doi: 10.31674/book.2024ecc.003

# A Brief Review on Recent Rh-Catalyzed C-H Bond Activation in Pyridines and Quinolines

**Rupankar Paira**

*Department of Chemistry, Maharaja Manindra Chandra College, Kolkata, India*

*Corresponding Author's Email: rