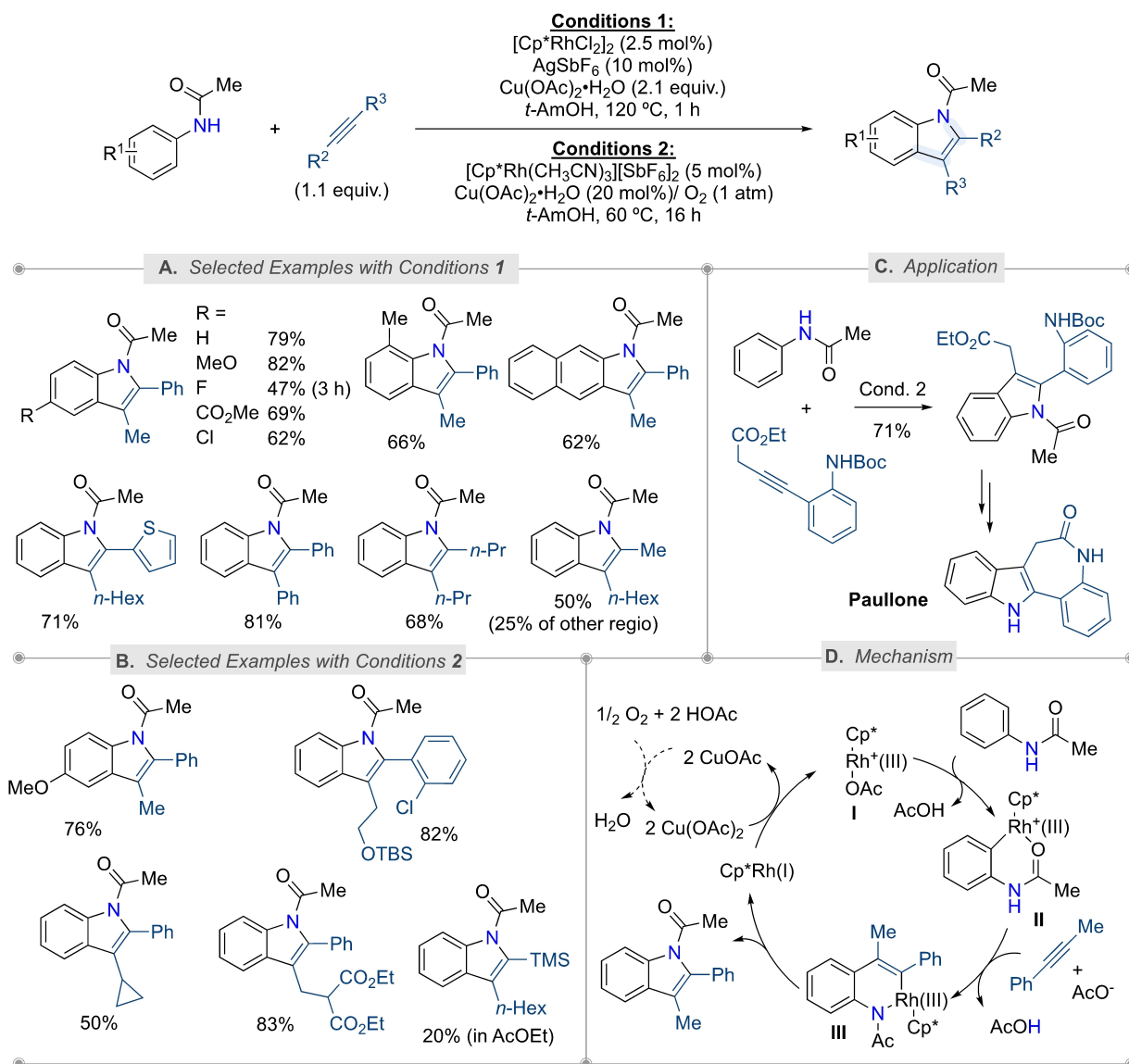
Marie Peng graduated from University of Rennes 1 after obtaining a BSc in chemistry, followed by a MSc in Molecular Chemistry. During her studies, she did a short stay in Chao-Jun Li's group at McGill University (Canada) working on umpolung carbanions for conjugate additions in hydrazone chemistry. Then, she joined Prof. Jean-François Soulé and Dr. Henri Doucet's team for her MSc II internship and Ph.D at the Institute of Chemical Science in Rennes in 2019. During this time, her research mainly focused on the development of novel rhodium-catalyzed C–H bond functionalization strategies.



Henri Doucet received his PhD in chemistry working with Prof. P. H. Dixneuf and Dr. C. Bruneau at Rennes 1 University (France) in 1994. After post-doctoral appointments at Oxford university (UK) with Prof. J. M. Brown; and Nagoya university, (Japan) with Prof. R. Noyori, he moved to the University of Marseille (France) as CNRS researcher in the group of Prof. M. Santelli. In 2006 he moved to Rennes 1 University. His research interests include organic synthesis by metal-catalyzed processes and green chemistry.



Jean-François Soulé obtained his PhD at the Institute of Chemistry of Natural Substances (Prof. Beau), France, focusing on boron-multi-component reactions. Following a postdoctoral stay at the University of Tokyo focusing on nanocatalyst heterogenization with Professor Kobayashi (2010–2013), he joined the CNRS at the Institut des Sciences Chimiques de Rennes, collaborating with Dr. Henri Doucet. He achieved his HDR in 2017, received the Thieme Chemistry Journal Award (2020), and the Jean-Pierre Sauvage Prize. In 2022, he became a full professor at Chimie ParisTech, PSL University. He conducts his research at the i-CleHS institute focusing on organometallic catalysis for C–H bond functionalizations.



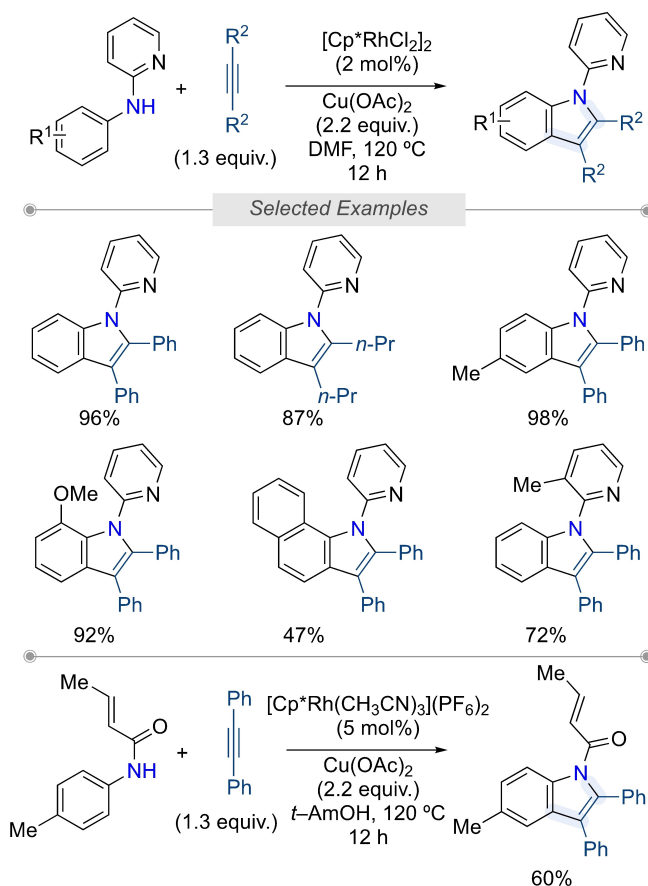
Scheme 1. Indole synthesis via Rh(III)-catalyzed oxidative coupling of acetanilides and internal alkynes.

thesis with alkyl-alkyl di-substituted alkynes due to regioselectivity issues.

With the emergence of Cp*Rh-catalyzed C–H bond functionalizations, several sterically or electronically tuned cyclopentadienyl ligands have been investigated in rhodium catalysis to improve selectivity and/or reactivity.^[13] In 2014, Tanaka and co-workers employed an electron-deficient Cp^RRh catalyst, namely [Cp^RRhCl₂]₂,^[14] to succeed in Fagnou's indole synthesis at room temperature (Scheme 4).^[15] Indeed, the electron-deficient dicationic Rh(III) complex, derived from [Cp^RRhCl₂]₂, demonstrates enhanced reactivity compared to Cp*Rh²⁺. This is because its electron-deficient nature makes it particularly effective at facilitating the C–H bond activation of acetamides through an electrophilic metalation mechanism, thereby improving the efficiency of the process. For instance, the reactions of acetanilide with diphenylacetylene proceeded at room temperature under air to give the corresponding indoles in

quantitative yield, while using Cp*Rh²⁺, a lower yield of 28% was obtained. The reaction is quite general, as diversely substituted indoles have been prepared by this method, including those containing sensitive groups such as alkyl halides. The reaction was not limited to acetamide as a directing group, as carbamate (NHBOc) and benzamide (COPh) have also been successfully employed. The authors mentioned that this electron-deficient rhodium catalyst displays a preference for annulation across electron-rich substrates over electron-deficient substrates.

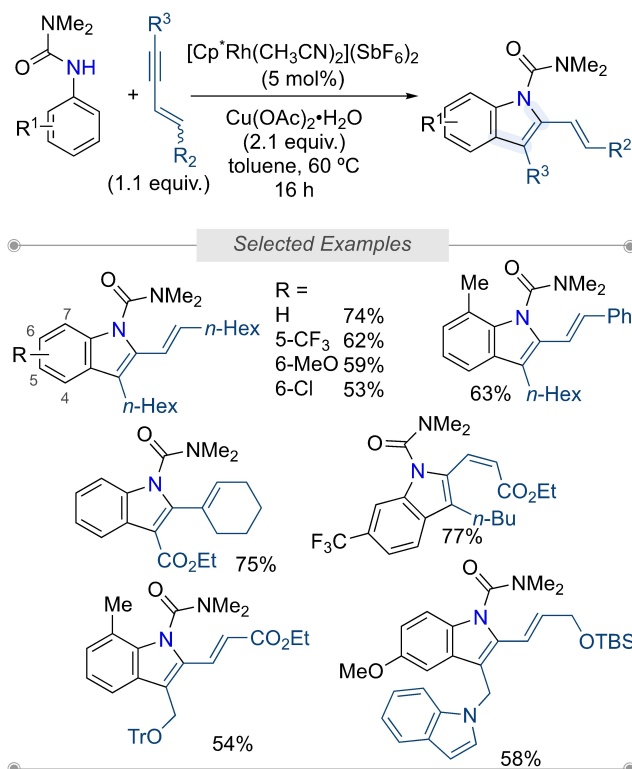
In 2014, Huang and co-workers also reinvestigated the Fagnou reaction starting from anilines in the presence of acetic anhydride (Scheme 5).^[16] The reaction goes through the *in situ* anilides formation from anilines and acetic anhydride, then after C–H bond annulation, the addition of NaOH allows the “one-pot sequential” diacylation to afford the NH-indole derivatives. The reactivity was affected by the nature of the cationic



Scheme 2. Rh(III)-catalyzed oxidative C–H bond annulation of *N*-aryl-2-aminopyridines with alkynes.

counterion, and the best result was obtained with $\text{Cp}^*\text{Rh}(\text{H}_2\text{O})_3(\text{OTf})_2$ as the catalyst precursor. It should also be mentioned that these conditions did not require additional copper, as O_2 acts as the sole oxidant enabling to regenerate $\text{Cp}^*\text{Rh(III)}$ from $\text{Cp}^*\text{Rh(I)}$ at the end of the catalytic cycle.

In 2013, Huang reported a novel synthetic approach for unprotected indoles through a triazene-directed C–H annulation using alkynes (Scheme 6).^[17] The optimized reaction conditions were found using 5 mol% $[\text{RhCp}^*\text{Cl}_2]_2$ associated with AgSbF_6 (20 mol%) in the presence of 2 equivalents of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as an external oxidant in methanol at 90 °C. Diversely substituted triazenyl arenes (F, Cl, Br, I, NO_2 , MeO, Me) were efficiently coupled with alkynes (diaryl or dialkyl). Moreover, excellent regioselectivity was achieved when non-symmetrical alkynes were employed. The authors demonstrated the potential of this reaction by preparing specific indoles for materials applications or drug molecules. The author proposed a catalytic cycle involving 1,2-rhodium shift ring contraction (path a) or an N=N insertion mechanism (path b) as key steps (Scheme 6B). After the classical C–H bond metalation directed by the middle nitrogen atom of the triazene moiety (complex I) and insertion of the alkynes, the resulting 7-membered metalacycle II is obtained. In path a, II rearranges into a more stable six-membered Rh complex III, then reductive elimination releases the indole product and Rh(I), which is reoxidized by

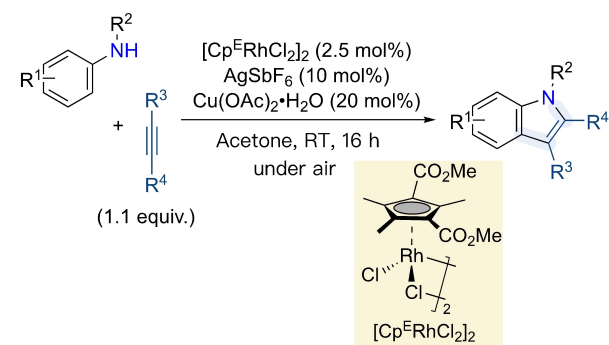


Scheme 3. Indole synthesis via Rh(III)-catalyzed oxidative coupling of *N*-aryleurea and enynes.

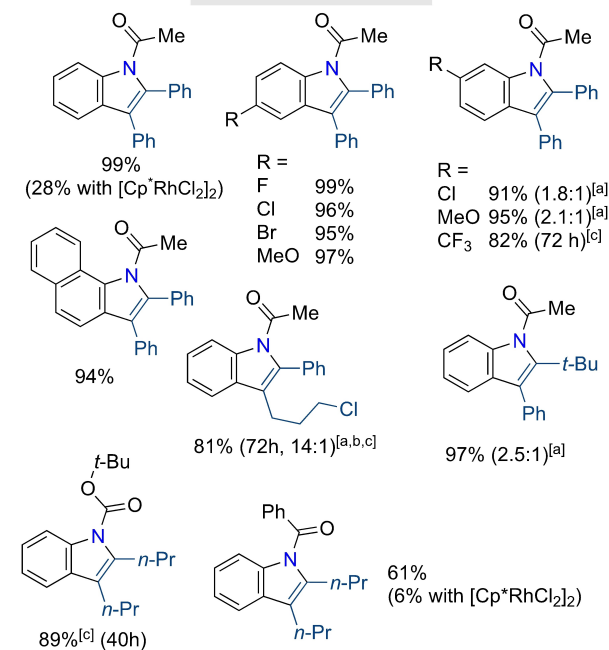
$\text{Cu}(\text{OAc})_2$. In path b, N=N insertion to Rh–C, followed by subsequent reduction and hydrolysis, would also generate the desired heterocycle.

In 2014, Nicholls and co-workers extended Fagnou's indole synthesis to *N*-aryleurea, in which the NHCONR_2 group acts as the directing group (Scheme 7).^[18] The conditions were similar to the first conditions reported by Fagnou [stoichiometric amount of $\text{Cu}(\text{OAc})_2$], albeit 1,2-dichloroethane was used as the solvent. Various *ortho*-, *para*-, and *meta*-substituted *N*-aryleureas with either electron donating (e.g., alkyl, MeO) or electron-withdrawing functional groups (e.g., I, Br, Cl, F, or CO_2Me) were efficiently coupled with diphenylacetylene. Dialkyl-substituted acetylenes displayed better reactivity than diaryl-substituted acetylenes, while aryl-alkyl-substituted acetylenes regioselectively reacted.

The same year, Liu and co-workers succeeded in the C–H bond annulation of *N*-aryleureas to form indolyl scaffolds (Scheme 8A).^[19] The reaction was catalyzed by $[\text{Cp}^*\text{RhCl}_2]_2$ using unprecedented 1,3-dinitrobenzene as a terminal oxidant. Various substituted (e.g., alkyl, methoxy, halo, cyano) *N*-aryleureas were efficiently coupled with internal alkynes. In most cases, substrates holding an electron-withdrawing group gave lower yields. Other substituents at the R^2 position on the hydrazine, such as benzyl or linear alkyl chlorides, were also tolerated. Based on control experiments to clarify the role of 1,3-dinitrobenzene as a terminal oxidant, the authors have proposed the catalytic cycle depicted in Scheme 8B. Firstly, $[\text{Cp}^*\text{RhCl}_2]_2$ reacts with NaOAc to generate the



Selected Examples



[a] Ratio of regioisomers. The major regioisomer is shown.

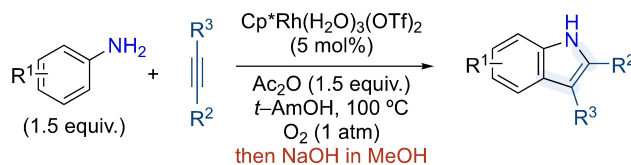
[b] 3 equiv. of acetanilide, 1 equiv. of alkyne.

[c] [Cp*RhCl₂]₂ (5 mol%), AgSbF₆ (20 mol%), Cu(OAc)₂·H₂O (40 mol%).

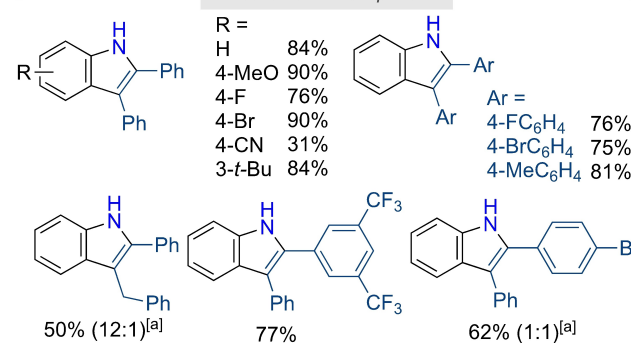
Scheme 4. Room-temperature oxidative annulation of anilides with internal alkynes Using [Cp*RhCl₂]₂ catalyst.

active catalyst [Cp*Rh(OAc)₂], which undergoes CMD process with *N*-arylaceto-hydrazide to form the rhodacycle II. Then, alkyne coordination followed by insertion affords the seven-membered rhodacycle III, which rearranges into a more stable six-membered rhodium complex IV. Then, reductive elimination releases the annulation product and [Cp*Rh(I)]. Finally, external oxidant 1,3-dinitrobenzene reoxidizes [Cp*Rh(I)] in the presence of acetic acid to regenerate the active catalyst [Cp*Rh(OAc)₂].

As reported by Saá and co-workers, indolyl scaffold could also be generated through Cp*Rh(III)-catalyzed oxidative couplings of anilides with allyl carbonates using a slight excess of AgSbF₆ salt and Cu(OAc)₂ as oxidant (Scheme 9A).^[20] This approach is equivalent to C–H bond annulation of anilides with terminal alkynes, as it gives rise to indoles with substituents at position 2 but not position 3. 18 examples were reported by introducing methyl, methoxy, fluoro, or chloro substituents at *para*-, *meta*-, or *ortho*-positions of the anilides. The reaction is



Selected Examples



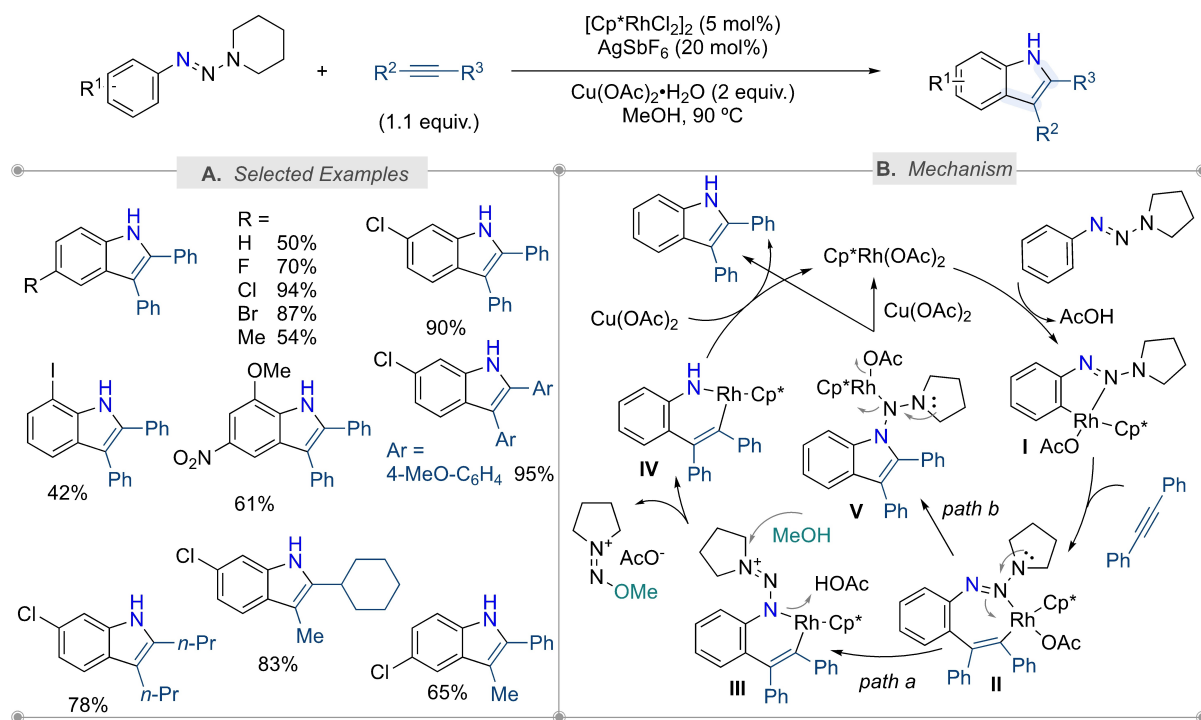
[a] ratio of regioisomers

Scheme 5. Rh(III)-catalyzed oxidative C–H bond annulation of anilines with alkynes.

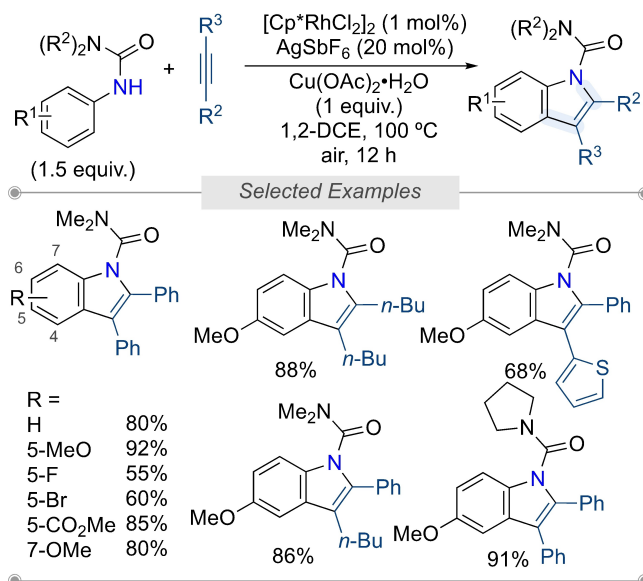
limited to the use of AcNH- as directing group. Moreover, the yields are inferior when allyl partners are substituted, such as 1-methyl-2-propenylmethyl carbonate or *E*-2-butenyl acetate. The authors proposed a catalytic cycle based on deuterium labeling and KIE experiments (Scheme 9B). After the initial formation of the previously proposed rhodacycle II through *ortho*-C–H bond cleavage of anilides via a CMD process, migratory insertion of the allyl double bond into the Rh–C bond gives a seven-membered rhodacycle IIIa. β -Oxygen elimination delivers the new olefin-coordinated Rh(III) species IV through an oxidative Mizoroki-Heck/ β -elimination pathway. Alternatively, the same species III could be formed by coordination of the allyl-bearing carbonate oxygen to Rh(III) species IIIb which facilitates an intramolecular Sn2' process. *Syn*-amidorrhodation in IV, followed by β -hydrogen elimination and isomerization, then releases the observed product. Finally, the reduced [Cp*Rh(I)] catalyst is oxidized by copper(II) acetate.

A more atom-economical protocol for the synthesis of C2-substituted indoles was reported by Kim and co-workers using allyl acetate instead of carbonates (Scheme 10).^[21] However, the reaction is limited to access to 2-methylindoles, as only allyl acetate has been employed. The reaction conditions are similar to those previously reported, namely 2.5 mol% [Cp*RhCl₂]₂ associated with 10 mol% AgSb₆ in the presence of a stoichiometric amount of Cu(OAc)₂ as oxidant.

In 2016, Li and co-workers discovered the synthesis of *N*-unprotected indoles through Rh(III)-catalyzed C–H bond annulation of imidamides with α -diazo β -ketoesters (Scheme 11A).^[22] The reaction occurs in the presence of [Cp*RhCl₂]₂ catalyst associated with CsOAc in the presence of AcOH in DCE at 80 °C. An amide is co-generated from C–N cleavage of the imidamide and C–C(acyl) cleavage of the diazo compounds. Diversely substituted *N*-unprotected indoles were isolated in good to high yields by varying the substituent on imidamides. However,



Scheme 6. Synthesis of indoles through triazene-directed C–H bond annulation.

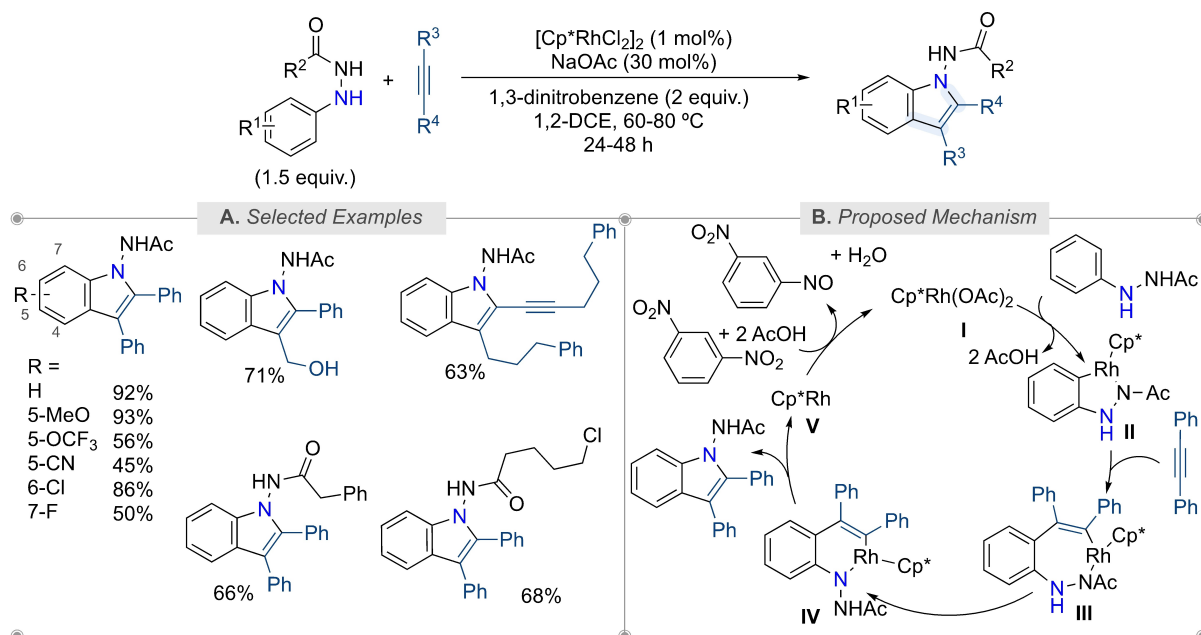
Scheme 7. Rh(III)-catalyzed oxidative C–H bond annulation of *N*-aryleurea with alkynes.

the reaction is limited to the use of α -diazo β -ketoesters entailing that *N*-unprotected indoles hold an ester substituent (or acetyl) at the C3 position. The authors proposed the mechanism depicted in Scheme 11B. After the formation of active catalyst $[\text{RhCp}^*(\text{OAc})_2]$, C–H bond cleavage of imidamides occurred through an *ortho*-coordination assisted CMD mechanism (*this rhodacyclic intermediate I has been isolated with Cl ligand instead of AcO*). Then, coordination of the diazo substrate and nitrogen elimination gives rhodium carbene species II. The

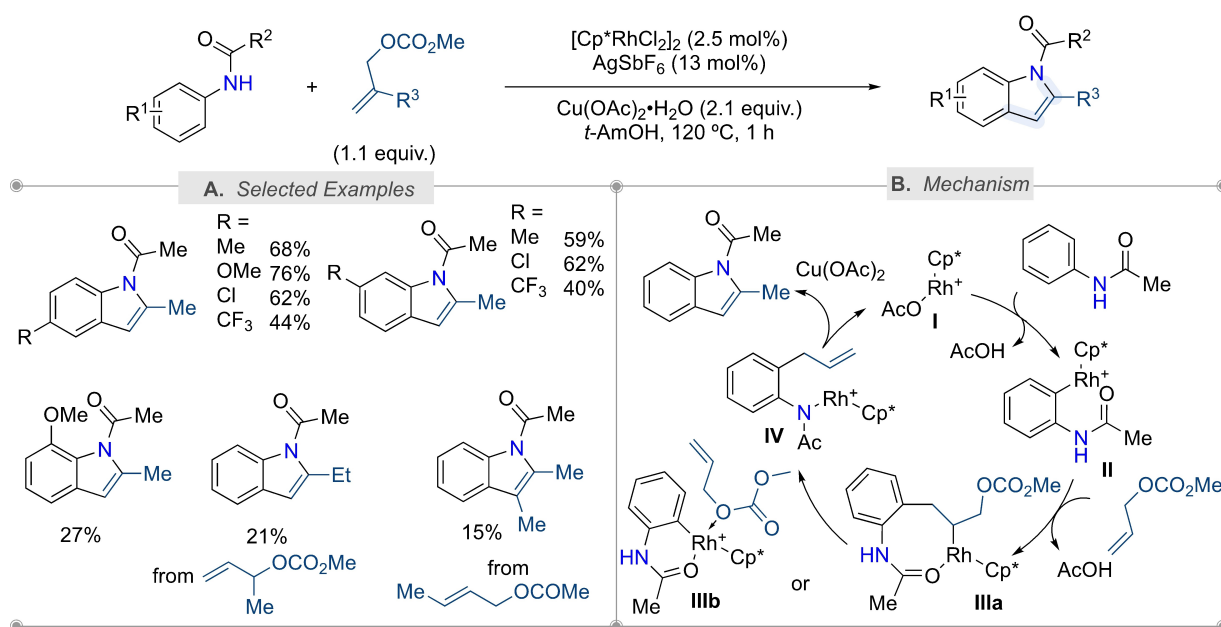
Rh–Ar bond undergoes migratory insertion into the carbene unit to give intermediate III. The Rh–C(alkyl) bond then undergoes migratory insertion into the C–N bond to afford amide species IV. Acidic hydrolysis released V and the active Rh(III) catalyst. Finally, unprotected indole is formed from V by the elimination of amide.

Zhou, Liu, and co-workers later reported a similar protocol using α -chloroketones instead of α -diazo β -ketoesters (Scheme 12A).^[23] The optimum catalytic system was found using $[\text{Cp}^*\text{RhCl}_2]_2$ (5 mol%), AgOAc (50 mol%), and NaHCO_3 (200 mol%) in MeOH at 90°C for 24 h. *N*-Phenylamidines bearing various electron-donating, electron-withdrawing, or halogen substituents reacted with diversely mono- and di-substituted α -chloro ketones to give the corresponding 2-substituted-3-acylindoles in good to high yields. The reactivity trend shows better yields with electron-donating groups on the benzamidine ring. Moreover, C-alkyl imidamides were also successfully employed. The authors proposed the following catalytic cycle (Scheme 12B). The reaction of *N*-phenylamidine with $[\text{Cp}^*\text{Rh}(\text{OAc})_2]$ through a CMD mechanism affords the cyclometalated intermediate I. After coordination of α -chloro ketone by the oxygen atom to the Rh center, nucleophilic substitution affords the seven-membered rhodacyclic intermediate II, followed by Rh–C(alkyl) migratory insertion into the C=N bond to afford III. Finally, the desired indole is produced by aromatization with the release of NH_3 .

In 2017, Xi and co-workers accomplished the C–H bond annulation of azobenzenes with vinyl ketones to deliver 2-acyl-NH-indole compounds using Rh(III) catalysis (Scheme 13A).^[24] The optimized conditions, namely 5 mol% $[\text{Cp}^*\text{RhCl}_2]_2$ in the presence of 2 equivalents of $\text{Cu}(\text{OAc})_2$, tolerated synthetically



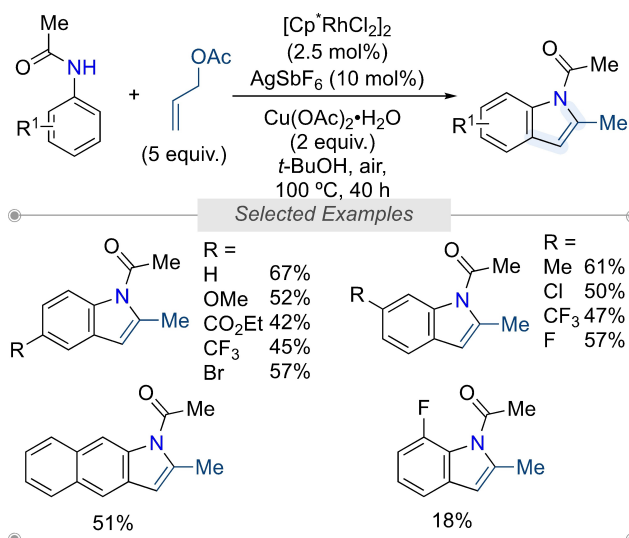
Scheme 8. Rh(III)-catalyzed Oxidative C–H bond annulation of *N*-arylacetoimidates with alkynes using a nitrobenzene oxidant.



Scheme 9. Indoles synthesis via Rh(III)-catalyzed tandem C–H allylation – oxidative cyclization of anilides.

useful functional groups, such as Me, OMe, F, CF₃, Cl, and Br, on azobenzene to give the expected indole products in moderate to good yields. Various vinyl aryl ketones and *N,N*-dimethyl acrylamides were also efficiently coupled. Interestingly, the reaction is regioselective with unsymmetrically substituted azobenzenes; the reaction occurred on the electron-poorer aryl ring. The authors proposed the mechanism shown in Scheme 13B. First, the C–H bond cleavage of azobenzene by Rh(III) species gives five-membered rhodacycle species I, followed by alkene coordination and insertion to afford the seven-membered

rhodacycle II. In the presence of Cu(OAc)₂, a rearrangement involving nucleophilic addition toward the N–N bond delivers IV, which further undergoes N–N bond cleavage and aromatization to give NH-free indole products.



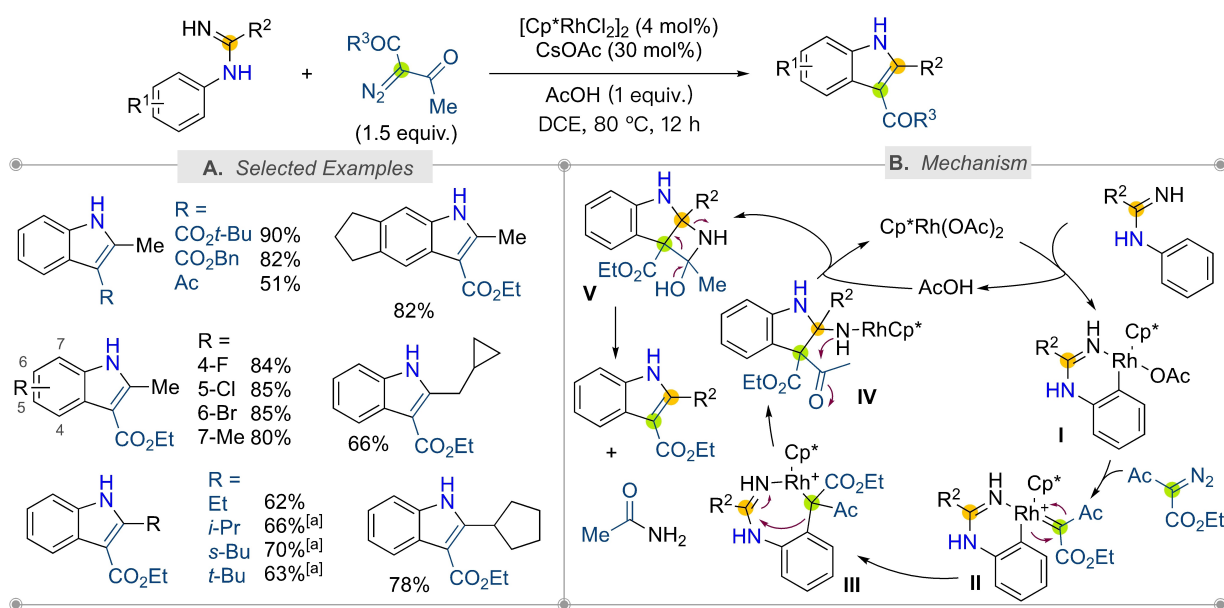
Scheme 10. Synthesis of 2-methylindoles from anilides and allyl acetate using Rh catalysis.

2.2. C–H Bond Functionalization Using Internal N–O Bond as Oxidant

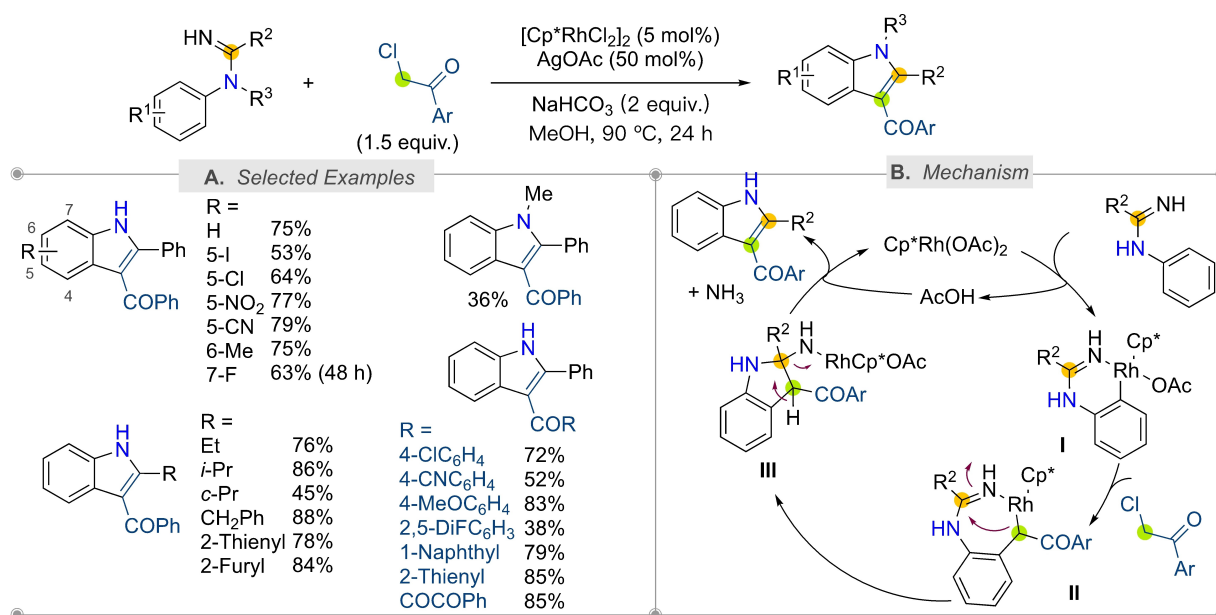
Despite the outstanding advances in Rh(III)-catalyzed C–H bond annulation to prepare indolyl scaffolds, the use of a stoichiometric amount of oxidants, often $\text{Cu}(\text{OAc})_2$, remains a significant weakness of these synthetic methodologies in terms of green chemistry. Recent developments in redox-neutral strategy employing an oxidizing directing group have made these protocols more eco-friendly.^[6] In 2015, Wang, Wan, and co-workers reported the first example of redox-neutral Rh(III)-

catalyzed C–H bond annulation of nitrones with alkynes to prepare indoles (Scheme 14A).^[25] The nitron acts as a directing group and oxidizing agent, allowing the regeneration of Rh(III)-catalysts through the N–O bond. One of the two aryl substituents on the indole ring arises from the Caryl ring of the nitron and the other from the alkyne moiety through C–C bond cleavage, thus, providing the indole products with exclusive regioselectivity. Optimized conditions still required a stoichiometric amount of copper salts. The scope of the reaction is quite general, tolerating ether, alkyl, aryl, ester, nitro, fluoro, chloro, or trifluoromethyl substituents at diverse positions. After a mechanistic study, the authors proposed the complex mechanism depicted in Scheme 14b. In a first step, nitron-assisted C–H bond affords five-membered rhodacycle intermediate I, followed by alkyne insertion to generate the seven-membered rhodacycle intermediate IIa (path a), which undergoes reductive elimination to provide cationic heterocyclic intermediate IIIa together with Rh(I) complex. Then, oxygen-atom transfer followed by oxidative addition occurs to generate intermediate IV. This intermediate might be alternatively generated from I through alkyne insertion at the N-oxide side of the Rh center (intermediate IIb). Intramolecular electrophilic attack of the imino moiety of IV furnishes intermediate V. Then transmetalation with Cu coupled with a $\beta\text{-H}$ elimination gives VI, which generates the desired indole by eliminating one molecule of PhCHO. It should be noted that Cu does not serve as an oxidant in this reaction, as the N–O bond plays this role.

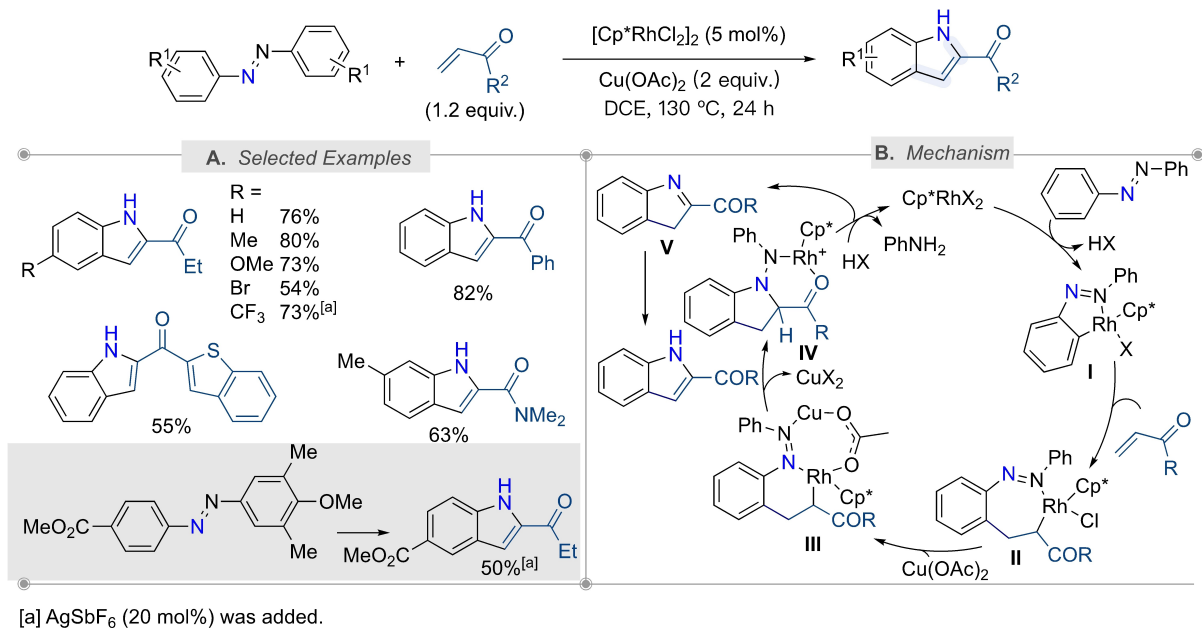
Interestingly, when sterically hindered nitrones were employed, the reaction also afforded 2,3-di-substituted indoles without C–C bond cleavage but through a different pathway, as shown by Liu, Lu, and co-workers (Scheme 15B).^[26] The conditions are slightly different, employing PivOH instead of $\text{Cu}(\text{OAc})_2$ and a well-defined cationic Rh(III) complex. This



Scheme 11. Rh(III)-catalyzed C–H, C–C, and C–N bond cleavages for the synthesis of N-unprotected indoles from imidamides and diazo ketoesters.



Scheme 12. Synthesis of 3-acylindoles through Rh(III)-catalyzed annulation of *N*-phenylamidines with α -chloro ketones.

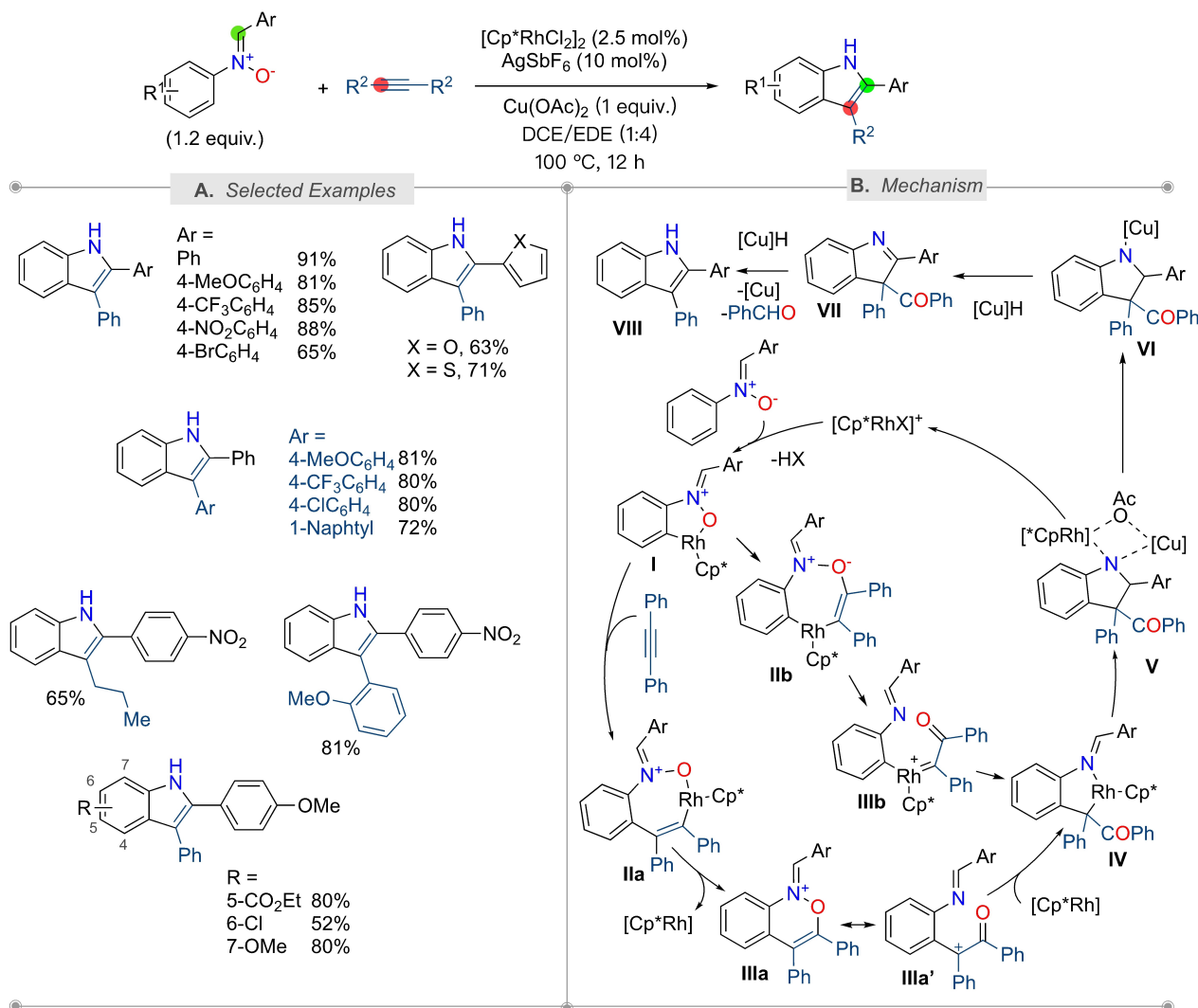


Scheme 13. 2-Acyl-NH-indole synthesis from azobenzenes and vinyl ketones using Rh(III)-catalysis.

change may induce a different pathway, especially for the final step, which is now hydrolysis of IV to deliver the enolate intermediate V, which is in equilibrium with the keto intermediate VI. Then, the second hydrolysis occurred with the liberation of mesitylaldehyde, followed by cyclization to afford the desired indole products. The scope of the reaction was similar to previously reported conditions. A mixture of regioisomers was obtained with unsymmetrical alkynes unless aryl-alkyl di-substituted alkynes were employed.

Nitrones can also be annulated with diazo compounds to prepare indolyl scaffolds. Two conditions were published at

almost the same time.^[27] Although the same conditions were employed, namely, [Cp*RhCl₂]₂ (5 mol%) associated with AgSbF₆ (16–20 mol%) in the presence of Cu(OAc)₂, two different products were obtained. In the first case, the reaction run in 1,4-dioxane at 100 °C gave *N*-hydroxyindole (Scheme 16, Conditions A),^[27a] while in 1,2-dichloroethane (DEC) at 120 °C, the reduced indoles were obtained (Scheme 16, Conditions B).^[27b] The scope of both reactions is relatively identical, tolerating electron-donating or electron-withdrawing groups. Both mechanisms start with the cyclometalation of nitron to generate rhodacycle I through C–H bond activation. Then, α -acyldiazo-



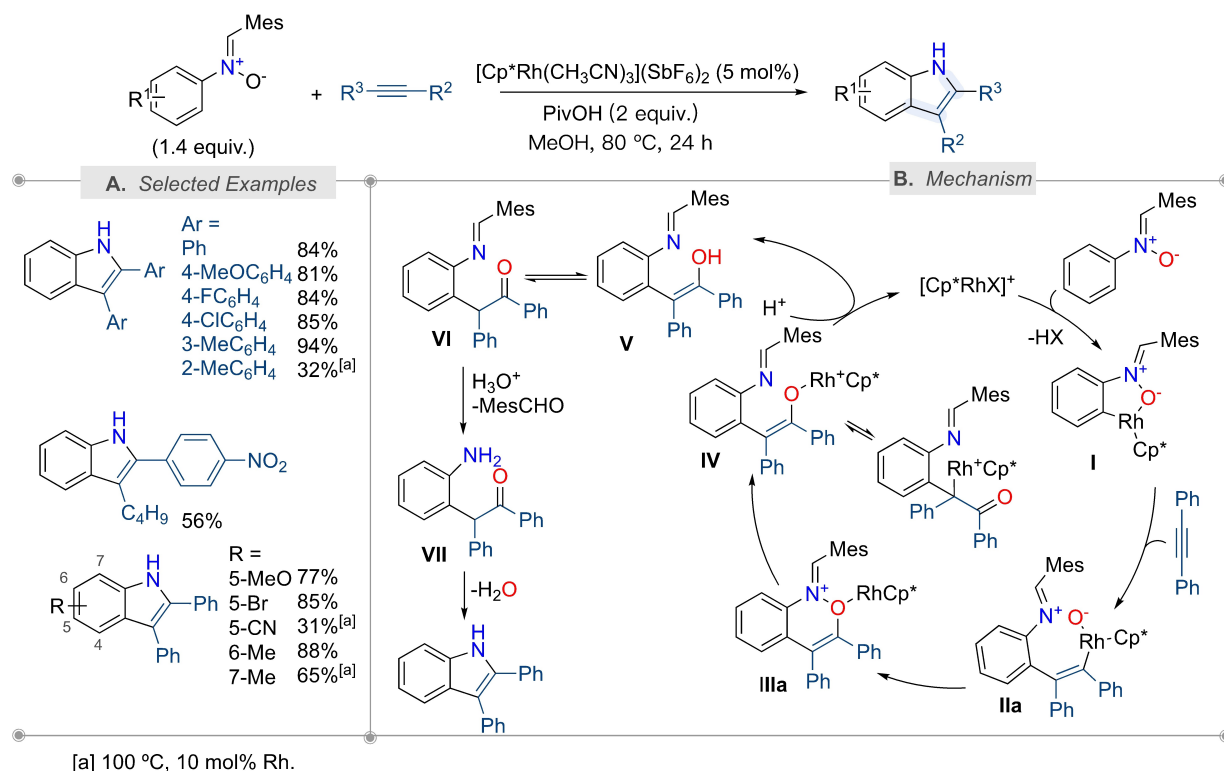
Scheme 14. Rh(III)-catalyzed C–H bond annulation of nitrones with alkynes.

cetate reacts with I to form a rhodium(III) carbene intermediate II. Migratory insertion of the Rh–C bond into the activated carbene generates the six-membered rhodacyclic intermediate III, in which an electrophilic attack of the imino moiety occurs to form the 5-membered ring heterocycle IV. Then transmetalation of the Rh catalyst with the copper salt and subsequent β -hydride elimination releases intermediate VIIa or b. At last, with the elimination of one acetic acid unit, the desired products are obtained. The mechanism of final deoxygenation remains unclear, and the role of DCE as solvent and hydride provider^[28] should be further explored in detail.

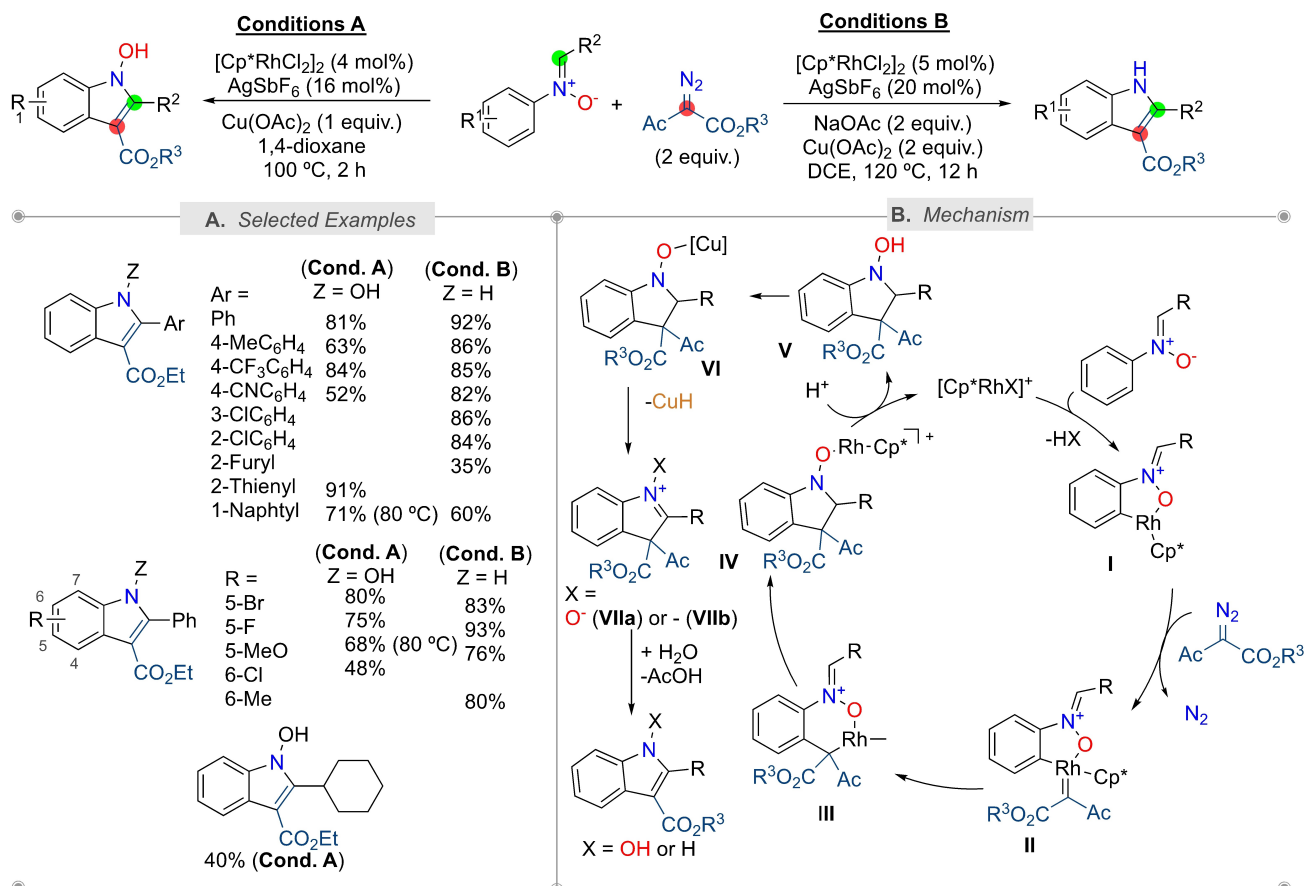
In 2016, Wang and co-workers reported an Rh(III)-catalyzed redox-free C–H bond annulation of aniline *N*-oxides with internal alkynes (Scheme 17).^[29] The reaction conditions are standard for C–H bond activation catalyzed by Cp*Rh(III) catalyst, albeit no additional oxidant is required. Indeed, the N–O bond plays the role of directing group for the C–H bond cleavage and also of oxidant through an O-atom transfer. Excellent functional group tolerance was observed. After the classical formation of five-membered cyclometalated species I

via *ortho* C–H activation of aniline *N*-oxides, alkyne insertion into the Rh–C bond generates seven-membered rhodacyclic intermediate II (Path A). Then, reductive elimination of the C–O bond of II gives intermediates III or IV (tautomerization from III through OAT) with the releases of Rh(I) catalyst. Then, oxidative addition affords enolate intermediates V or VI, and such intermediates could react with aniline *N*-oxides to release VII and close the catalytic cycle. Finally, in the presence of silver(I), the C–N bond cleavage followed by intramolecular nucleophilic cyclization gives the final indole product. However, a catalytic cycle based on Rh(III)/Rh(V) was also proposed, in which the alkyne insertion into the Rh–O bond leads to intermediates VIII, IX, and V (Path B). At the same time, You and co-workers reported the same Rh(III)-catalyzed redox-free C–H bond annulation of aniline *N*-oxides with internal alkynes, albeit they employed a catalytic amount of Ag(I) salts.^[30]

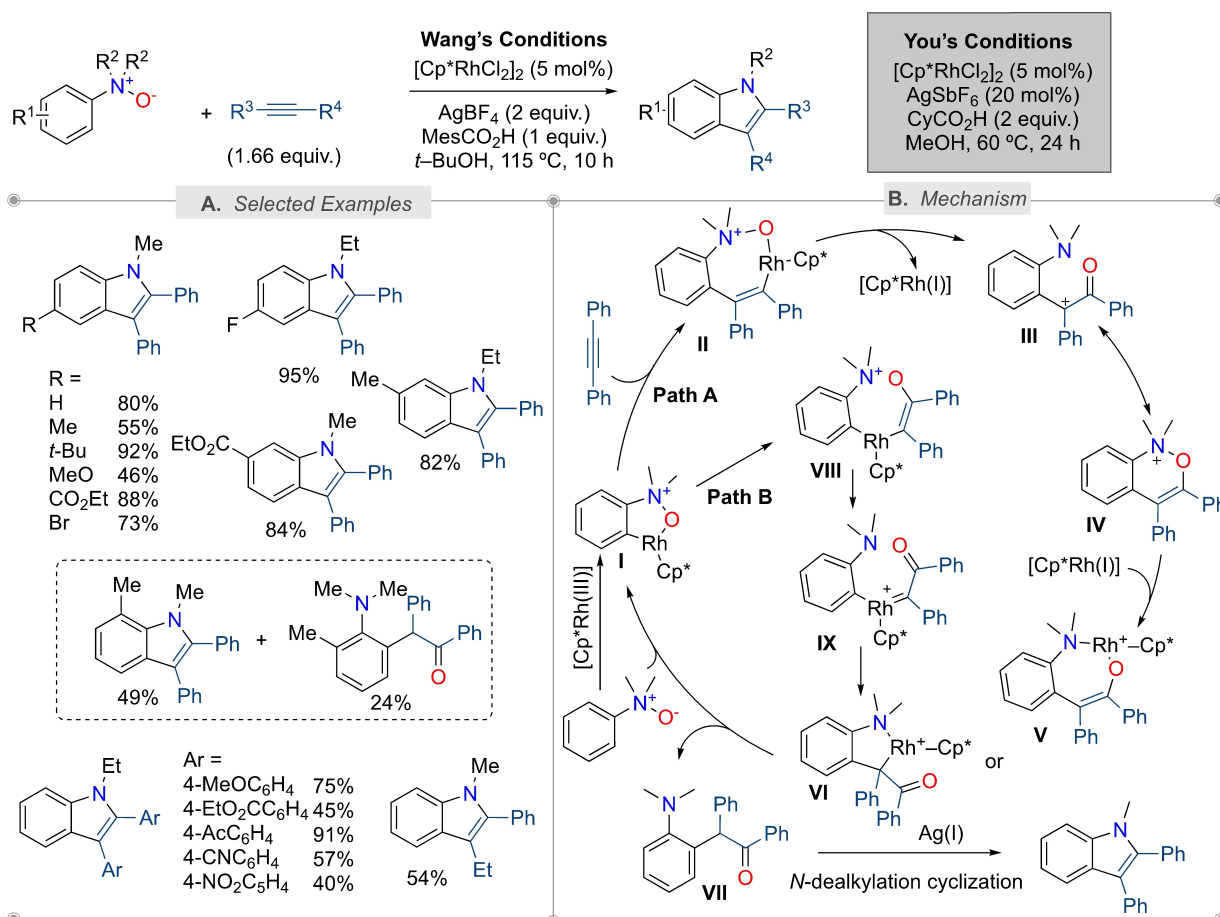
In 2021, Anbarasan and co-workers developed the Rh(III)-catalyzed redox-free annulation of *N*-acetoxyacetanilides with alkynes to synthesize substituted indole derivatives (Scheme 18).^[31] The reaction conditions are straightforward as



Scheme 15. Rh(III)-catalyzed C–H annulation of aryl nitrones with alkynes for the synthesis of indole derivatives.



Scheme 16. Rh(III)-Catalyzed C–H annulation of aryl nitrones with diazo compounds for the synthesis of indole derivatives.



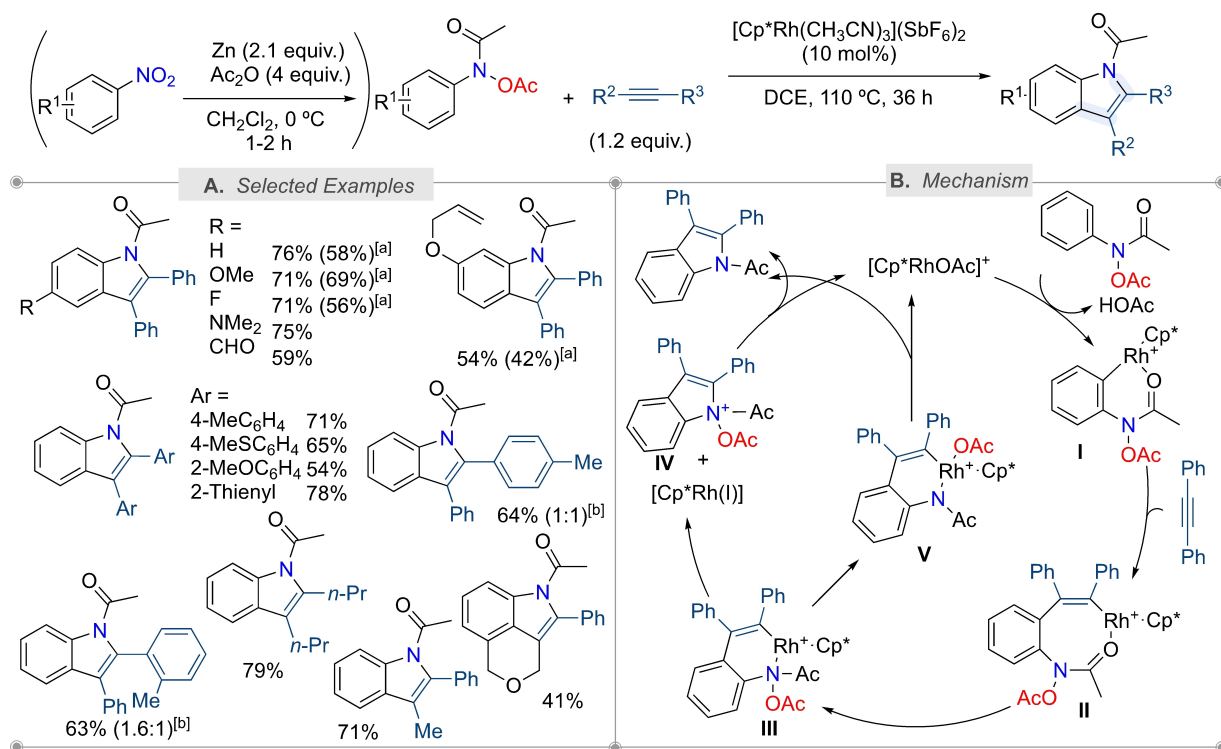
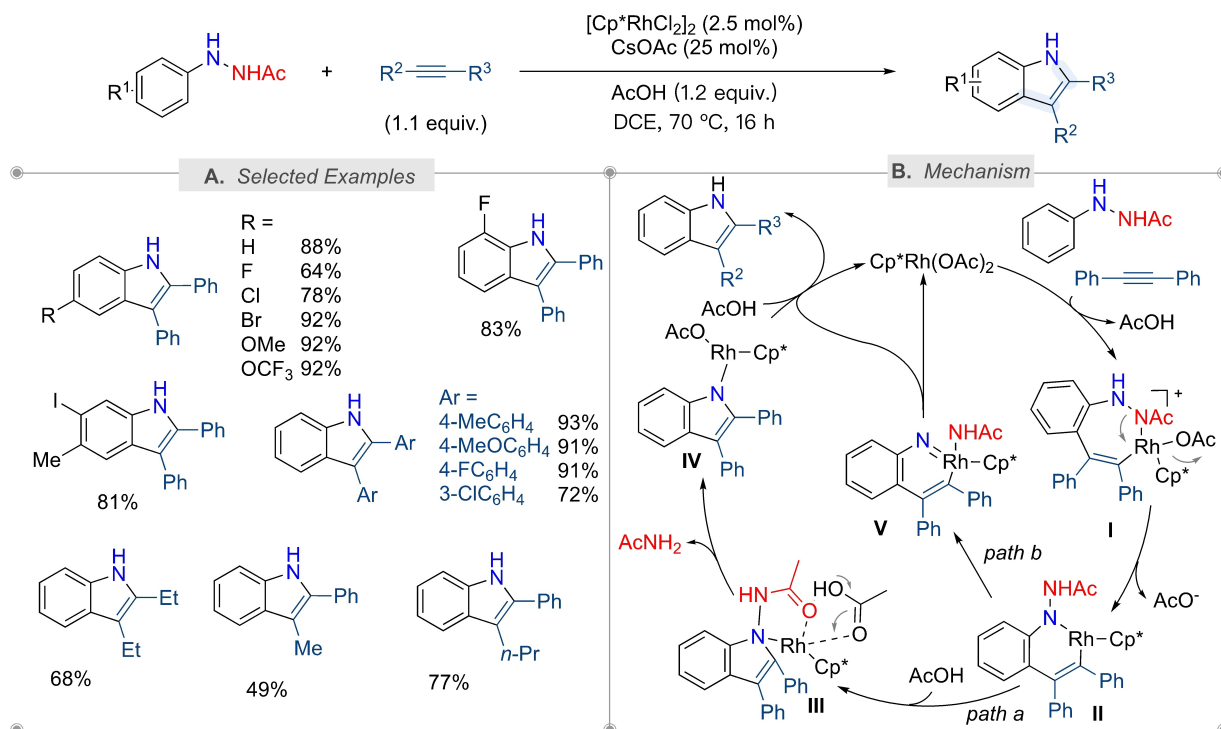
Scheme 17. Rh(III)-catalyzed redox-free C–H annulation of aniline *N*-oxides with internal alkynes.

no additives are required, and only cationic Rh(III) complex in DCE was used. Substituted 2,3-diarylindoles holding a wide range of functional groups (alkyl, ether, ester, halo, formyl, acetamide, and amino) were prepared from various substituted *N*-acetoxyacetanilides and symmetrical/unsymmetrical alkynes in good to excellent yields. Even the intermolecular version has been investigated. Moreover, they described a one-pot procedure from nitroarenes through a reduction carried out by Zn powder in the presence of Ac_2O . Based on deuterium exchange, competitive reaction, and stoichiometric experiments, the authors proposed the catalytic cycles depicted in Scheme 18B. The reaction starts with the C–H bond cleavage and the formation of six-membered rhodacycle complex **I** via acyl oxygen-directed metalation of the *ortho* C–H bond. This complex was isolated. Then, insertion of the alkyne into the Rh–C bond delivers **II**, followed by a rearrangement of the eight-membered ring in intermediate **II** to produce intermediate **III**. Then, two pathways are possible. *In path A*, a C–N bond formation through reductive elimination from **III** to ammonium ion **IV**, along with the formation of $\text{Cp}^*\text{Rh(I)}$, occurs. The Rh(I) undergoes oxidative addition and hydrolysis to give the indole and regenerate the active rhodium species. *In path B*, oxidative addition of the N–O bond in **III** would result in Rh(V) species **V**,

which on reductive elimination would afford the product and regenerate the active catalyst.

2.3. C–H Bond Functionalization Using Internal N–N Bond as Oxidant

In 2013, Glorius and co-workers offered a new method for synthesizing unprotected indoles from 2-acetyl-1-arylhydrazines and alkynes through rhodium(III)-catalyzed redox-neutral C–H bond annulation (Scheme 19).^[32] This work represents an early example of the use of the N–N bond as an internal oxidant for the regeneration of catalysts in C–H bond functionalization. The optimized conditions, 2.5 mol% of $[\text{Cp}^*\text{RhCl}_2]_2$ associated with 25 mol% of CsOAc in the presence of 1.2 equivalents of AcOH, allowed the formation of diversely substituted indoles in high yields from well-decorated acetyl-1-arylhydrazine partners (e.g., F, Cl, Br, I, CN, OCF₃, or CO₂Me) and symmetrical diaryl, or dialkyl internal alkynes. Moreover, reactions with alkyl phenyl acetylenes proceeded with complete regioselectivity. From mechanistic investigation, notably using [¹⁵N]-2-acetyl-1-phenylhydrazine, the authors proposed the catalytic cycle depicted in Scheme 19B. Like other reactions, the reaction starts with an *ortho*-directed C–H bond metalation followed by alkyne

Scheme 18. Rh(III)-catalyzed annulation of *N*-acetoxyacetanilides with substituted alkynes.

Scheme 19. Rh(III)-catalyzed hydrazine-directed C–H bond activation: redox-neutral and traceless by N–N bond cleavage.

insertion to afford seven-membered rhodacycle I. This metallacycle rearranges into a more stable six-membered Rh complex II, which might undergo a reductive elimination, protonation,

and oxidative addition to break the N–N bond with the aid of acetic acid to form intermediate III, which is finally protonated by acetic acid to yield the desired indole and regenerate the

catalyst (path a). Alternatively, the authors proposed that **II** could lead to a cyclic Rh(V)-nitrene intermediate **V** by acylamino migration, and **V** could easily undergo reductive elimination to form the desired heterocycle and regenerate the Rh(III) catalysts (path b). DFT calculation performed by Lin and co-workers also evoked an Rh(V)/Rh(III) scenario for this transformation.^[33]

C–H bond annulation of 2-acetyl-1-arylhydrazines was not limited to the use of internal alkynes as annulative reagents, as Wang reported the use of diazo compounds for preparing 1-aminoindoles (Scheme 20).^[34] However, in this case, no oxidant was required; therefore, the N–N bond is not cleaved. The reaction was run in water using 2.5 mol% of [Cp*RhCl₂]₂ associated with 25 mol% of CsOAc in the presence of 0.5 equivalents of AcOH. Like the previous methodologies, a broad tolerance to functional groups was observed, including halogen atoms, cyano, and ester groups. [Cp*Rh(OAc)₂] is proposed to be the active catalyst undergoing C–H bond cleavage followed by generation of Rh(III)-carbene **II**. Subsequently, migratory insertion of the carbene into the Rh–C bond might deliver rhodacyclic intermediate **III**, which is protonated by acetic acid to release **IV** and Rh(III). Then, intramolecular condensation with the elimination of water affords the indolyl scaffold.

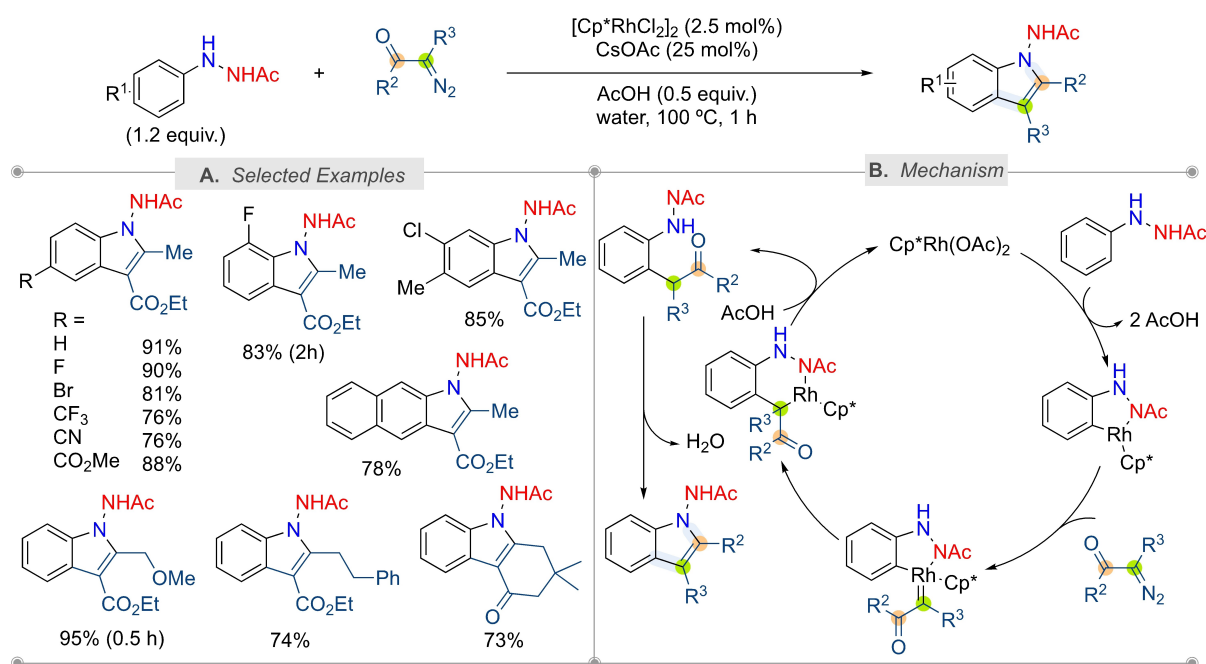
In 2013, Zhu and co-workers also reported the synthesis of indoles through C–H bond annulation using the N–N bond as an internal oxidant, albeit from *N*-nitrosoanilines (Scheme 21).^[35] They developed two sets of conditions (acid and basic) to ensure a broad functional group tolerance. In contrast to acid conditions, the basic ones are compatible with *N*-nitrosoaniline holding an electron-withdrawing CN at the *para*-position, and the reaction is regioselective with *meta*-substituted (Me) electron-rich *N*-nitrosoaniline derivative. A few months later, an additive-free version was reported by Huang and co-workers using 8 mol% [Cp*Rh(OAc)₂] in MeOH at 90 °C.^[36] Comprehen-

sive mechanistic studies by Zhu,^[35] under acidic conditions, support [RhCp*]²⁺ as catalyst resting state (switchable to [RhCp*(OOCtBu)]⁺ under specific circumstances) and C–H activation as the turnover-limiting step. The key step is the regeneration of the catalyst from alkenylrhodium intermediate **VI**, which occurred by internal oxidation through H⁺-promoted concerted N–N bond cleavage –C–N bond formation with the concomitant abstraction of NO[−], later decomposed into detectable N₂O and H₂O.

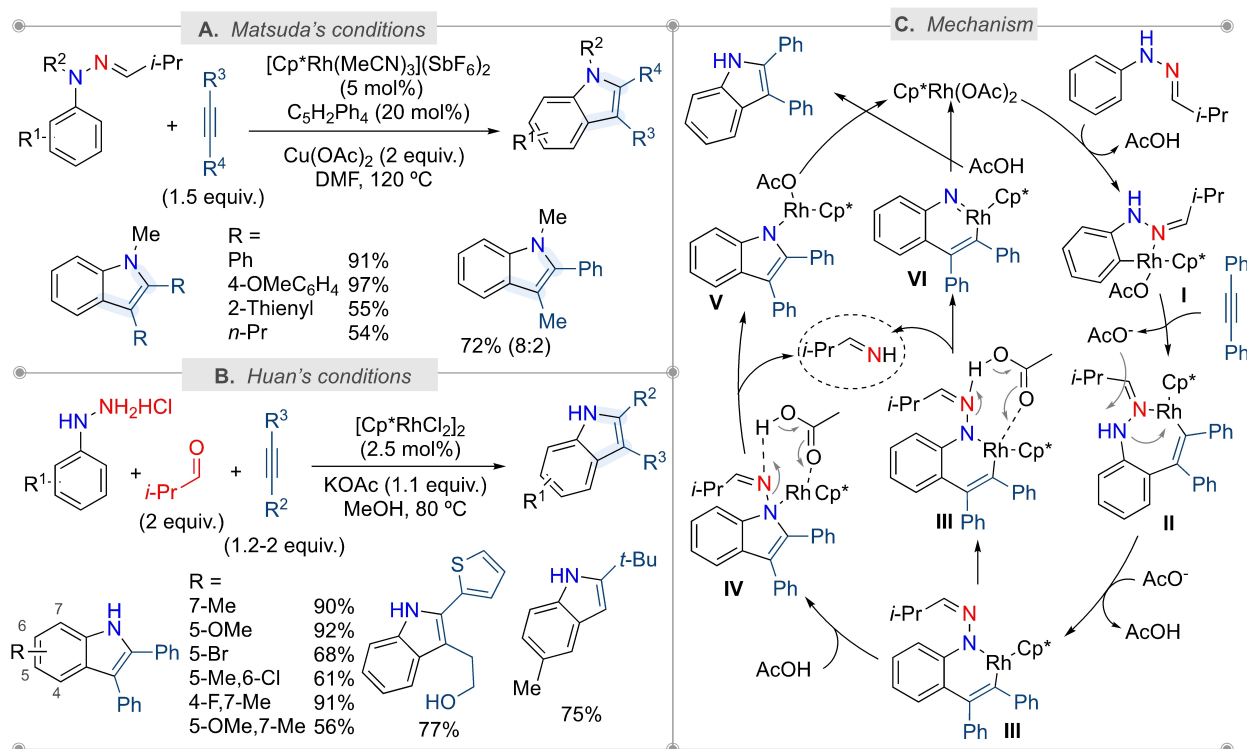
This C–H bond annulation reaction was later extended to the synthesis of 2-alkenylindoles and 2-alkenylindole-3-carboxylates using propargyl alcohols instead of internal alkynes as annulative reagents (Scheme 22).^[37] After C–H bond annulation, dehydration of the tertiary alcohol occurred, leading to the formation of the vinyl substituents. However, this transformation required the use of AgOAc or Cu(OAc)₂; therefore, the authors could not completely rule out an external oxidation process. Post-functionalizations of such building blocks have allowed the preparation of various polycycles such as 2-acylindole, benzocarbazole, indoloquinoline, pyridoindolone, cyclopentaindolone, and indenodolone.

In 2020, Messaoudi and co-workers employed this *N*-nitrosoanilines C–H bond annulation approach with alkynes for preparing 2,3-substituted β -*N*-glycosyl indoles (Scheme 23).^[38] They prepared various β -*N*-nitrosophenyl glucopyranoside derivatives before subjecting them to C–H bond annulation in the presence of 5 mol% [Cp*RhCl₂]₂ in conjunction with AgSbF₆ (20 mol%) in DCE at 90 °C. Various 2,3-disubstituted *N*-glycosyl indoles were prepared in moderate to good yields depending on the substitution of both partners. Interestingly, the reaction was also applied to prepare bioactive compounds.

In 2014, Matsuda and co-workers succeeded in the C–H bond annulation of alkylidenehydrazine, in which the N–N



Scheme 20. Rh(III)-catalyzed synthesis of 1-aminoindoles from 2-acetyl-1-arylhydrazines and diazo compounds.

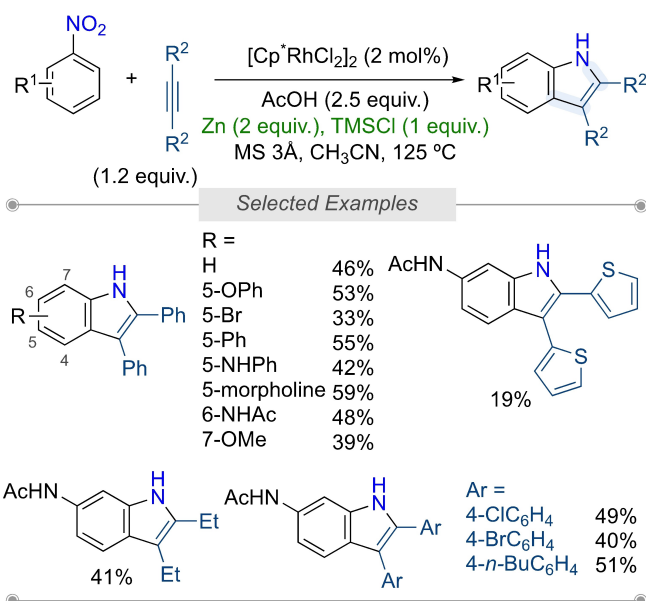


Scheme 24. Rh(III)-catalyzed synthesis of indoles from 1-alkylidene-2-arylhydrazines and alkynes via C–H and N–N bond cleavages.

the results in the absence of this copper salt. In the meantime, Huan and co-workers reported the same transformation but with the *in situ* formation of alkylidene from *N*-arylhydrazines and isobutyraldehyde (Scheme 24B).^[40] The authors called this strategy autoformed and auto-cleavable directing group. This time, no external oxidant was required, and the reaction scope was quite general. They proposed the mechanism depicted in Scheme 24C. First, hydrazone was rapidly formed *in situ* from hydrazine and *i*-PrCHO, with the release of 1 equivalent of HOAc. Then, cyclometalation followed by alkyne insertion affords seven-membered rhodacycle II, which rearranges to a more stable six-membered rhodacycle III. Reductive elimination of III gives IV, and H⁺-promoted N–N cleavage generates V. Protonation of V delivers the indole product and regenerates the Rh(III) catalyst. They also proposed an alternative mechanism in which the N–N cleavage occurs in III to afford Rh(V) nitrene intermediate V, which could undergo reductive elimination to form the indole product.

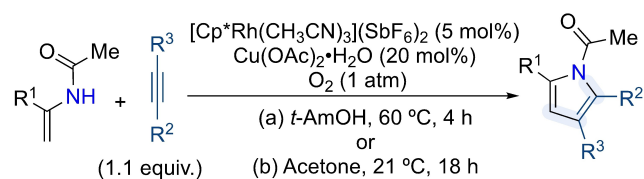
2.4. C–H Bond Functionalization under Reductive Conditions

In 2020, Patureau and co-workers prepared indoles from nitroarenes and alkynes *via* Rh(III)-catalyzed C–H bond annulation using zinc metal to reduce *in situ* NO₂ into NH functions (Scheme 25).^[41] This method from nitroarenes as abundant feedstocks by-passes the reduction steps required to prepare *N*-functionalized anilines, commonly used in Rh(III)-catalyzed C–H bond annulation. Using [Cp*RhCl₂]₂ in the presence of elemen-

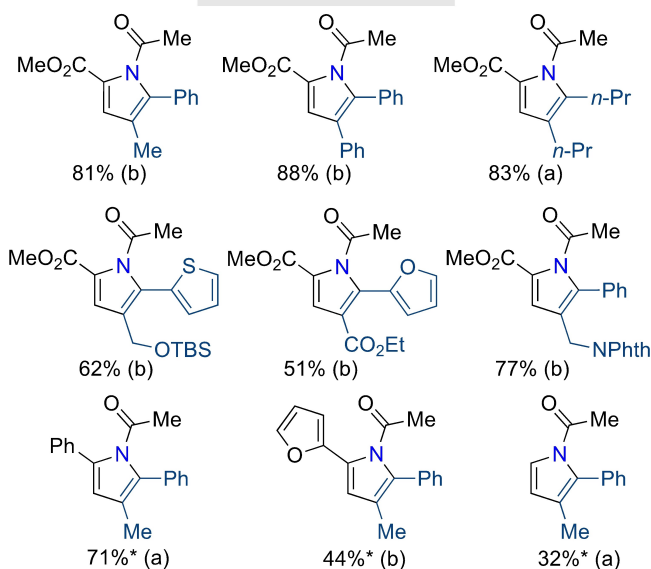


Scheme 25. Rh(III)-catalyzed C–H bond annulation of nitroarenes with alkynes.

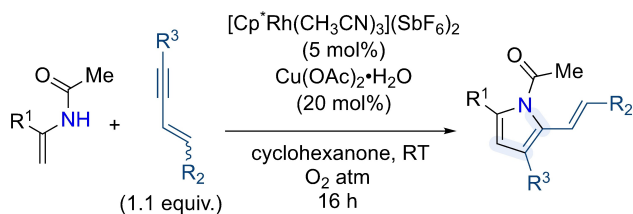
tal zinc in conjunction with TMSCl as a reductant system, they achieved the C–H bond annulation of diversely substituted nitroarenes with symmetrical alkynes. The authors did not report a reaction pathway, but they showed some control experiments with a different intermediate that can be obtained from the reduction of nitroarenes. They concluded that the C–H bond annulation event did not proceed from anilines, 1,2-



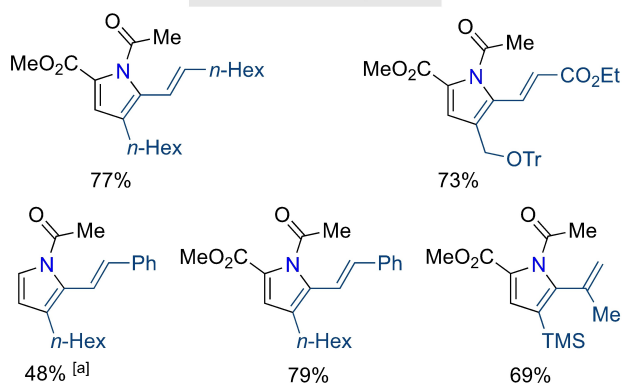
Selected Examples



* With 2 equiv of enamide.

Scheme 26. Pyrrole Synthesis via Rh(III)-catalyzed oxidative coupling of enamides and internal alkynes.


Selected Examples

[a] *N*-Vinylacetamide (3 equiv.)
Scheme 27. Pyrrole synthesis via Rh(III)-catalyzed oxidative coupling of enamides and enynes.

diphenylhydrazine, and trace amounts with azobenzene, while slightly better yield was observed with nitrosobenzene (14%) or *N*-phenylhydroxylamine (5%) opening the way for multiple intermediates.

3. Preparation of Pyrrole Scaffolds

3.1. C–H Bond Functionalization under Oxidative Conditions

In 2010, during their investigations on Rh(III)-catalyzed C–H bond annulation reaction of acetanilides for the preparation of indoles (Scheme 1B),^[9] Fagnou and co-workers also explored the extension of this method to vinylic C–H bond functionalization in the context of pyrroles synthesis (Scheme 26).^[9] The reaction is quite general, with different substituted enamines and internal alkynes. The reaction can also be performed at room temperature, provided it was run in acetone.

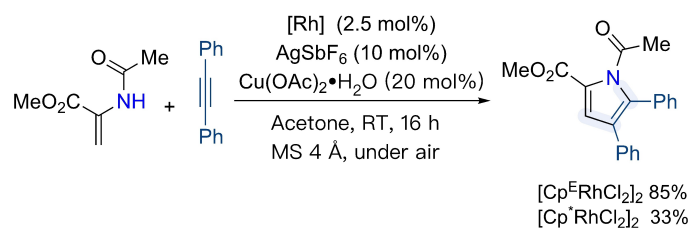
During their investigations on indole synthesis from *N*-aryurea and enynes (Scheme 3),^[12] Huestis and co-workers also extended this enyne chemistry to the synthesis of 2-alkenyl pyrroles using an enamide coupling partner (Scheme 27).^[12] The reaction was accomplished at room temperature in cyclohexanone using NHAc as directing group. Consistent with the indole chemistry, triphenylmethyl and *tert*-butyldimethylsilyl-ethers were well tolerated on the enyne coupling partners. TMS-functionalized enynes were also employed to deliver C3-TMS-substituted pyrrole building blocks. Pyrroles having a styryl or *N*-vinylacetamide substituent at C2 were also prepared.

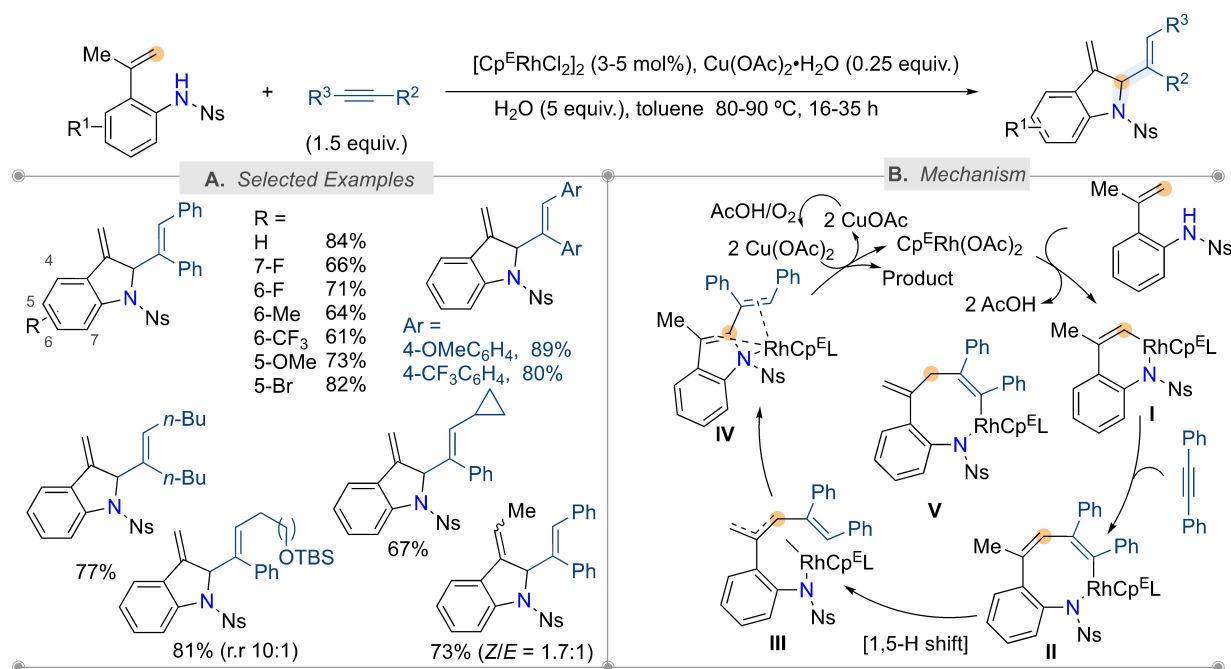
Tanaka and co-workers have shown that electron-deficient [Cp^FRhCl₂]₂ outperformed commercially available [Cp^{*}RhCl₂]₂ in the synthesis of pyrrole through rhodium(III)-catalyzed oxidative coupling of enamides and internal alkynes at room temperature (Scheme 28).^[15]

4. Preparation of Indoline and Related Heterocycles

4.1. Oxidative Couplings Using External Oxidant

In 2018, Mascareñas, Gulías, and co-workers prepared indolinyl scaffolds by C–H bond annulation of 2-alkenyl anilides with alkynes using electron-deficient [Cp^FRhCl₂]₂ (3 mol%) associated with 0.25 equivalent of Cu(OAc)₂ in toluene (Scheme 29).^[42] The


Scheme 28. Effect of the catalysts in Rh(III)-catalyzed oxidative coupling of enamides and internal alkynes.



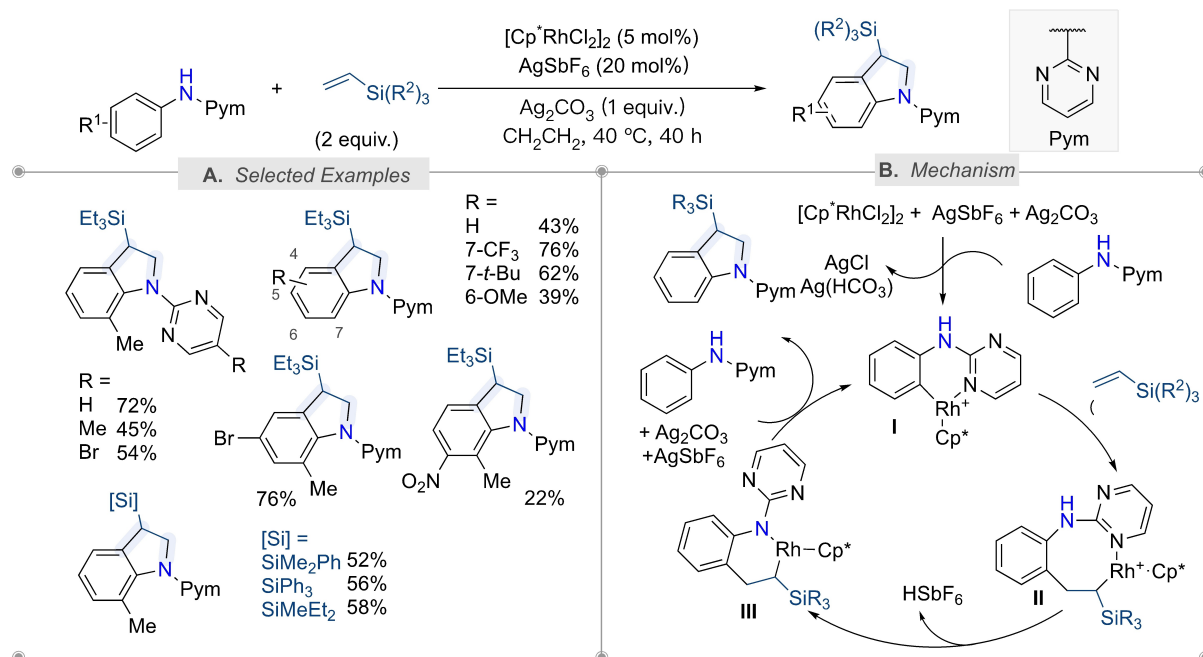
Scheme 29. Rh(III)-catalyzed C–H bond annulation of 2-alkenyl anilides with alkynes to access to 2-substituted indolines.

presence of oxygen plays the role of terminal oxidant in this reaction. The use of an electron-deficient catalyst is essential for the outcome of the reaction, as $[\text{Cp}^*\text{RhCl}_2]_2$ catalyzes this transformation in only 16% yield. Moreover, the choice of the group at the nitrogen atom (R) is also an essential factor as other tested groups than Ns gave lower yields (R=Tf 40%, or Ts 25%) or no reaction (R=H, Ac). The optimized conditions tolerate various functional groups on the 2-alkenyl anilides partners. Moreover, symmetrical alkynes with electron-rich or electron-poor aromatic substituents have been employed as annulating reagents. In the case of non-symmetrical alkynes, the transformation exhibited high regioselectivity; with the Rh–C bond predominantly inserted into the alkyne at the carbon bearing the aryl group. The reaction is not limited to *ortho*-propenylanilides, as the authors reported one example with but-1-en-2-yl substituent, but the corresponding indoline product was obtained as a mixture of *Z* and *E* isomers in a 1.7:1 ratio. A catalytic cycle using rhodium acetate complexes as active catalysts has been proposed. The activation of an olefinic C–H bond to give rhodacycle I, followed by carbometalation to generate II, and a 1,5-hydrogen shift to generate the key π -allyl intermediate III, which evolves by reductive elimination to form the corresponding indoline product. The resulting Rh(I) complex is then reoxidized to Rh(III) by the Cu(II) salt and air. The authors also proposed an alternative pathway for forming III from V through 1,3-rhodium migration.

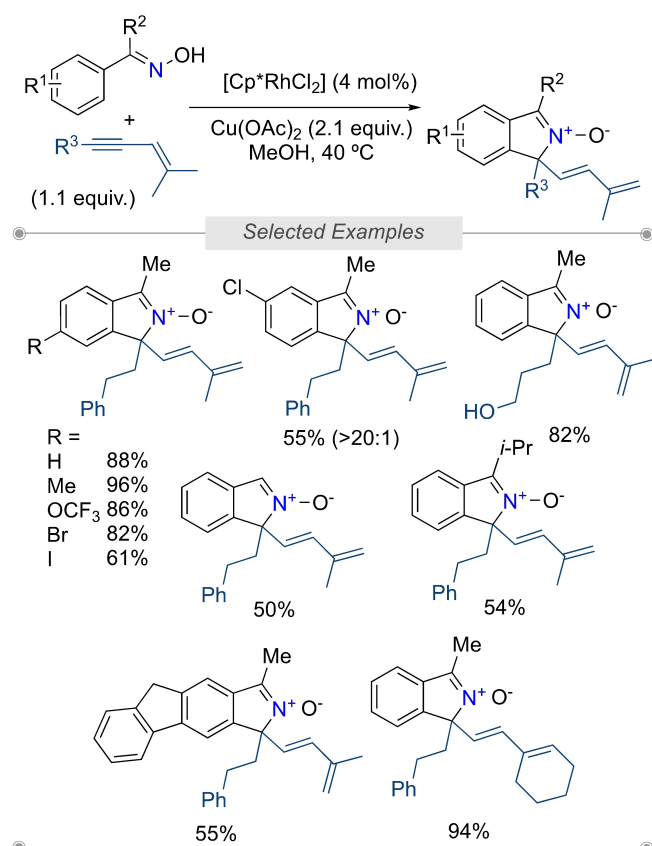
In 2021, Chatani and co-workers showed that aniline derivatives that contain a pyrimidine directing group reacted with vinylsilanes using $[\text{Cp}^*\text{RhCl}_2]_2$ to form C3-substituted indolines (Scheme 30).^[43] The reaction proceeds *via* C–H bond alkylation – internal amination cascade reaction. Aniline derivatives holding electron-donating or electron-withdrawing groups

at the *ortho* position, including the highly bulky *tert*-butyl group, afforded the expected indoline products. The reaction showed high functional group compatibility, including substituents such as OMe, F, Cl, Br, CF₃, and NO₂ groups. Alkyl- and phenyl-substituted vinylsilanes can be used for this transformation, while reactions with siloxy-substituted vinylsilane gave a mixture of the indoline product with the linear alkenylated product. Based on a deep mechanistic investigation, the authors build the catalytic cycle depicted in Scheme 30B. The catalyst I is generated from $[\text{Cp}^*\text{RhCl}_2]_2$ in the presence of AgSbF₆, Ag₂CO₃, and aniline through the directed *ortho*-rhodation. The coordination of an alkene to the rhodium complex I, followed by the migratory insertion of an alkene into an Rh–C bond, generates the eight-membered Rh complex II. The insertion of an alkene into the Rh–C bond is governed by steric repulsion between the Cp*Rh moiety and SiR₃ group. A subsequent 1,3-Rh migration with the elimination of HSBF₆ forms the six-membered complex III, which undergoes reductive elimination to form the indoline with the regeneration of the active complex I in the presence of aniline, AgSbF₆, and Ag₂CO₃.

Zwitterionic isoindole 2-oxide derivatives can be synthesized from oximes and alkynes through a Rh(III)-catalyzed C–H bond annulation process, as demonstrated in Scheme 31.^[44] While these studies primarily focused on 1,3-enynes, it is anticipated that the reaction could be extended to other types of alkynes. This method exhibits a broad tolerance for various functional groups. However, it is generally observed that higher yields are achieved with ketoximes that have electron-withdrawing substituents. The reaction necessitates the use of two equivalents of Cu(II) as oxidant. It should be noted that oximes can be also employed albeit providing modest yield of 50%.



Scheme 30. Rh(III)-catalyzed [3 + 2] annulation of aniline derivatives with vinylsilanes.

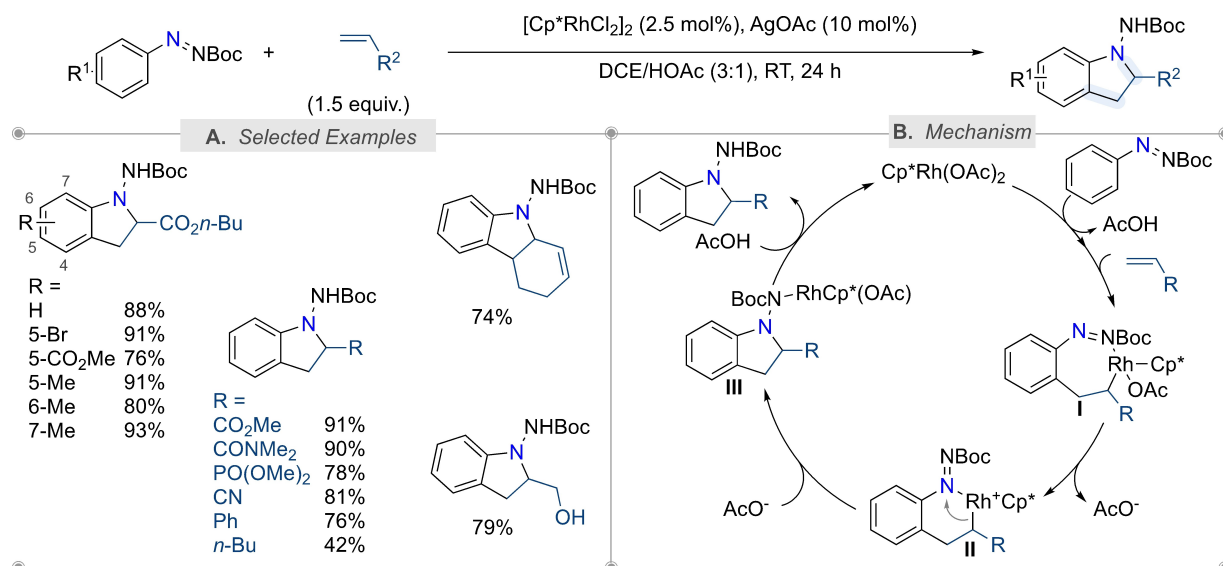


Scheme 31. Preparation of zwitterionic indole 2-oxides via Rh(III)-catalyzed C–H bond annulation of oximes with alkynes.

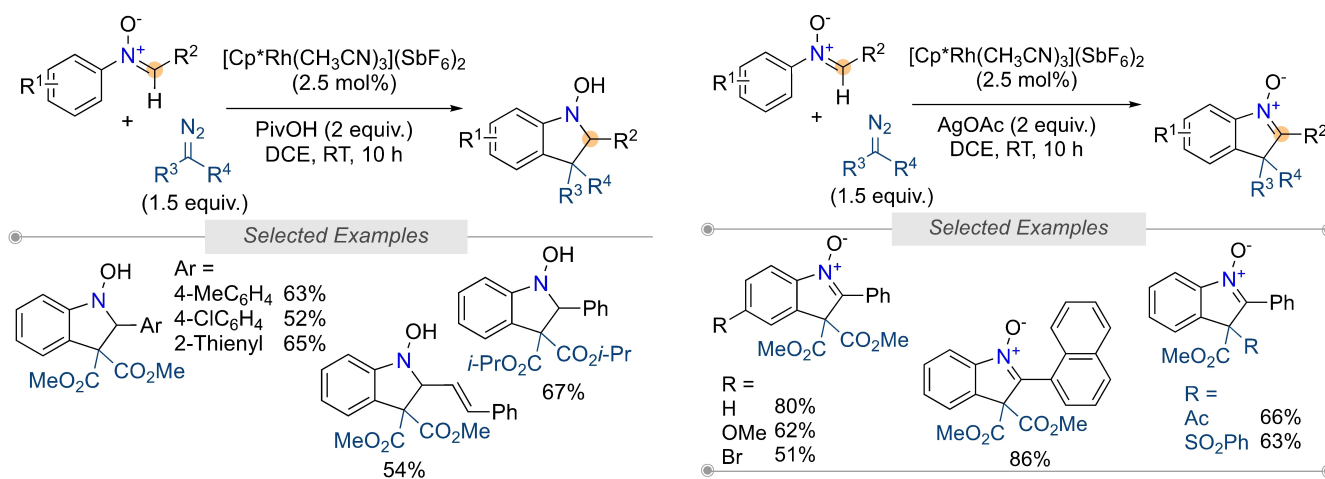
4.2. Redox-Free Conditions

In 2015, Glorius and co-workers reported the synthesis of 1-aminoindolines from aryl-substituted diazenecarboxylates and alkenes through the concomitant C–H bond alkylation and *N*-alkylation reaction (Scheme 32).^[45] The conditions are mild, as the reaction could be performed at room temperature in the presence of [RhCp*(OAc)₂] (2.5 mol) and AgOAc (10 mol%) in a mixture of HOAc and DCE (1:3). A variety of important functional groups such as halogens (F, Cl, and Br), ester, and methoxy groups on the aryl-substituted diazenecarboxylates were well tolerated. Different alkenes such as acrylates, acrylamides, acrylonitrile, styrenes, and alkyl alkenes have been employed in this reaction delivering the 2-substituted 1-aminoindoline products in good to high yields. Based on a set of mechanistically insightful experiments, the authors proposed that [RhCp*(OAc)₂] is the active catalyst. After cyclometalation of aryl-substituted diazenecarboxylates followed by alkene insertion into the Rh–C bond, the 7-membered ring rhodacycle I rearranges to the more stable six-membered coordinately saturated Rh species II. Complex II undergoes a nucleophilic addition to the N=N bond to form intermediate III, which is finally protonated by HOAc to yield the desired 1-aminoindoline.

Indoline scaffolds can also be built from nitron and diazomalonate *via* Rh(III)-catalyzed C–H bond annulation, as demonstrated by Zhou and co-workers (Scheme 33).^[46] In the presence of an acid, the reaction proceeds first through rhodium(III)-catalyzed chelation-assisted (N–O) insertion of aromatic C(sp²)–H bonds into diazo compounds, followed by direct intramolecular nucleophilic attack of the C(sp³)–Rh intermediate on the C=N bond to afford the corresponding *N*-



Scheme 32. Rh(III)-catalyzed cyclative capture approach to diverse 1-aminoindoline derivatives at room temperature.



Scheme 33. Rh(III)-catalyzed C–H bond annulation of nitrones with diazomalones.

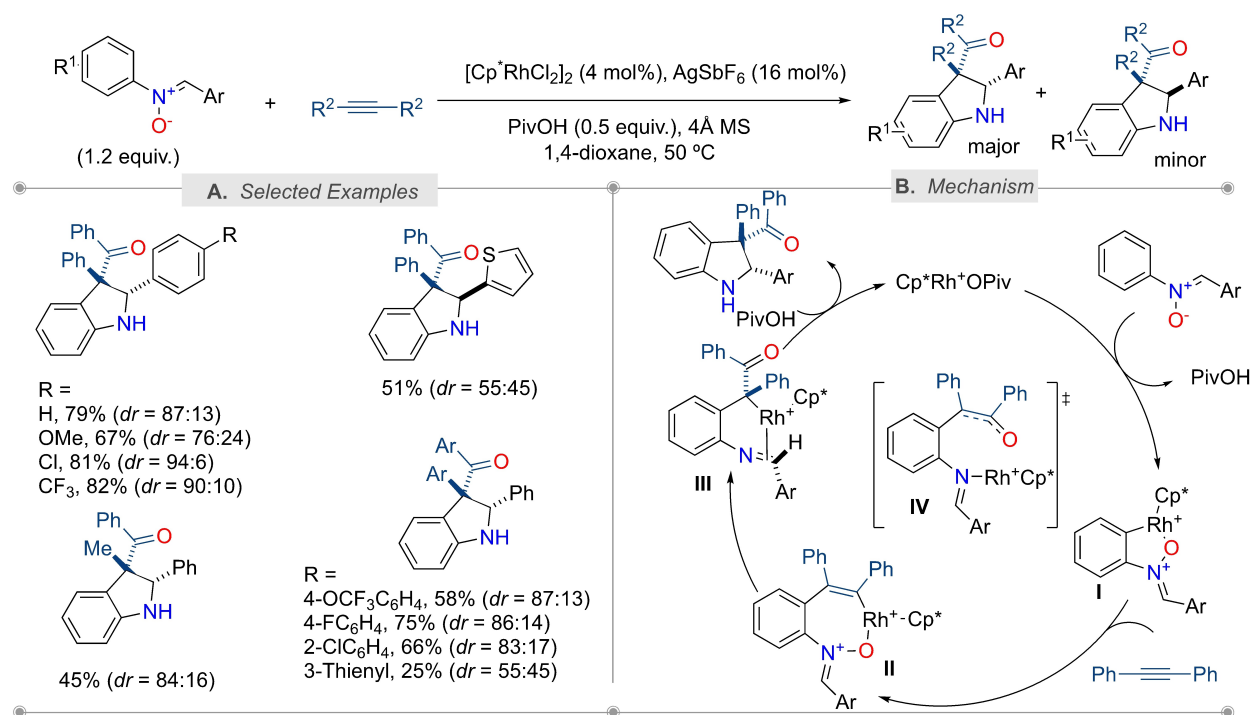
Scheme 34. Rh(III)-catalyzed C–H bond annulation of nitrones with diazomalones under oxidative conditions.

hydroxyindoline compounds (Scheme 33, left). Interestingly, over-oxidation occurred in the presence of a base (AgOAc), delivering the 3-indole-*N*-oxide derivatives (Scheme 33, right).

In their exploration of synthesizing indoline through Rh(III)-catalyzed C–H bond annulation of nitronone with diazomalone (illustrated in Scheme 33), Zhou and colleagues made a notable discovery. They found that conducting the reaction in the presence of a base, specifically AgOAc, which also serves as an oxidant, enabled access to zwitterionic indole 2-oxide derivatives (Scheme 34).^[46] This dual functionality of AgOAc as both a base and an oxidant significantly enhanced the scope of the reaction, opening up new pathways for the synthesis of complex indole derivatives.

4.3. By Merging O-Atom Transfer

In 2015, Chang and co-workers reported the first example of Rh(III)-catalyzed coupling reaction of aryl nitrones with internal alkynes under external oxidant-free conditions (Scheme 35).^[47] They proposed a dual role of the rhodium catalyst: *i*) C–H bond activation/functionalization and *ii*) O-atom transfer process. The cyclization proceeds smoothly under mild conditions giving rise to indoline products in good yields together with moderate to high diastereoselectivity with an excellent functional group tolerance (e.g., Me, OCF₃, F, Cl, Br). Li and co-workers later reported the same reaction and almost the same conditions (EtOAc instead of 1,4-dioxane).^[48] Most indoline products were obtained as a mixture of diastereoisomers, and the major isomer has two phenyl groups at the C-2 and C-3 positions of a newly generated five-membered ring in an *anti*-relationship. The authors proposed the mechanism depicted in Scheme 35B.



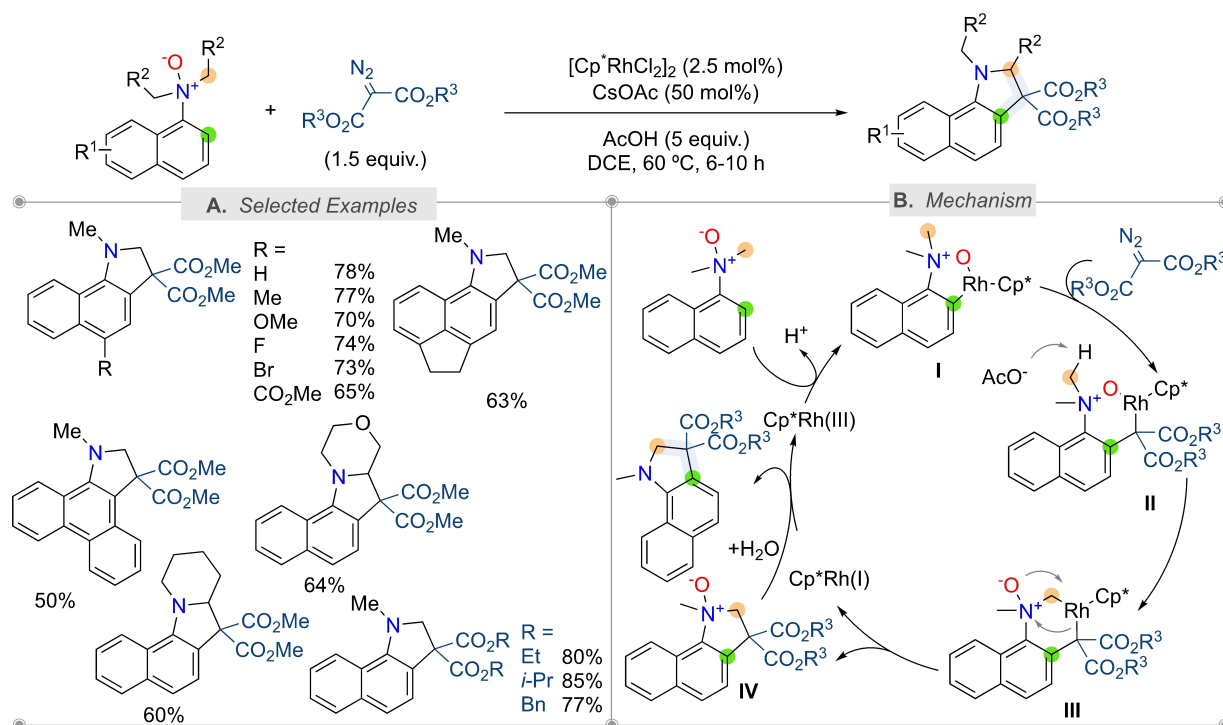
Scheme 35. Rh(III)-catalyzed C–H bond annulation of aryl nitrones to indolines under external oxidant-free conditions.

After the classical formation of rhodacycle **I** via a CMD process and alkyne insertion into the Rh–C bond, the alkenyl intermediate **II** is formed. Then, a subsequent O-atom transfer (OAT) might occur in two pathways: (i) cleavage of the N–O bond to form Rh(V) oxo species that undergoes the reductive elimination to afford an Rh(III)-enolate **IV** or (ii) reductive elimination of **II** to form a benzoxazine and Rh(I) followed by oxidation of Rh(I) to Rh(III) via N–O cleavage leading to **IV**. A rearrangement of rhodium enolate **IV** and then cyclization proceeds via **III**.

In the same year, Zhou, Yang, Zhu, and co-workers described the C–H bond annulation of arylamine *N*-oxides with diazo compounds, in which an *O*-atom transfer plays the role of an internal oxidant (Scheme 36).^[49] Various 1H-benzo[*g*]indolines were prepared in good yields whatever the substituent on the *N,N*-dimethyl-1-naphthylamine *N*-oxides (Me, MeO, F, Br, CO₂Me). Primary C(sp³)–H bonds and secondary C(sp³)–H bonds have been annulated to provide the tetracyclic products. The N–O bond acts as a directing group to allow the formation of complex **I** from [RhCp*(OAc)₂] and *N,N*-dimethyl-1-naphthylamine *N*-oxides. Then, coordination of the diazo substrate, followed by denitrogenation and Rh-aryl migratory insertion, affords **II**. Then, with the assistance of acetate, **II** undergoes a methyl C(sp³)–H activation to give more stable complex **III** with a new C–Rh bond formed. Subsequent C–C reductive elimination of **III** produces **IV**. Finally, rhodium(I) oxidation with *N*-oxide irreversibly gives the indoline product. The authors also proposed an alternative pathway via an Rh-iminium intermediate.

In 2023, our research group reported a breakthrough in the synthesis of 3,3-disubstituted oxindoles. This was achieved through a Rh(III)-catalyzed *ortho*-C–H bond functionalization of

nitroarenes with 1,2-diaryllalkynes and carboxylic anhydrides, as illustrated in Scheme 37.^[50] A distinctive feature of our approach is the utilization of NO₂ as a directing group for C–H bond activation, eliminating the need for stoichiometric oxidants. The reduction of NO₂ to NH is facilitated through a series of rearrangements, as outlined in our proposed mechanism. Our initial trials with the commercially available [Cp*RhCl₂]₂ complex yielded moderate catalytic activity (below 49%). To enhance this, we developed a novel catalyst, [Cp^{TEMP}*RhCl₂]₂. This catalyst features a Rh atom surrounded by a functionally modified cyclopentadienyl ligand [Cp^{TEMP}* = 1-(3,4,5-trimethoxyphenyl)-2,3,4,5-tetramethylcyclopentadienyl]. The electron-rich nature and elliptical shape of this Cp ligand are crucial for better reaction outcomes. The reaction protocol necessitates using 5 to 10 equivalents of nitroarenes, which can be substituted with various functional groups, including Br, I, F, and esters. As for the alkyne components, only 1,2-diaryllalkynes have been successfully employed. Notably, 1,2-diaryllalkynes with two distinct aryl groups enable the formation of oxindoles featuring an α -carbonyl quaternary stereogenic center. A range of carboxylic anhydrides can also be employed in this reaction. Through the isolation of three key rhodacycles and DFT calculations performed by Houk's group, we proposed a catalytic cycle depicted in Scheme 37B. The catalytically active species **A** is generated from [Cp^{TEMP}*RhCl₂]₂ and AgSbF₆ in the presence of Ac₂O through chloride abstraction and ligand exchange. Nitro coordination to the metal center leads to the formation of rhodacycle **B** by C–H bond cleavage and the release of AcOH, likely via a CMD mechanism. This step is the rate determining step. Subsequent steps involve alkyne coordination and insertion into the Rh–C bond to form seven-



Scheme 36. Rh(III)-catalyzed C–H bond annulation of arylamine *N*-oxides with diazo compounds.

membered rhodacycle **D**, followed by an O-atom transfer yielding the η^3 -benzyl nitroso complex **H**. The reaction possibly proceeds through reductive elimination to form cationic heterocyclic intermediate **F** and Rh(I), followed by oxidative addition of the N–O bond to generate the Rh–O bond of Rh(III)-enolate intermediate **G**. This intermediate rearranges into C-enolate form **H** with η^3 -benzyl coordination. The nucleophilic attack of the nitroso group on the carbonyl group, leading to intermediate **I**, is indicated by grey arrows. A subsequent 1,2-aryl shift, akin to semipinacol rearrangement, results in the *N*-oxido Rh(III) complex **J**. In the final stage, from complex **J**, ligand exchange with AcO[−] regenerates the active catalytic species **A** for the next cycle, along with the formation of compound **K**. In 1,2-dichloroethane, we propose that a nucleophilic attack on **K** produces **L**, followed by a 1,2-hydride shift yielding NH-oxindole and 2-chloroacetaldehyde, as confirmed by GC-MS analysis. Subsequently, NH-oxindole evolves into acylated oxindole assisted by Ac₂O in a non-catalyzed pathway.

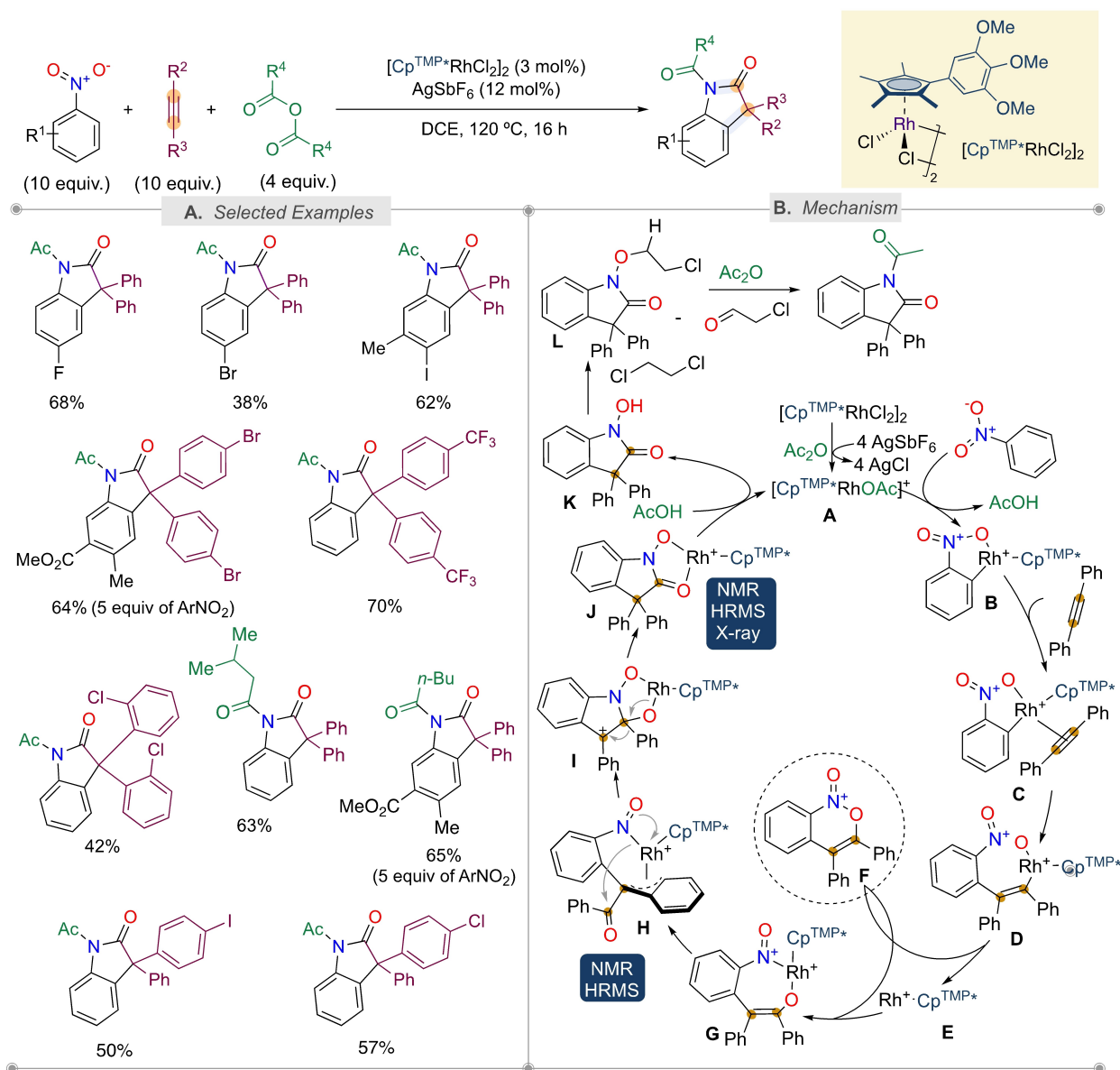
5. Preparation of Isoquinolones, Hydrogenated Analogs, and Related Heterocycles

In this section, we turn our attention to the C–H bond annulation of amide derivatives, examining how variations in redox strategies and annulating agents influence the synthesis of heterocyclic compounds. The type of annulating agent and the specific redox conditions employed play crucial roles in

determining the reaction pathways and the heterocycles obtained. This discussion will highlight the adaptability of redox and annulation strategies in crafting complex molecular architectures, focusing on the transformative power of these variables in the realm of heterocyclic synthesis.

5.1 C–H Bond Functionalization under Oxidative Conditions

In 2010, isoquinolone heterocycles were prepared from amides and alkynes using Rh(III)-catalyzed C–H bond annulation, a catalytic transformation developed by Rovis and co-workers (Scheme 38).^[51] The reaction conditions are similar to those described by Fagnou for indoles synthesis,^[8] AgSbF₆ (2.5 mol% of [RhCp*Cl₂]₂ as a catalyst with Cu(OAc)₂ (2.1 equivalents) as a stoichiometric oxidant in *t*-AmOH]. Electron-rich and electron-poor *N*-methyl benzamides reacted in good yields. *Meta*-substituted benzamides gave isoquinolone products as single regioisomers (less hindered position), while *ortho*-substituted ones afforded the isoquinolone products in slightly lower yields. Moreover, heteroaryl carboxamides have also been employed. The reaction displayed a broad substrate tolerance among internal alkynes, including unsymmetrical dialkyl alkynes, for which good regioselectivity was observed. After conducting mechanistic studies (deuterium-labeling experiments and competitive reactions), the authors proposed the following mechanism (Scheme 38B). In the presence of Cu(OAc)₂, the active catalyst [Cp*₂Rh(OAc)_n] is formed. After the classical, C–H bond activation *ortho*-directed by the amide group (**I**) and alkyne insertion, 7-membered rhodacycle **II** with



Scheme 37. Rh(III)-catalyzed C–H bond activation of nitroarenes, alkyne insertion, O-atom transfer and rearrangements for the synthesis of 3,3-disubstituted oxindoles.

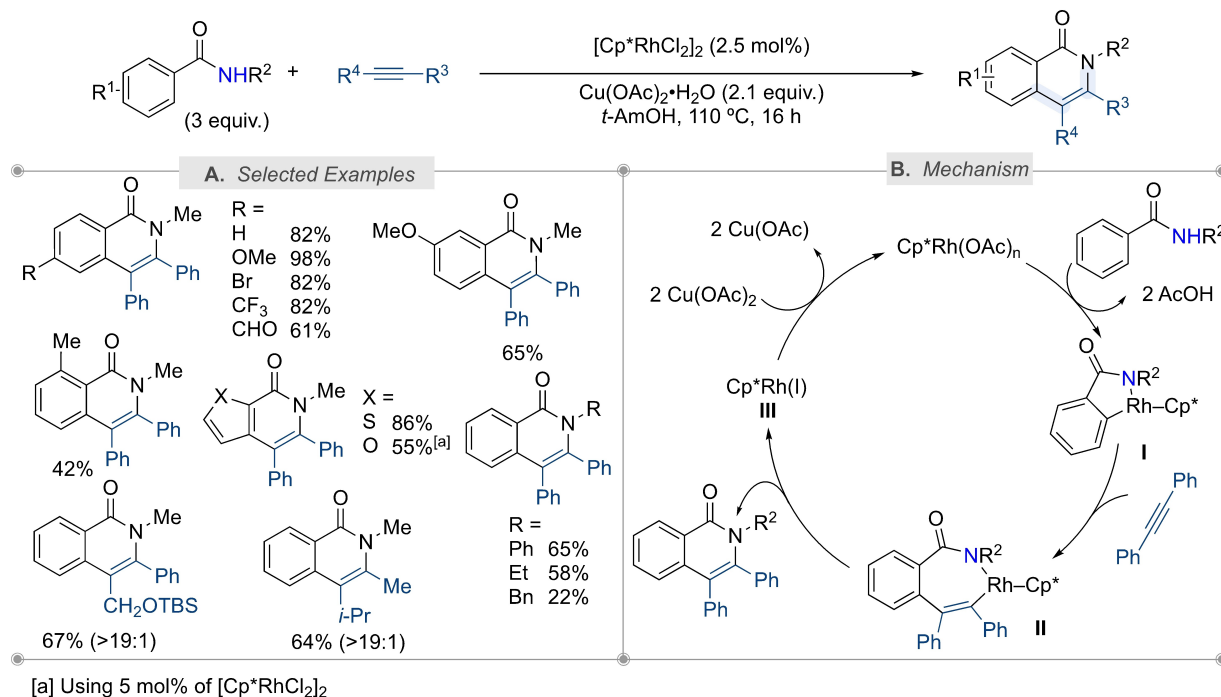
an open coordination site is generated. Then, reductive elimination formed the desired isoquinolone and generated a rhodium(I) species that can undergo oxidation to regenerate the catalytically active rhodium(III) complex with $\text{Cu}(\text{OAc})_2$.

In 2010, building on existing methodologies for the synthesis of isoquinolones, Li and colleagues introduced a modification by employing Ag_2CO_3 as the oxidant, instead of the commonly used Cu salts, in the oxidative *ortho* C–H bond annulation of benzamides and alkynes (Scheme 39).^[52] This reaction was conducted in CH_3CN , demonstrating that both *N*-alkyl and *N*-aryl secondary benzamides could be effectively transformed into isoquinolones. While the method predominantly uses diphenylacetylene, notable examples highlighted the use of a dialkyl-substituted alkyne. Furthermore, primary benzamides were shown to react with two alkyne units, leading

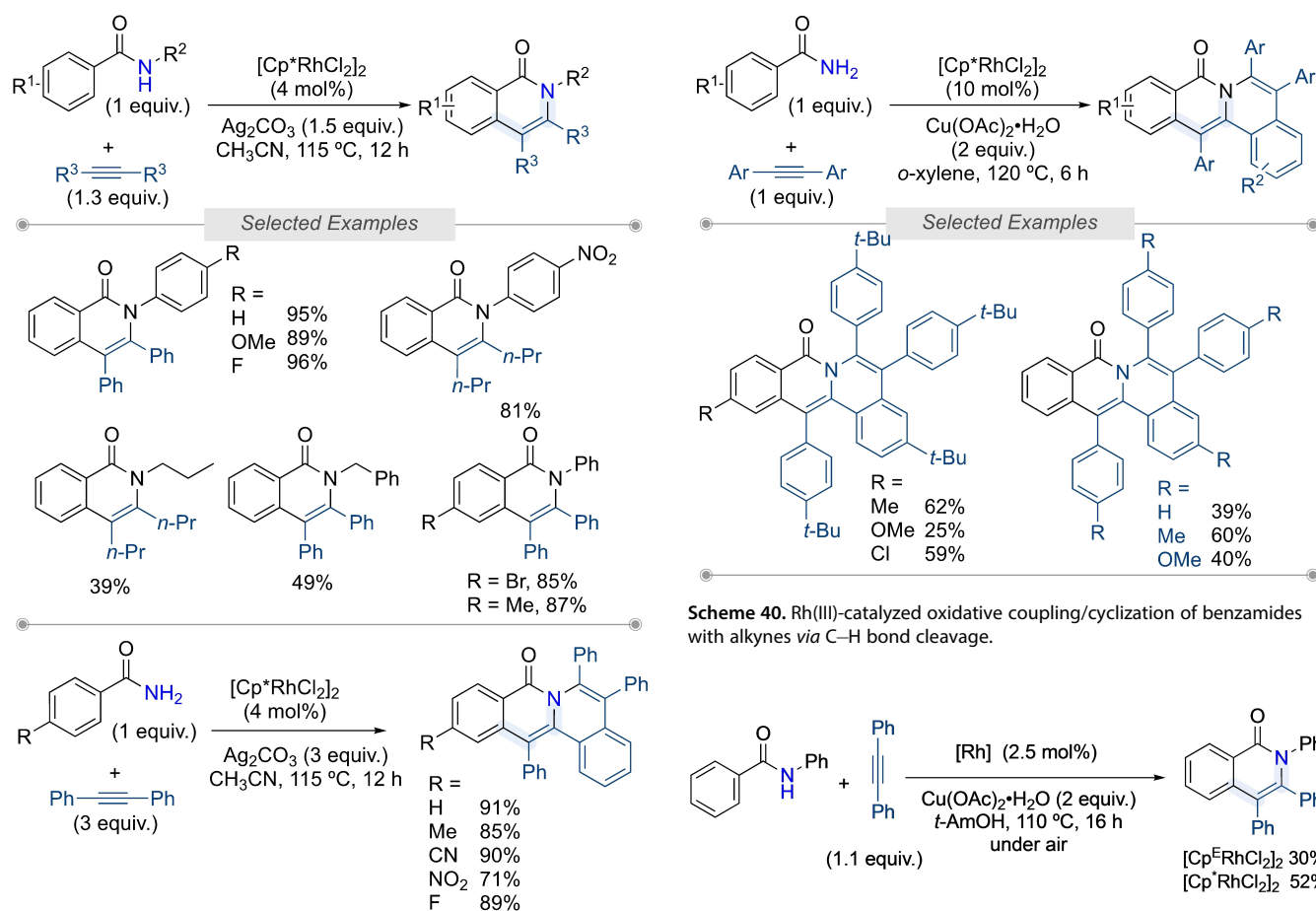
to tricyclic products through a double C–H activation and oxidative coupling process.

Satoh, Miura, and co-workers reported a similar transformation in the same year, albeit using alkynes and primary amides in a 1 to 1 ratio to achieve the double C–H bond annulation reaction to prepare tetracyclic compounds (Scheme 40).^[53]

In 2014, during their investigation on indole synthesis through Rh(III)-catalyzed C–H bond annulation of *N*-protected anilines (Scheme 4),^[15] Tanaka and co-workers also described one example of the formation of isoquinolone scaffold when they conducted the reaction from *N*-phenylbenzamide and 1,2-diphenylacetylene in the presence of $[\text{Cp}^*\text{RhCl}_2]_2$ associated with 2 equivalents of $\text{Cu}(\text{OAc})_2$ in *tert*-amyl alcohol (Scheme 41). Interestingly, in contrast with 5-membered ring formation,



Scheme 38. Rh(III)-catalyzed oxidative cycloaddition of benzamides and alkynes via C–H/N–H activation.



Scheme 39. Rh(III)-catalyzed oxidative coupling between primary or secondary benzamides and alkynes: synthesis of polycyclic amides.

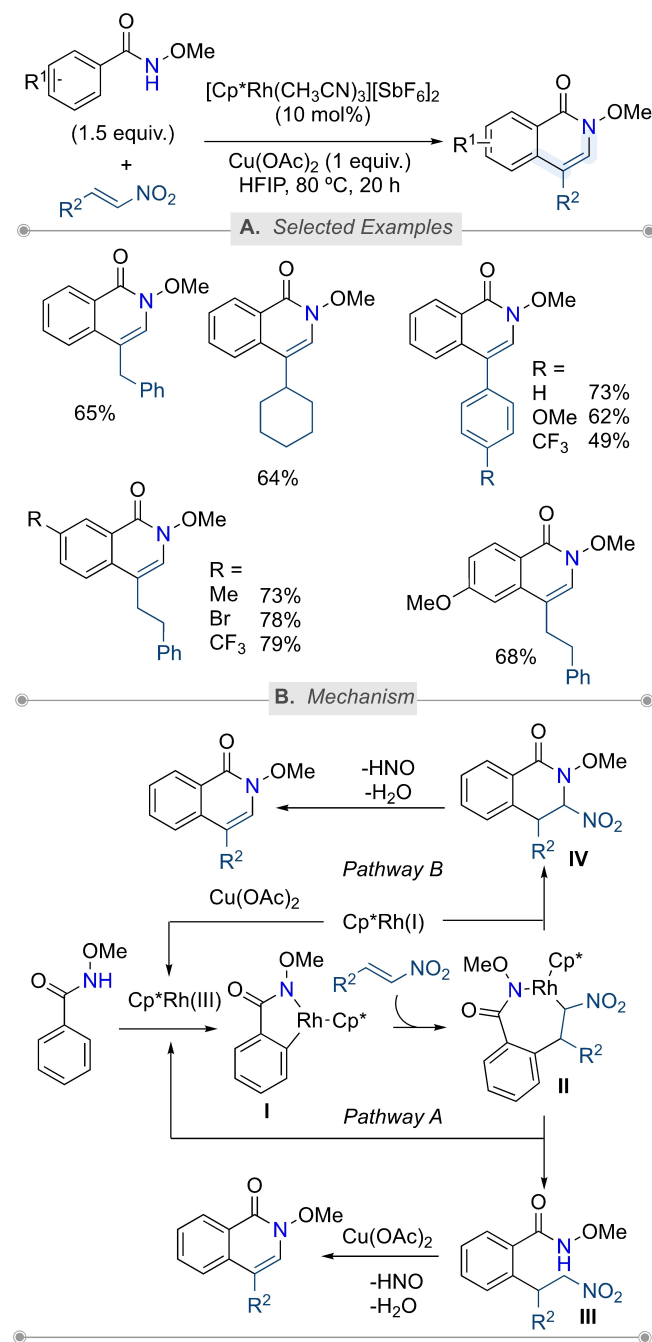
Scheme 41. Preparation of isoquinolone scaffold via Rh(III)-catalyzed oxidative coupling of *N*-phenylbenzamide and an internal alkyne.

$[\text{Cp}^*\text{RhCl}_2]_2$ displays a better activity than electron-deficient $[\text{Cp}^*\text{RhCl}_2]_2$ catalysts for forming isoquinolone scaffold.

Ward, Ellman, and co-workers reported the innovative use of nitroalkenes as alternatives to alkynes in the Rh(III)-catalyzed C–H bond annulation of *N*-methoxybenzamides for synthesizing 4-substituted isoquinolones. They employed the cationic complex $[\text{Cp}^*\text{Rh}(\text{CH}_3\text{CN})_3][\text{SbF}_6]_2$ alongside $\text{Cu}(\text{OAc})_2$, which serves a dual role (Scheme 42).^[54] Firstly, it acts as an oxidant to regenerate Rh(III) from Rh(I), and secondly, it promotes dinitrative C–N bond formation. Various aliphatic nitroalkenes with benzyl, cyclohexyl, and isopropyl substituents, and β -

nitrostyrene featuring either electron-rich or electron-poor substituents, were successfully utilized. Additionally, no significant impact on the yield from variations in the substitution patterns on the aryl ring of *N*-methoxybenzamide or *N*-isopropoxy-substituted benzamide was observed. The authors propose a catalytic cycle that begins with a concerted metalation/deprotonation of *N*-methoxyamide to form rhodacycle I. Subsequent coordination and insertion of nitroalkene yield rhodium nitronate II. From this, two plausible pathways could lead to isoquinolone. *Pathway A* involves protonolysis, regenerating the active rhodium catalyst and releasing nitroalkane III, that can undergo cyclization and denitration mediated by $\text{Cu}(\text{OAc})_2$. Alternatively, *pathway B* suggests that reductive elimination from II would yield dihydroisoquinolone IV and a reduced Rh(I) species, which would be reoxidized to the active Rh(III) catalyst by $\text{Cu}(\text{OAc})_2$. The subsequent elimination of the nitro group from IV would then yield isoquinolone.

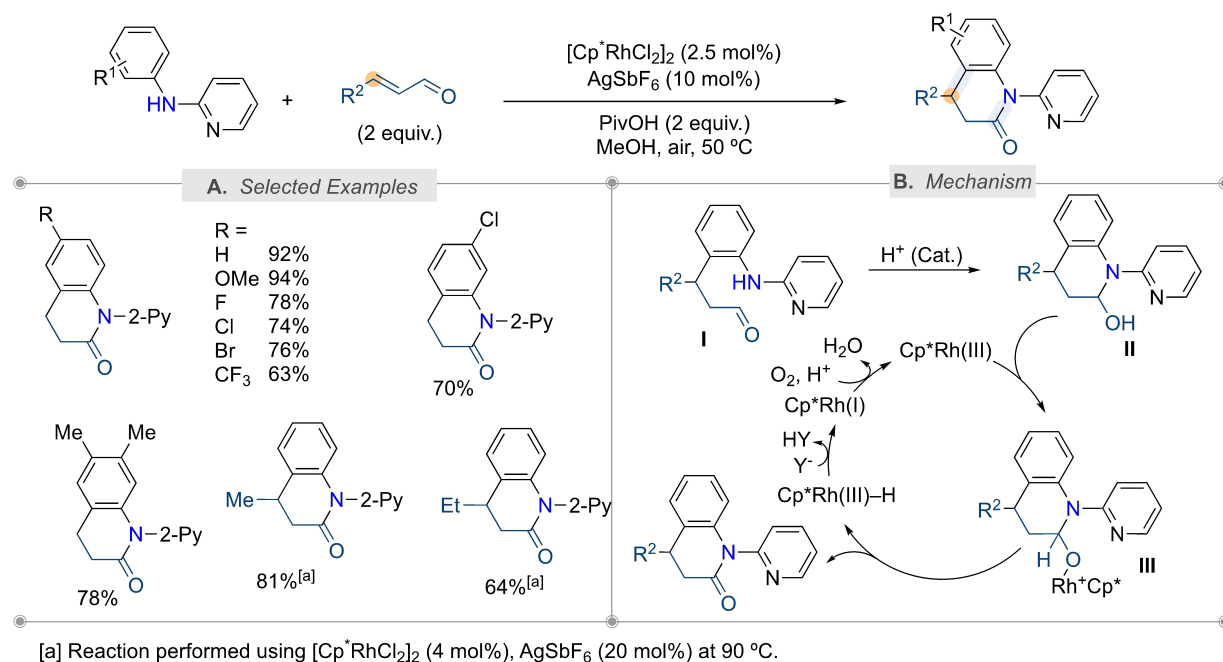
In 2017, Huang and co-workers reported the C–H bond annulation of *N*-arylpyridin-2-amines with α,β -unsaturated aldehydes for synthesizing dihydroquinolines using rhodium catalysis (Scheme 43).^[55] The optimized conditions, namely $[\text{Cp}^*\text{RhCl}_2]_2$ (2.5 mol%) and AgSbF_6 (10 mol%) in the presence of PivOH (2 equivalents) in MeOH at 50°C , tolerate various electron-withdrawing or electron-donating functional groups on the benzene rings of *N*-arylpyridin-2-amines. Most reactions were performed with acrylaldehyde, but 3-methyl and 3-ethyl propenals have also been employed. After the *ortho*-C–H bond alkylation of *N*-arylpyridin-2-amines catalyzed by Rh(III) in a regular catalytic cycle, the amino group of intermediate I intramolecularly adds to the carbonyl group, forming α -hydroxyl tetrahydroquinoline intermediate II. The ligand exchange of the $\text{Cp}^*\text{Rh}(\text{III})$ complex with intermediate II leads to rhodium intermediate III. Then, β -hydride elimination of intermediate III results in tetrahydroquinoline and $\text{Cp}^*\text{Rh}(\text{III})\text{H}$. After the addition of anion Y^- onto $\text{Cp}^*\text{Rh}(\text{III})\text{H}$, losing HY by reductive-elimination leads to $\text{Cp}^*\text{Rh}(\text{I})$, which is oxidized into $\text{Cp}^*\text{Rh}(\text{III})$ by oxygen in the air.



Scheme 42. Rh(III)-catalyzed synthesis of isoquinolones by annulation of *N*-methoxyamides and nitroalkenes.

5.2. C–H Bond Functionalization Using Internal N–O or N–N Bonds as Oxidants, or Redox-Neutral Conditions

Guimond and Fagnou pioneered an external-oxidant-free, rhodium-catalyzed synthesis of isoquinolones through C–H activation of *N*-methoxybenzamides, followed by coupling them with internal alkynes or alkenes (Scheme 44).^[56] They shown that this C–H bond annulation reaction, can be performed in higher yield at room temperature with low catalyst loading (0.5 mol%) using *N*-methoxy or *N*-(pivaloyloxy)benzamides as starting materials. The reaction demonstrates broad applicability, accommodating a variety of substituents on the benzamides and a wide range of both internal and terminal alkynes, including propargyl alcohol. Additionally, various alkenes, such as dienes, are also compatible. Although the catalytic cycle was initially unclear, it is now understood that following reductive elimination, Rh(I) under-



Scheme 43. Rhodium(III)-catalyzed C–H bond annulation of *N*-arylpiperidin-2-amine with α,β -unsaturated aldehydes.

goes oxidative N–O addition to regenerate to the active Rh(III) species, a mechanism akin to that depicted in Scheme 18B.

In 2011, during their investigation on Rh(III)-catalyzed directed C–H bond olefination using an oxidizing directing group, Glorius and co-workers succeeded in preparing tetrahydroisoquinolones (Scheme 45).^[57] In the presence of 2.5 mol% of [Cp*⁺RhCl₂]₂, 30 mol% CsOPiv, and 20 mol% PivOH in MeOH, *N*-(pivaloyloxy)benzamides were annulated using mere alkenes. This reaction works with acrylates and styrenes. Moreover, under standard reaction conditions, gaseous ethylene (5 bar) has also been employed as an alkene coupling partner.

It should be noted that this transformation was later investigated in asymmetric catalysis using biochemically modified cyclopentadienyl (Cp) ligands to create an artificial metalloenzyme, as demonstrated by Ward and Rovis.^[58] Additionally, the use of Rh(III) surrounded by a chiral cyclopentadienyl ligand was successfully demonstrated by Cramer.^[59]

In 2016, You and colleagues demonstrated the application of isoquinolones synthesis to *N*-methoxyferrocenecarboxamide for the construction of molecules with planar chirality (Scheme 46).^[60] Initially, they conducted the reaction in a racemic fashion using various internal alkynes. Furthermore, they presented an example using a chiral rhodium(III) catalyst, achieving a modest enantiomeric excess (ee) value of 46%.

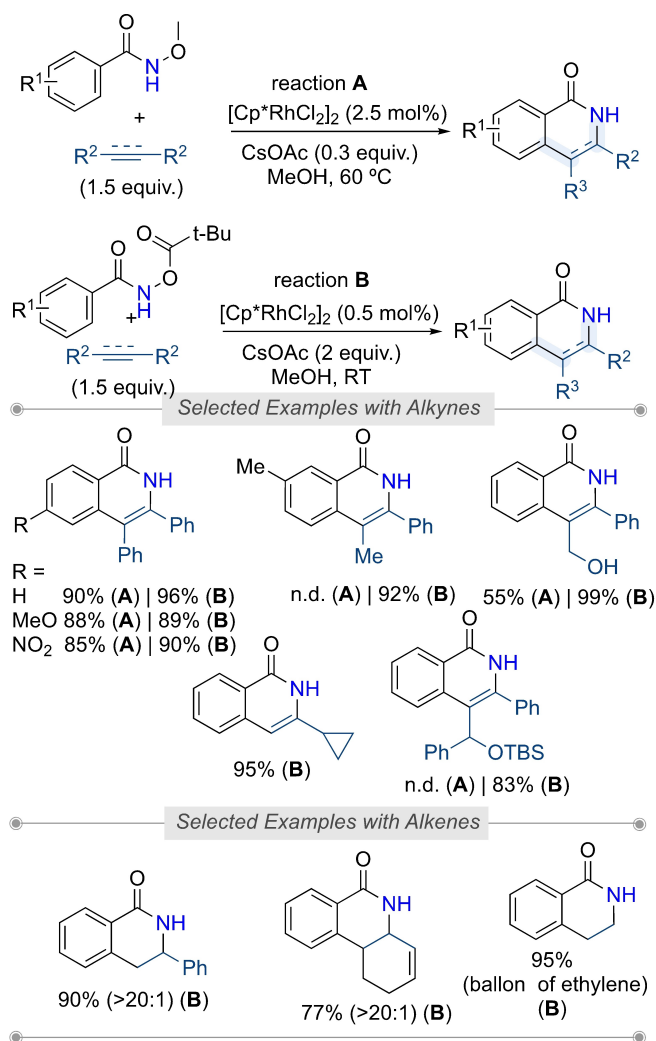
By 2022, this transformation was revisited, and they successfully obtained ferrocenes with planar chirality, achieving ee values of up to 99%. This improvement was attributed to a specifically designed catalyst, namely trisubstituted chiral cyclopentadienyl (Cp)-derived Rh complexes, combined with a sterically hindered carboxylic acid (1-MeCHA = 1-methylcyclohexane-1-carboxylic acid) as an additive (Scheme 47).^[61] The

absolute configuration of one of the product was assigned as *R_p* by X-ray diffraction analysis of an enantiopure sample.

In 2022, a new study focused on employing propargyl alcohols in Rh(III)-catalyzed C–H bond annulation of *N*-(pivaloyloxy)benzamides (Scheme 48).^[62] Interestingly, the authors demonstrated that a hydrogen bonding network between propargylic alcohol and pivaloyloxy groups directs the regioselectivity. For example, when using 1-phenylbut-2-yn-1-ol, the opposite regioselectivity was achieved. Regarding the scope of the reaction, it proves to be very broad once again.

A study by Zhang, Fan, and their colleagues has demonstrated that when 4-hydroxy-2-alkynoates are employed as annulative agents, an interesting chemical behavior is observed (Scheme 49).^[63] Not only do they participate in Rh(III)-catalyzed C–H bond annulation, but they also undergo lactonization in a non-catalyzed pathway. This additional reaction leads to the formation of tricyclic compounds, namely furo[3,4-*c*]isoquinoline-1,5(3*H*,4*H*)-diones. The scope of these reactions is quite broad, indicating a significant versatility of this method for synthesizing complex molecular structures.

In 2021, Li and co-workers successfully synthesized isoquinolones from *N*-iminopyridinium ylides and alkynes, catalyzed by [Cp*⁺RhCl₂]₂ (Scheme 50).^[64] Remarkably, the process eliminates the need for additional oxidants, as the catalyst is self-regenerating through oxidative addition of the N–N bond and subsequent release of pyridine. The reaction's scope is broad, tolerating various substituents like MeO, Me, I, Br, Cl, F, CF₃, and OCF₃ on the *N*-iminopyridinium ylides, including those at the *ortho*-position. Furthermore, the reaction is not restricted to 1,2-diaryllkynes, as dialkylalkynes and ynamides have also been successfully converted into isoquinolones. Through a series of control experiments, the authors suggested a plausible mecha-

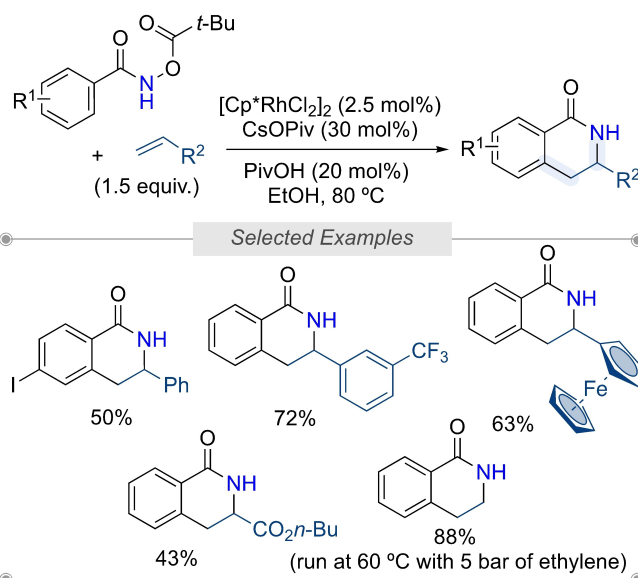


Scheme 44. *N*-Methoxybenzamides or *N*-(pivaloyloxy)benzamides as internal oxidants in the Rh(III)-catalyzed synthesis of isoquinolones.

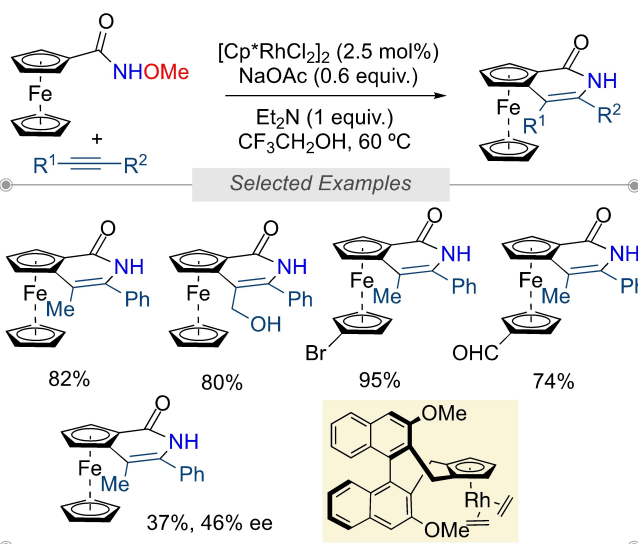
nism, illustrated in Scheme 50B. Initially, the active Rh(III) catalyst engages with the *N*-iminopyridinium ylide, triggering *ortho*-C–H bond cleavage to form a five-membered rhodacycle **A**. This is followed by the insertion of the alkyne to create rhodium intermediate **B**. Subsequent metal migration and C–N bond formation led to intermediate **C**, whose protonation yields the target isoquinolones, accompanied by the release of a pyridine molecule.

5.3. C–H Bond Functionalization under Redox-Free Conditions

In a 2015 study, Wang and co-workers employed a redox-free approach by utilizing Rh(III)-catalyzed C–H bond activation coupled with carbene migratory insertion to synthesize isoquinolones from *N*-methoxybenzamide, achieving high yields with excellent regioselectivity using the $[\text{Cp}^*\text{RhCl}_2]_2/\text{AgSbF}_6$ catalyst system (Scheme 51).^[65] This redox-free condition was made possible thanks to the carbene insertion mechanism. *N*-

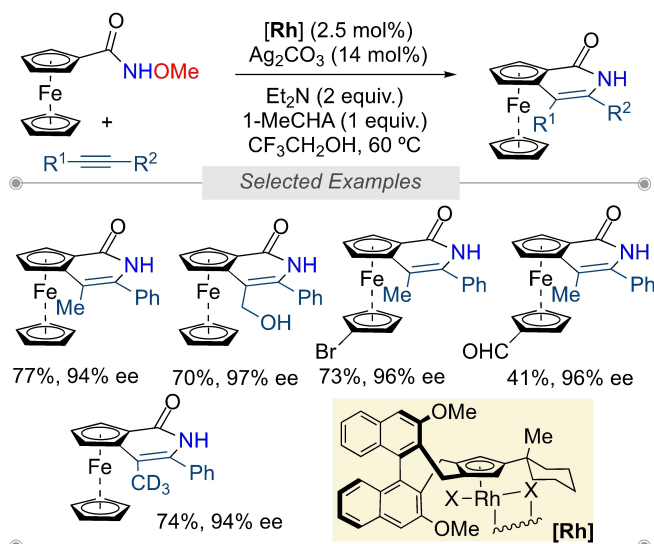


Scheme 45. Rh(III)-catalyzed C–H bond annulation of *N*-(pivaloyloxy)benzamides with alkenes for tetrahydroisoquinolones synthesis.

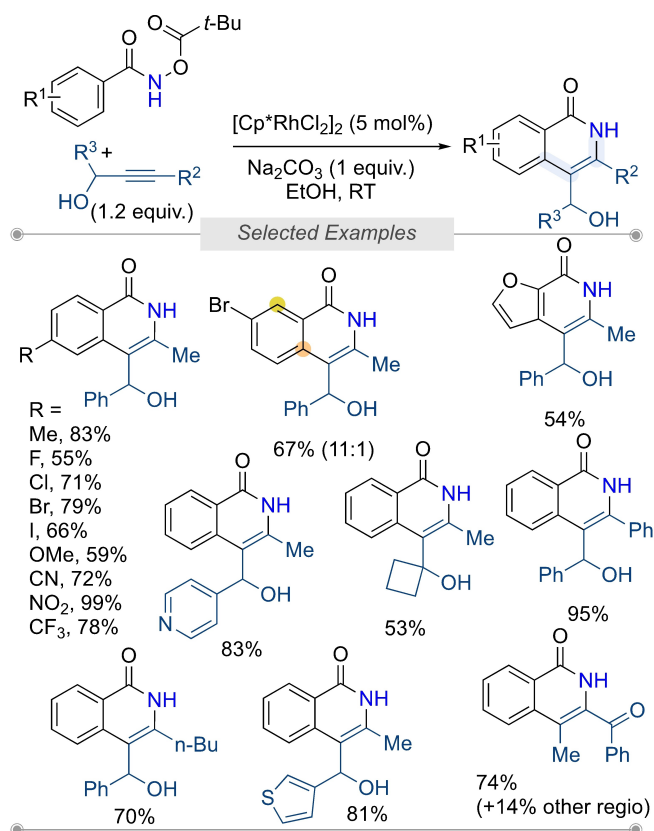


Scheme 46. Synthesis of ferrocene-based pyridinones through Rh(III)-catalyzed C–H bond annulation with alkynes.

Methoxybenzamides with electron-donating groups at the *para*-position gave high yields, while reaction with those holding an electron-withdrawing group resulted in significantly lower yields. Additionally, diazo substrates generally produced moderate to good yields, and unsymmetrical diketones under optimal conditions exclusively produced one regioisomer with high yields. The authors proposed a mechanism starting with *N*-methoxybenzamide reacting with $\text{Cp}^*\text{Rh(III)}$ through directed C–H cleavage to form rhodacycle **I**. This is followed by the generation of Rh(III)–carbene **II**, whose migratory insertion into the Rh–C bond yields a rhodacycle intermediate **III**. Protonolysis of this intermediate releases the Rh(III) catalyst, initiating a new



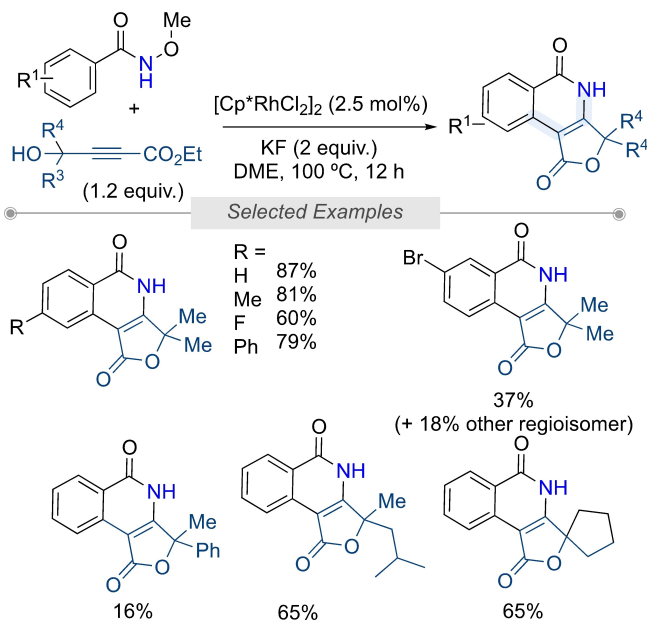
Scheme 47. Synthesis of chiral ferrocene-based pyridinones through Rh(III)-catalyzed C–H bond annulation with alkynes.



Scheme 48. Propargyl alcohols as annulative agents in Rh(III)-catalyzed synthesis of isoquinolones.

catalytic cycle. Tautomerization of the resulting intermediate leads to ring-closing elimination of water to produce the final product.

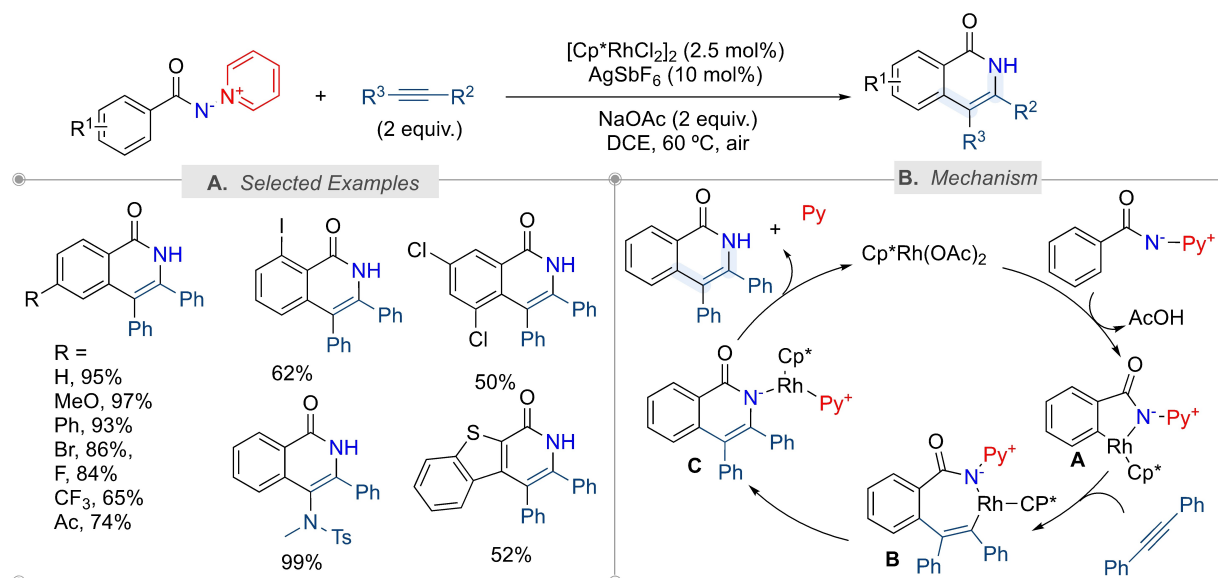
In 2017, Bolm's group pioneered the use of α -chloroaldehydes as alkyne equivalents in Rh(III)-catalyzed syntheses of



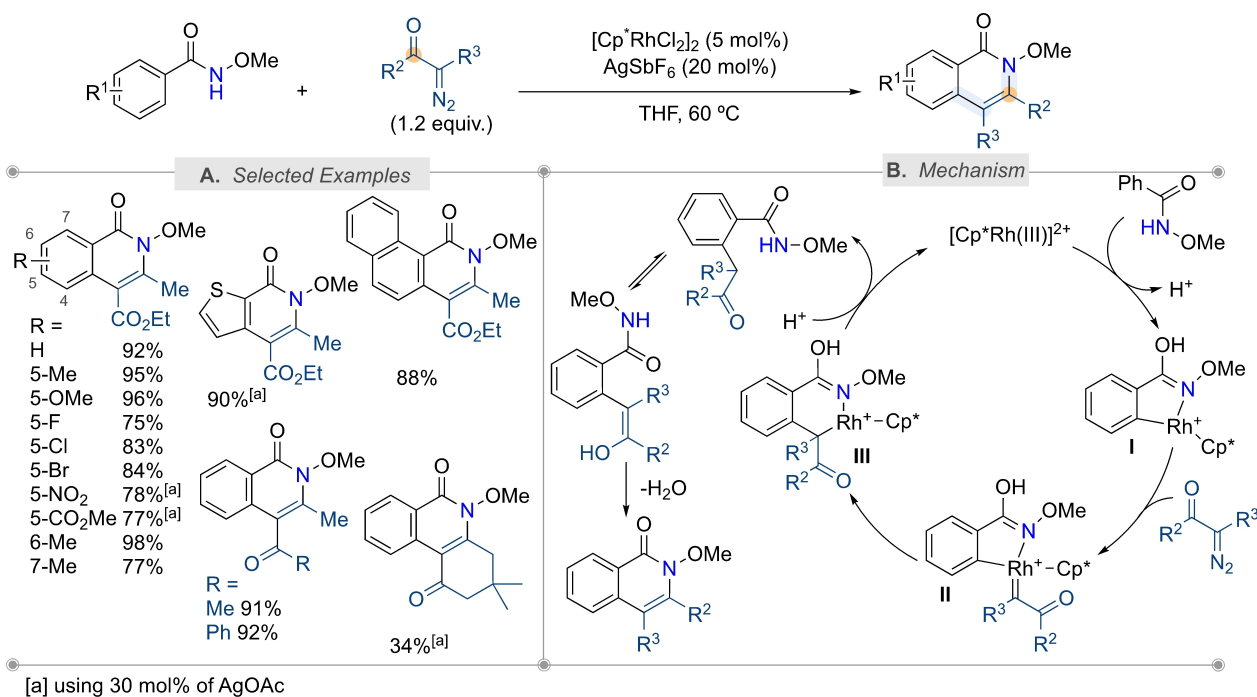
Scheme 49. 4-Hydroxy-2-alkynoates as annulative agents in Rh(III)-catalyzed synthesis of furo[3,4-c]isoquinoline-1,5(3H,4H)-diones.

isoquinolones from *N*-methoxybenzamides (Scheme 52).^[66] This reaction operated under redox-free conditions, requiring only a mixture of bases (NaOAc and NaHCO₃) in addition to the rhodium catalyst, and was carried out using microwave (MW) energy. The scope of benzamides employed was broadly similar to previous methods, and successfully incorporating various 2-chloroaldehydes, including unbranched alkyl-substituted substrates. However, the authors did not propose any catalytic cycles for this reaction.

In 2024, by employing α -(pseudo)halo ketones as annulative reagents, Glorius group succeeded in preparing isoquinolones (Scheme 53).^[67] Using this annulative agent, no more oxidant is required. Various α -(pseudo)halo ketones were evaluated, and the best results were obtained with OMs or OTs groups. Diversely substituted *N*-OMe substituted amides were employed. However, the OMe group was critical as no reaction occurred with other *N*-substituted amides (with H, Me, Ph, OPiv). Besides the aryl ketones, they found that a dialkyl ketone derivative, 2-oxopropyl tosylate, also worked efficiently. A classical mechanism based on a CMD process catalyzed by Rh(III) is proposed for the generation of I. However, the cyclization reaction occurred in a non-catalyzed process. Depending on the substitution patterns of the amide, the enols II could be more favored and slower down the cyclization process. Then, an intramolecular attack of the nitrogen atom to ketone affords III, which provides the desired product after dehydration.



Scheme 50. *N*-Iminopyridinium ylides as internal oxidants in the Rh(III)-catalyzed synthesis of isoquinolones.

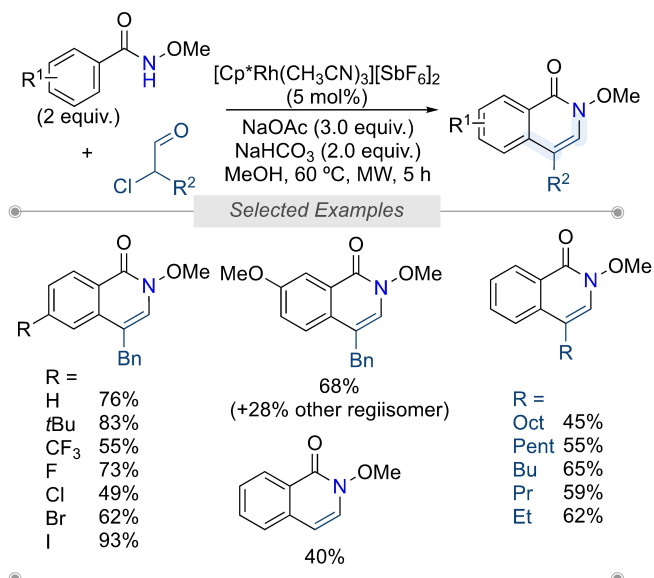


Scheme 51. Rh(III)-catalyzed C–H bond annulation of amides with α -diazo ketones as annulating agents.

6. Preparation of Quinolones and Related Heterocyclic Compounds

In this section, we explore the C–H bond annulation of aniline derivatives, focusing on how the choice of directing groups, redox strategies, and annulating agents significantly influences the synthesis outcomes. The selection of a suitable directing group is pivotal for controlling site selectivity and reaction efficiency in C–H activation, enabling the formation of complex heterocyclic structures. Furthermore, the redox conditions and

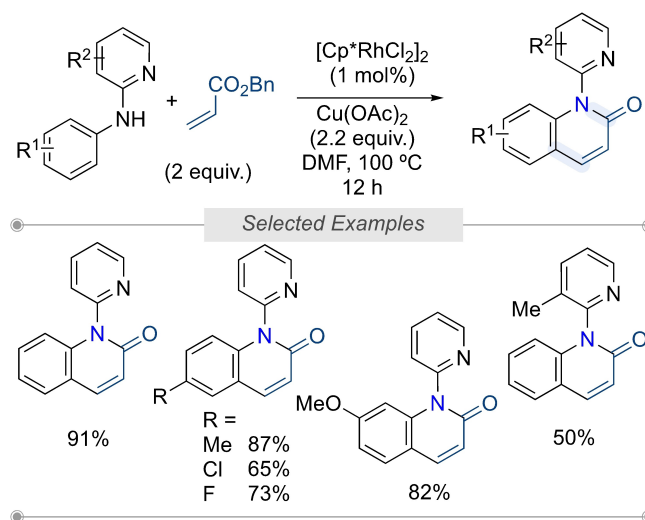
the type of annulating agent used can greatly affect the reaction pathway and the variety of heterocycles produced. These factors, when judiciously manipulated, allow for tailored synthetic approaches to generate diverse heterocyclic frameworks, showcasing the intricate interplay between directing groups, redox environment, and annulating agents in the annulation process. This detailed examination will highlight the versatility and adaptability of these methods in constructing sophisticated molecular architectures from simple aniline derivatives.



Scheme 52. Microwave-assisted synthesis of isoquinolones by Rh(III)-catalyzed annulation of *N*-methoxyamides with α -chloroaldehydes.

7.1 C–H Bond Functionalization under Oxidative Conditions

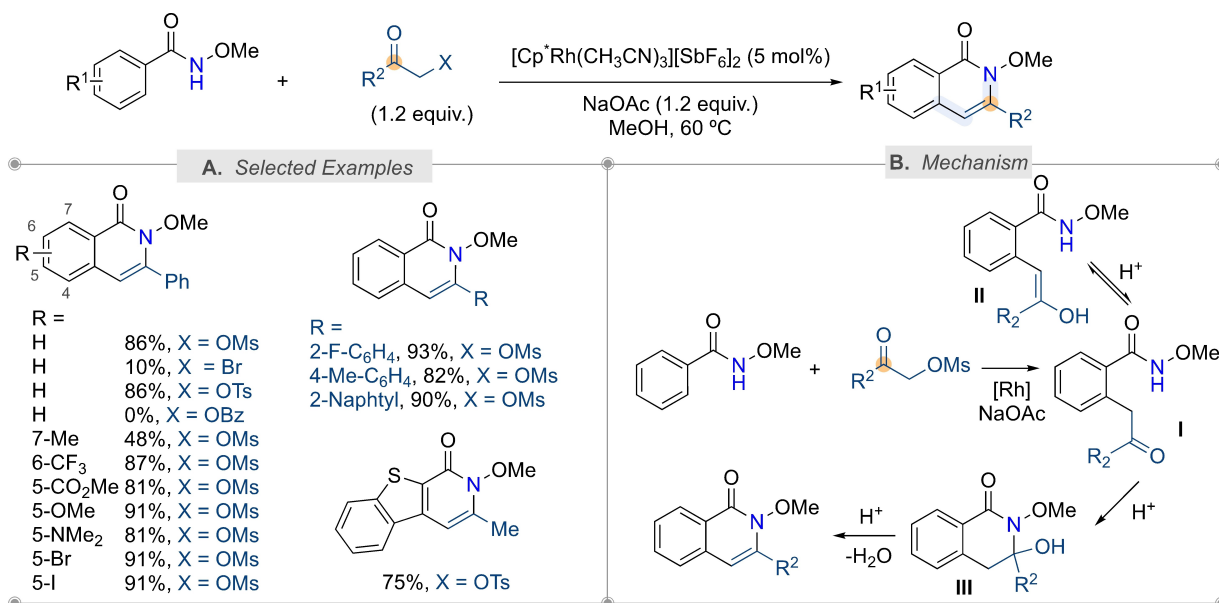
In 2010, Li and co-workers reported the oxidative C–H bond annulation of *N*-aryl-2-aminopyridines with benzylacrylate to generate quinolone scaffolds (Scheme 54).^[10] The optimized conditions were found using 1 mol% $[\text{Cp}^*\text{RhCl}_2]_2$ in the presence of 2.2 equivalents of $\text{Cu}(\text{OAc})_2$ as the oxidant in DMF at 100 °C over 12 h. Other alkyl acrylates have been successfully employed to deliver the same products. It should be mentioned that replacing benzylacrylate with styrene delivered the mono- and bis-alkenylated products.



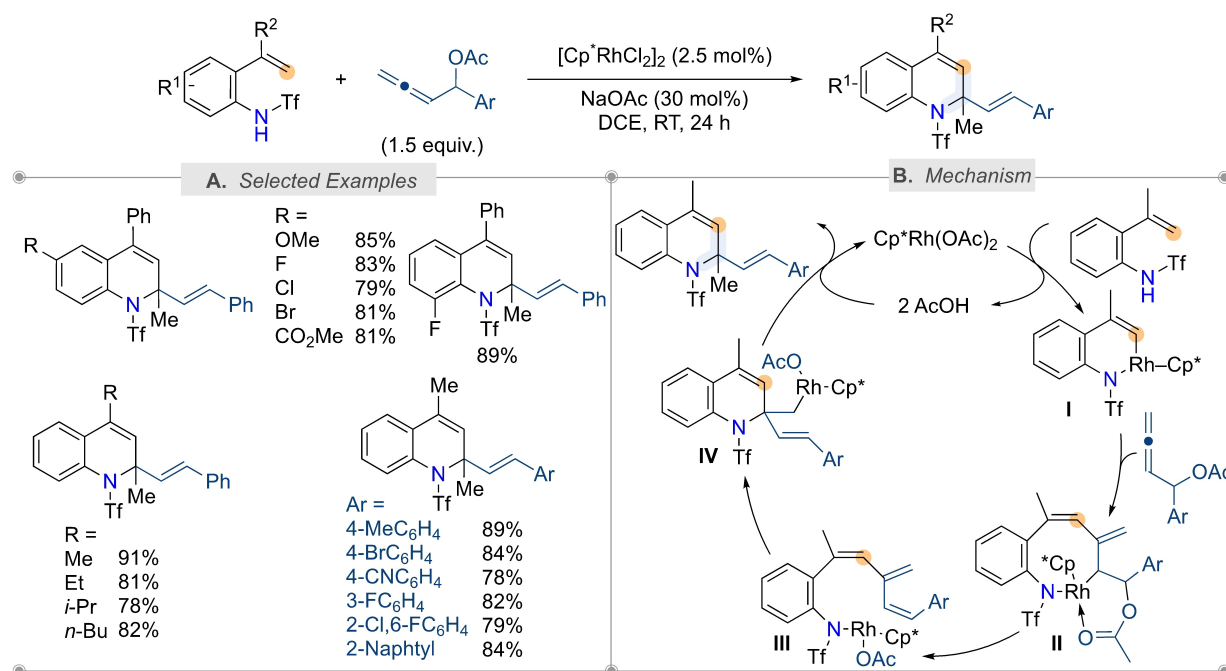
Scheme 54. Rh(III)-catalyzed oxidative C–H bond annulation of *N*-aryl-2-aminopyridines with acrylates.

7.1 C–H Bond Functionalization under Redox-Free Conditions

In 2022, Volla and co-workers reported the synthesis of dihydroquinolines from alkenyl anilides and allenyl acetates (Scheme 55).^[68] This formal [5 + 1] annulation of 2-alkenylanilides is catalyzed by 2.5 mol% of $[\text{Cp}^*\text{RhCl}_2]_2$, and 30 mol% of NaOAc in DCE at room temperature. Diversely substituted 2-alkenylanilides have been coupled with phenyl allene to afford the desired 1,2-dihydroquinoline derivatives in good to excellent yields ($\text{R} = \text{Me}, \text{OMe}, \text{F}, \text{Cl}, \text{Br}, \text{CO}_2\text{Et}$). Regarding the alkenyl substituent fragment, methyl, ethyl, *i*-propyl, *n*-butyl and phenyl derivatives were successfully used; while mere vinyl substituted aniline ($\text{R} = \text{H}$) and trisubstituted alkenylanilides did



Scheme 53. Rh(III)-catalyzed C–H bond annulation of amides with α -(pseudo)halo ketones as annulating agents.



Scheme 55. Rh(III)-catalyzed C–H bond annulation of 2-alkenylanilides and 2-alkenylphenols with allenyl acetates.

not show any reactivity for the annulation. Moreover, electron-donating and -withdrawing substituents at the *ortho*-, *meta*- and *para*-positions of the aryl ring of allenyl acetate were well tolerable, demonstrating the generality of this method. Based on deuterium-labeling, competitive, and control experiments, the authors have proposed the catalytic cycle depicted in Scheme 55B. First, vinyl C–H activation to form six-membered rhodacycle I occurs, followed by regioselective 2,3-migratory insertion of allene to give the eight-membered Rh(III) intermediate II. Subsequent β -oxygen elimination from species II gives the diene intermediate III, which undergoes intramolecular nucleophilic addition of the nitrogen-rhodium bond resulting in [5 + 1]-annulation. Finally, protonation of IV provides the desired 1,2-dihydroquinolines and regenerates the active Rh(III) catalyst.

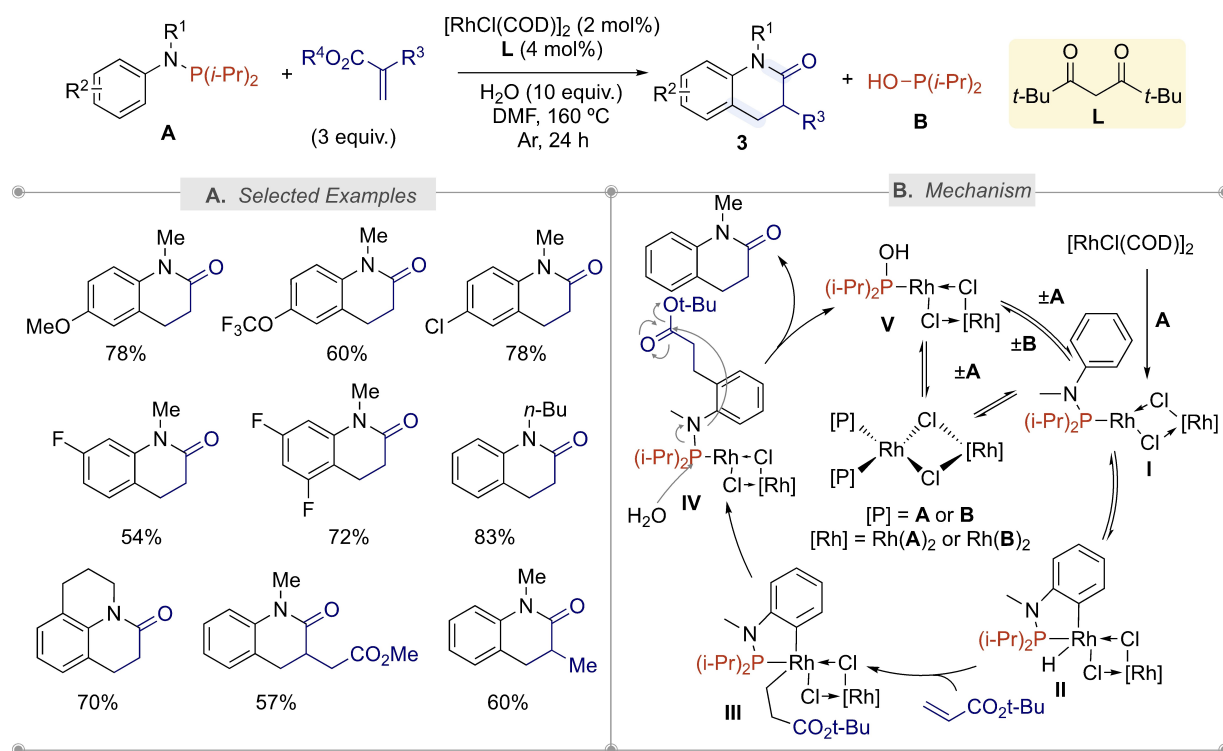
In 2023, our team reported the synthesis of dihydroquinolones from anilines and acrylates using Rh(I) catalysis (Scheme 56).^[69] This work built on the discovery that trivalent phosphorus (P(III)) serves as a directing group for C(sp²)–H bond functionalization in phosphines^[70] or indoles,^[71] combined with the observation that P(III) promotes alkylation reactions with acrylates under Rh(I) catalysis.^[72] Utilizing this knowledge, we used *N*-arylphosphanamines as starting materials. These compounds undergo *ortho*-alkylation with acrylates, followed by an *in situ* amidation reaction subsequent to N–P bond hydrolysis. The reaction tolerates various substituent on the anilines, including OMe, OCF₃, Cl, F. We have also expanded this method to α -substituted acrylates, such as dimethyl 2-methylsuccinate and methyl methacrylate. Through comprehensive mechanistic and kinetic studies, we proposed the following catalytic cycle reproduced in Scheme 56B. [RhCl(COD)]₂ complex initially reacts with phosphanamine A, forming the active

catalytic species I. This is followed by oxidative addition, resulting in the Rh(III)–H hydride complex II. The acrylate then undergoes a 1,2-insertion to form intermediate III. Reductive elimination subsequently generates compound IV. In the presence of water, the coordinated, functionalized phosphanamine undergoes hydrolysis, yielding the desired product along with the Rh complex V, which is associated with hydroxydiisopropylphosphane (B). The next catalytic cycle starts by a ligand exchange between B and A to give I. However, V or I may react with phosphine derivatives B or A in an inhibitory manner to form nonproductive coordination complexes $[\{\text{Rh}(\text{B})_2(\mu_2\text{-Cl})\}_2]$ and $[\{\text{Rh}(\text{A})_2(\mu_2\text{-Cl})\}_2]$.

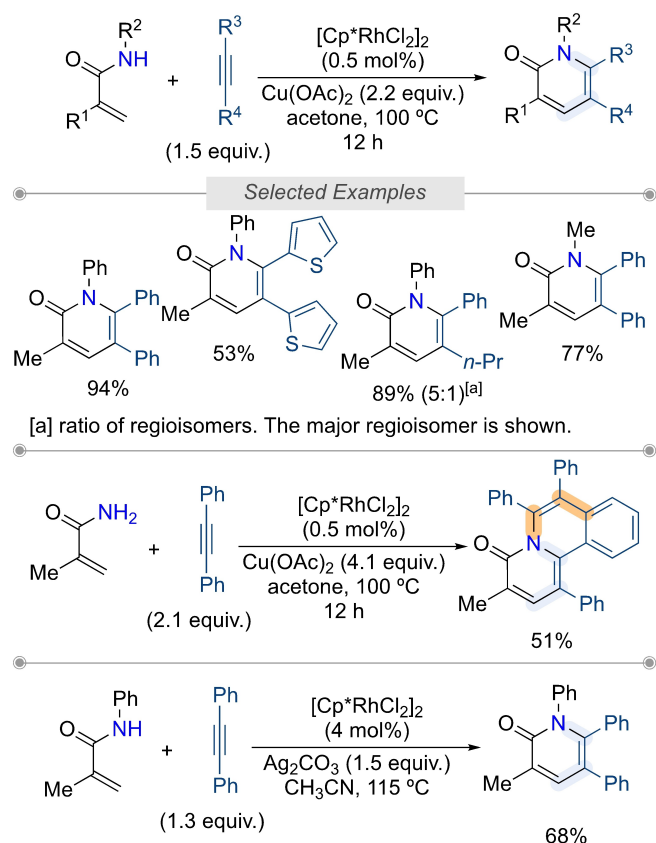
8. Preparation of Pyridone Scaffolds

8.1. C–H bond Functionalization under Oxidative Conditions

In 2010, Li and co-workers reported an elegant method to prepare 2-pyrrolidones from acrylamides and alkynes through Rh(III)-catalyzed C–H bond annulation (Scheme 57, top).^[11] Interestingly the C–H bond activation occurred exclusively on the vinylic C–H bond using 0.5 mol% [Cp*RhCl₂]₂ catalyst while using cationic Rh(III) complex afforded the functionalization of the aryl C–H bond.^[11] Again Cu(OAc)₂ was employed as the terminal oxidant to promote the C–N bond formation. In addition to the coupling of alkynes with secondary acrylamides, the coupling of primary methacrylamides with an excess of 1,2-diphenylacetylene gave a tricyclic product as a result of a second oxidative insertion of the second equivalent of 1,2-diphenylacetylene (Scheme 57, middle). The copper oxidant can be also replaced by Ag₂CO₃ (Scheme 57, bottom).^[52] This C–H



Scheme 56. Rh(I)-catalyzed cascade C(sp²)-H bond alkylation – amidation of anilines: phosphorus as traceless directing group.

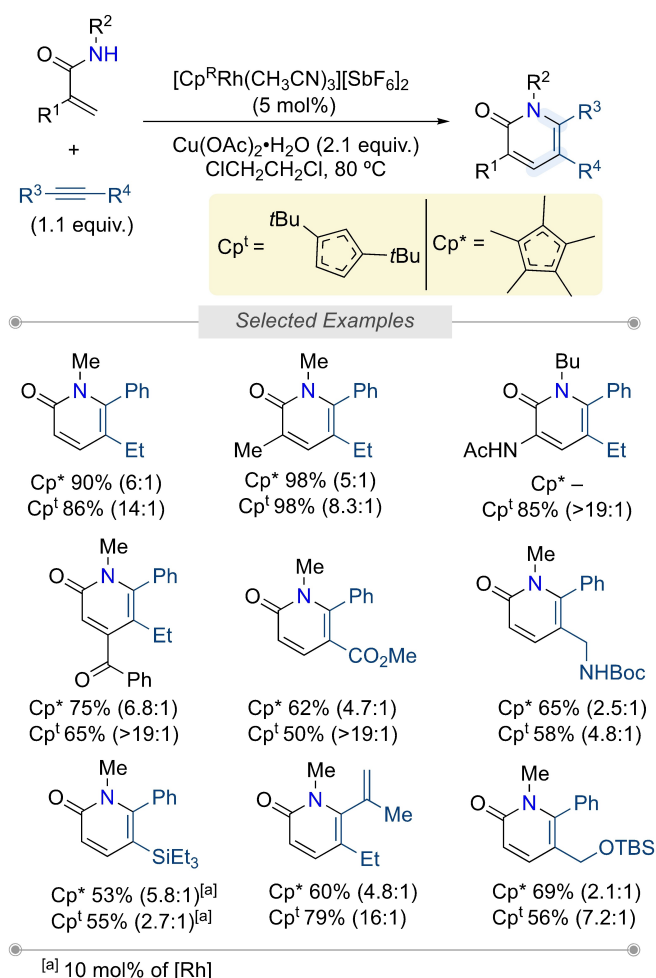


Scheme 57. Synthesis of 2-pyridones via Rh(III)-catalyzed oxidative C-H bond annulation of acrylamides with alkynes.

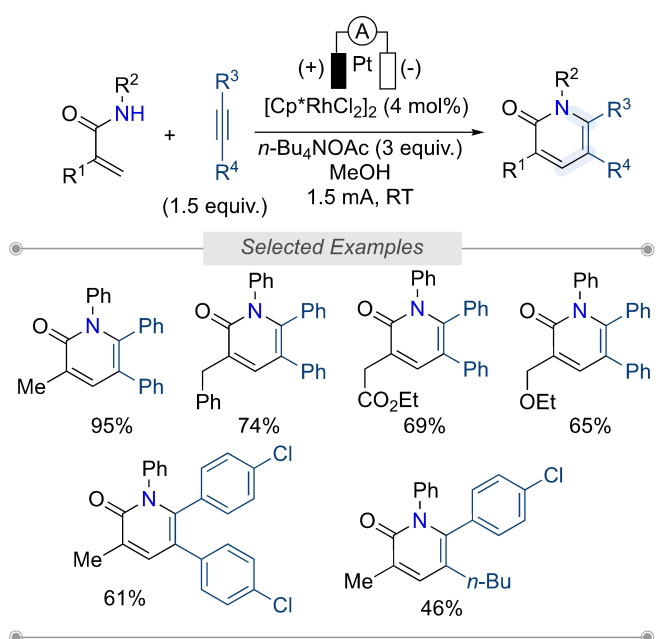
bond annulation strategy, initially targeting alkenyl C-H bonds, was later adapted by Park for intramolecular applications in the total synthesis of (±)-septicine, (±)-antofine, and (±)-tylophorine, using an internal N-O bond as the oxidant.^[73] However, this intramolecular approach falls outside the scope of this review and will not be explained in detail.

In 2011, Rovis and co-workers highlighted the limited exploration of Cp ligands in Rh(III)-catalyzed C-H bond activation, which prompted them to investigate the role of these ligands in the annulation of acrylamides with alkynes (Scheme 58).^[74] Compared to Cp^{*}Rh(III), the use of a cationic rhodium complex featuring a 1,3-di-*tert*-butyl cyclopentadienyl (Cp[†]) ligand significantly enhances the regioselectivity without sacrificing yield when using non-symmetrical internal alkynes. Extensive studies on the reaction scope demonstrated robust tolerance for various substitutions on the acrylamide and a range of substitution patterns on the alkynes. This is particularly notable for pyridone formation, including substitutions at the nitrogen position. Through detailed mechanistic investigations, the authors elucidated that the improved regioselectivity observed with Cp[†] is due to the important steric differentiation between a *tert*-butyl group and a hydrogen atom during the coordination and insertion steps of the alkyne. This study not only sheds light on the impact of ligand design on catalytic performance but also expands the synthetic utility of Rh(III)-catalyzed transformations.

In 2021, Hong, Mei, and co-workers revolutionized this transformation by employing an environmentally friendly electrochemical process (Scheme 59).^[75] This innovation elimi-



Scheme 58. Effect of Cp ligand design in Rh(III)-catalyzed C–H bond annulation of acrylamides with alkynes.



Scheme 59. Synthesis of 2-pyridones via Rh(III)-catalyzed electrochemical C–H bond annulation of acrylamides with alkynes.

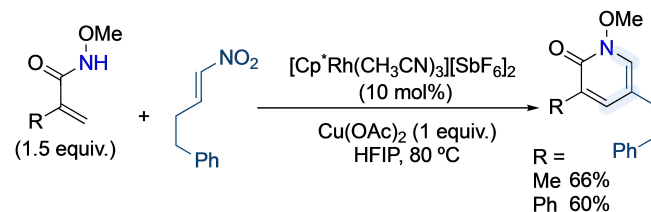
nated the need for stoichiometric copper oxidants. The optimal conditions involved using $[\text{Cp}^*\text{RhCl}_2]_2$ as the precatalyst, $n\text{-Bu}_4\text{NOAc}$ as the electrolyte, and MeOH as the solvent. The reaction was conducted in an undivided cell with two platinum electrodes, utilizing constant-current electrolysis at 1.5 mA for seven hours at 60 °C. This method proved versatile, tolerating acrylamides with various functional groups, including alkyl, ester, ether, and aryl. Under these standard conditions, α -pyridones were obtained in moderate to good yields using both symmetrical and unsymmetrical internal alkynes.

Nitroalkenes, in conjunction with $\text{Cu}(\text{OAc})_2$, can also be used as analogues to alkynes in Rh(III)-catalyzed C–H bond annulation of acrylamides for the synthesis of pyridones, as demonstrated by Ward and Ellman (Scheme 60).^[54] However, so far, only two examples have been documented: the coupling of α -methyl or α -phenyl N -methoxyacrylamide with (*E*)-(4-nitrobut-3-en-1-yl)benzene.

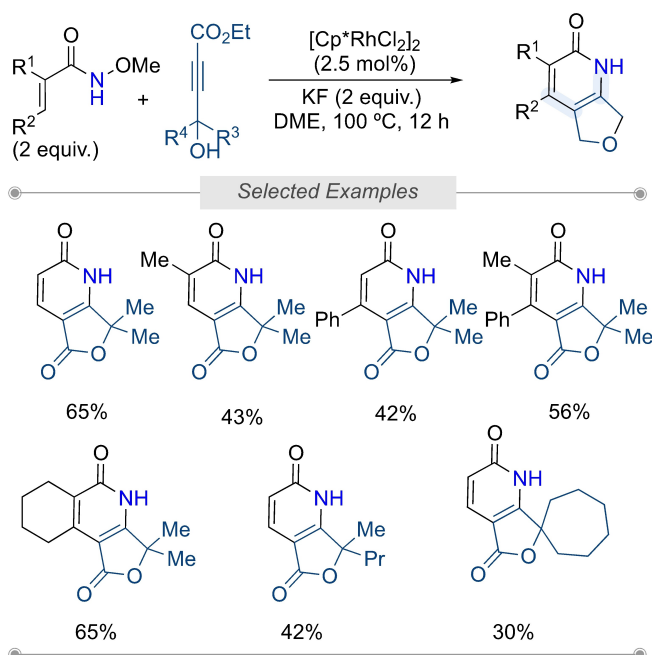
8.2. C–H Bond Functionalization Using Internal N–O or N–N Bonds as Oxidants, or Redox-Neutral Conditions

Rh(III)-catalyzed C–H bond annulation of acrylamides for synthesizing 2-pyridones can also be conducted using an N–O bond as an internal oxidant, thus avoiding the use of $\text{Cu}(\text{OAc})_2$. Notably, no studies were conducted using simple alkynes; instead, Zhang, Fan, and their colleagues employed 4-hydroxy-2-alkynoates, which facilitated the synthesis of furo[3,4-*b*]pyridine-2,5(1*H*,7*H*)-diones (Scheme 61).^[63] Several α -substituted, β -substituted, and α,β -disubstituted acrylamides participated smoothly in this reaction. The nature of the substituents, including methyl, propyl, phenyl, and 4-methylphenyl, did not significantly impact the efficiency of the reaction. Moreover, disubstituted acrylamides typically exhibited higher efficiencies than their monosubstituted counterparts. Intriguingly, cyclic acrylamides such as N -methoxycyclopent-1-ene-1-carboxamide and N -methoxycyclohex-1-ene-1-carboxamide were effectively integrated into this two-fold cyclization process. The study also highlighted a variety of diversely substituted 4-hydroxy-2-alkynoates for efficient complex structure formation.

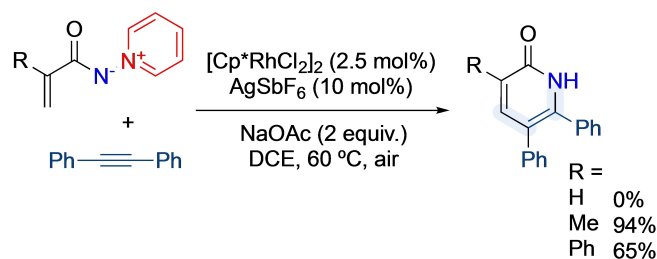
During their investigation into the synthesis of isoquinolones from N -iminopyridinium ylides, Li and co-workers utilized Rh(III) C–H bond annulation with alkynes, employing the N–N bond as an internal oxidant. They also extended this reactivity to synthesize pyridones, using N -iminopyridinium ylides derived from acrylic acids (Scheme 62).^[64] However, this method was



Scheme 60. Synthesis of 2-pyridones via Rh(III)-catalyzed C–H bond annulation of acrylamides with nitroalkenes.



Scheme 61. Rh(III)-catalyzed cascade reactions of vinylic *N*-alkoxyamides with 4-hydroxy-2-alkynoates.



Scheme 62. *N*-Iminopyridinium ylides as internal oxidants in the Rh(III)-catalyzed synthesis of pyridones.

successfully demonstrated in only two cases: with α -CH₃ and Ph-substituted acrylic acid derivatives. Unfortunately, derivatives of both acrylic and cinnamic acids did not react under the conditions tested.

In 2020, Cramer and co-workers described a novel synthesis method for 4-fluoro-2-pyridones using 1-alkynyl triazenes as convenient fluoroalkyne surrogates (Scheme 63).^[76] Their protocol involves a Cp^{*}Rh(III)-catalyzed C–H annulation of *N*-(pivaloyloxy)acrylamides with 1-alkynyl triazenes, leveraging an N–O bond as the internal oxidant. This is followed by treatment with HF•pyridine, which efficiently yields a broad range of 4-fluoro-2-pyridones. The initial Rh(III)-catalyzed C–H bond annulation yields 4-triazenyl pyridines due to a Lossen rearrangement. This method accommodates both electron-poor and electron-rich aryl substituents on the acryl hydroxamates, consistently delivering the desired fluoropyridones with full Lossen rearrangement, high regioselectivity in alkyne incorporation, and good overall yields. Alkyl-substituted acryl hydroxamates have also proven to be effective reaction partners. They proposed a plausible catalytic cycle for the formation of the

rearranged 4-triazenyl-2-pyridones. Cyclometalation of *N*-(pivaloyloxy)acrylamides occurs via a CMD pathway, facilitated by the Cp^{*}Rh(III) catalyst, leading to the formation of rhodacyclopentene intermediate I. Migratory insertion of the triazenyl alkyne then forms 7-membered rhodacycle II. The high regioselectivity observed in the carboration step is likely due to the strong polarization of the alkyne, favoring metalation at the β -carbon atom. Typically, reductive elimination leads to non-rearranged products; however, in the case of acryl hydroxamates, a slower C–N bond formation relative to a competing Lossen rearrangement occurs, resulting in the presumed formation of isocyanate III. Subsequent intramolecular addition of the vinyl rhodium unit across the C–N bond forms intermediate IV. Final protolysis releases the rearranged product.

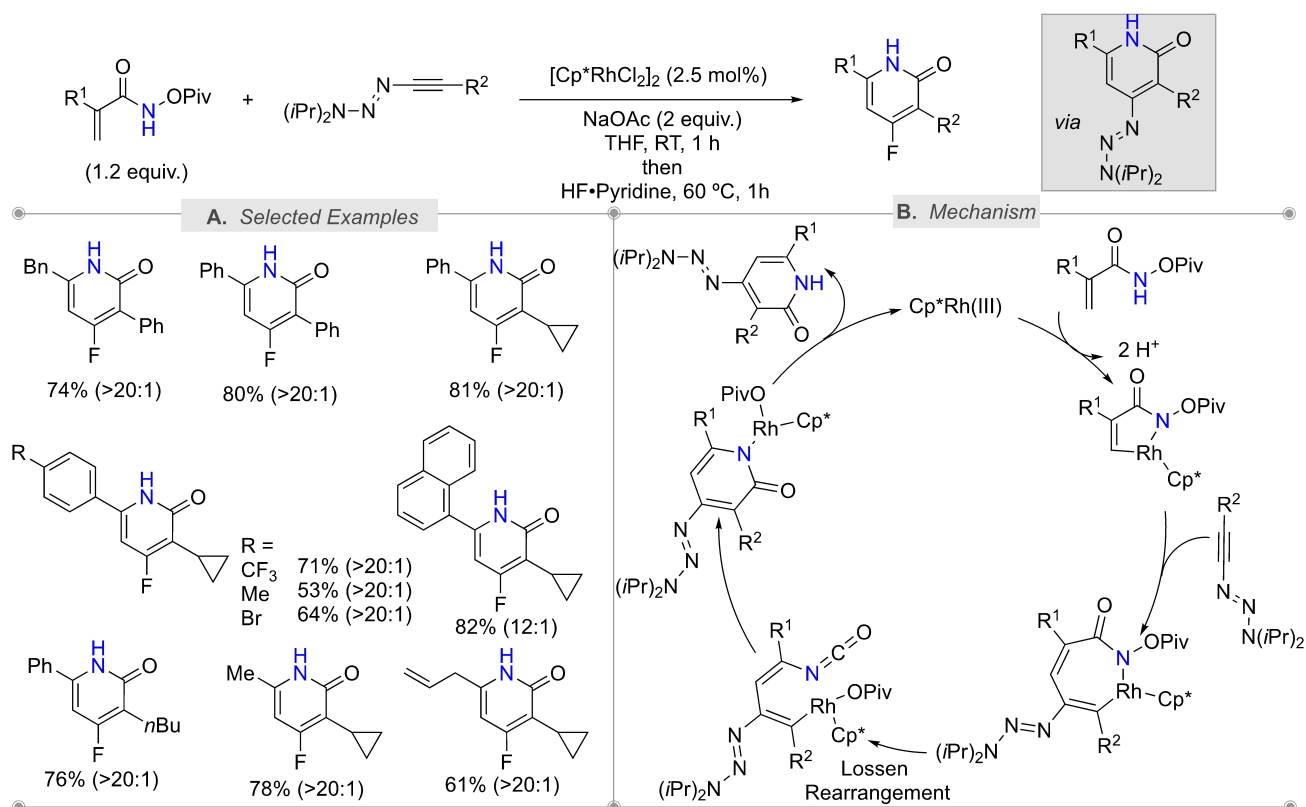
8.3. C–H Bond Functionalization under Redox-Free Conditions

In their research on the synthesis of isoquinolones through Rh(III)-catalyzed C–H bond activation and carbene migratory insertion, Wang and co-workers also explored the preparation of pyridones (Scheme 64).^[65] They achieved this by substituting *N*-methoxybenzamides with *N*-methoxymethacrylamide as the starting materials. In most cases, a catalytic amount of AgOAc is required to act as a base. The yields were generally very high in most cases, employing a mechanism akin to the one previously reported for isoquinolones (see, Scheme 51).

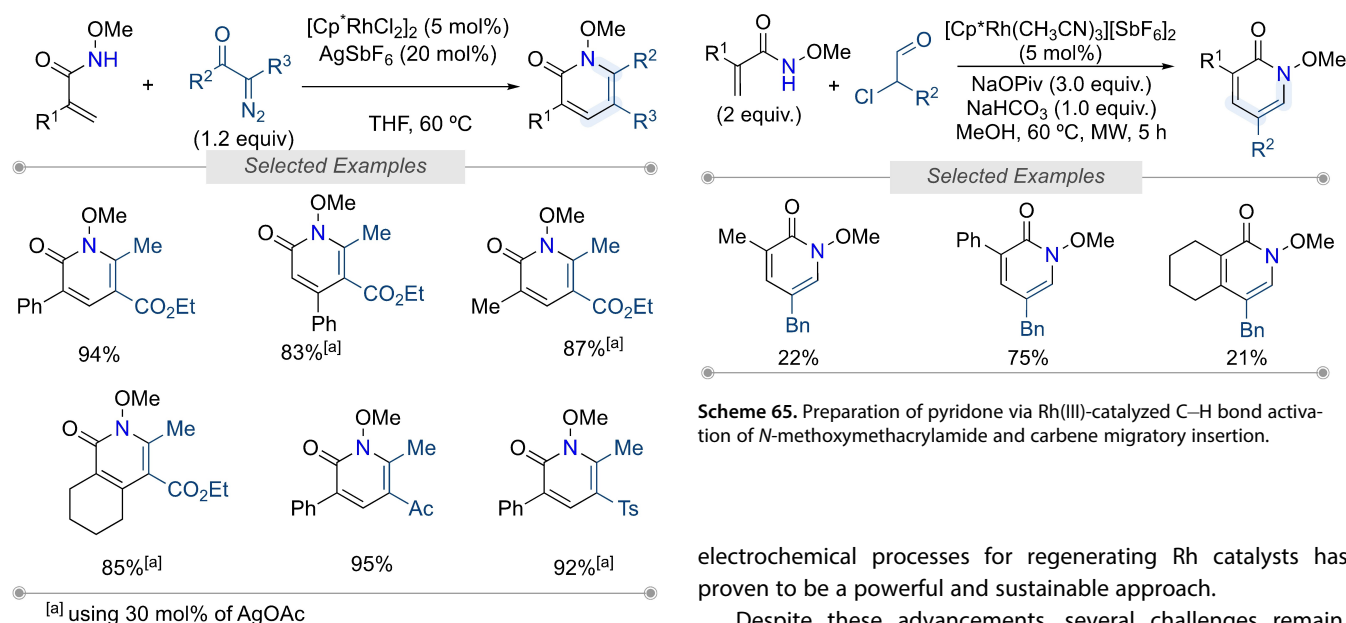
Bolm and colleagues successfully synthesized 2-pyridones from *N*-methoxyacrylamides via Rh(III)-catalyzed C–H bond functionalization, using α -chloroaldehyde as the annulating agent (Scheme 65).^[66] It is noteworthy that the reaction accommodates *N*-methoxyacrylamides with either α -alkyl or α -phenyl substituents, achieving better yields with phenyl substituents. However, no reaction occurred when this position is unsubstituted. Moreover, the scope of α -chloroaldehydes tested was limited to only 2-chloro-3-phenylpropanal.

9. Summary and Outlook

This review has underscored the recent advancements in Rh-catalyzed C–H bond annulation for synthesizing *N*-heterocycles from readily available materials. The significant contributions in this area have illustrated that novel and eco-friendly methods for heterocyclic scaffold synthesis, involving concurrent C–N/C–C bond formation initiated by C–H bond activation, pave the way for creating structurally diverse molecules. Rh-catalysis has been at the forefront of this chemistry, showing a wide tolerance for various functional groups, including X–halo bonds, particularly C–I bonds, which further allow post-modification processes to enhance molecular diversity. It is noteworthy that amide units have emerged as the most prevalent directing groups in controlling regioselectivity. Depending on the annulating partners, diverse *N*-heterocycles have been synthesized. Additionally, the design of specific oxidizing directing

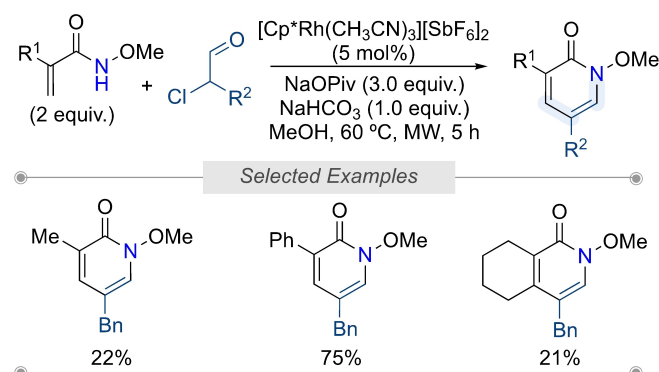


Scheme 63. Access to 4-fluoro-2-pyridones by a Rh(III)-catalyzed C–H bond activation – Lossen rearrangement – fluorination reaction.



Scheme 64. Preparation of pyridone via Rh(III)-catalyzed C–H bond activation of *N*-methoxymethacrylamide and carbene migratory insertion.

groups that negate the need for external oxidants has led to more diversified molecular structures through cascade reactions, incorporating an extra O-atom transfer step. More recently, the replacement of stoichiometric oxidants with



Scheme 65. Preparation of pyridone via Rh(III)-catalyzed C–H bond activation of *N*-methoxymethacrylamide and carbene migratory insertion.

electrochemical processes for regenerating Rh catalysts has proven to be a powerful and sustainable approach.

Despite these advancements, several challenges remain. Firstly, the reported C–H bond annulation reactions often require large amounts of catalysts and high temperatures. To address this, novel Cp^RRh(III) catalysts, such as electron-deficient Cp^FRh(III) or elliptical-shape Cp^{TMP*}Rh, have been developed. We believe that creating more reactive Cp^RRh(III) catalysts will be a key focus for unlocking new C–H bond annulation processes in the near future. Secondly, reactions involving oxidizing directing groups, compared to external oxidants, have seen limited success, with most of them relying on non-natural oxidizing

groups. Therefore, developing new strategies involving directing groups with a native N–O bond could open up fresh avenues to access desired N-heterocycles. Lastly, exploring innovative strategies for C–H bond annulation could provide streamlined pathways to N-heterocycles. This field shall expand significantly in near future, offering new prospects for the synthesis of functional materials and pharmaceuticals, both in academic research and industrial applications.

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Conflict of Interests

The authors declare no conflict of interest.

Keywords: Cascade Reaction · Catalysis · C–H bond functionalization · Heterocycles · Rhodium

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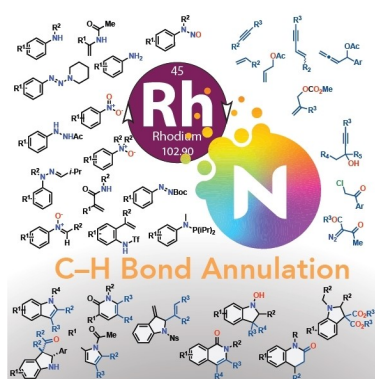
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REVIEW

This review examines rhodium-catalyzed C–H bond annulations for synthesizing 5- and 6-membered nitrogen-containing heterocycles, focusing on the underlying mechanisms and catalyst regeneration strategies. These include external oxidant, oxidizing directing group, redox-neutral, and electrochemical methods, highlighting advances in heterocyclic chemistry and catalyst efficiency.



*Dr. M. Peng, Dr. H. Doucet, Prof. Dr. J.-F. Soule**

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Rhodium-Catalyzed C–H Bond Annulation for the Synthesis of 5- and 6-Membered N-Heterocyclic Building Blocks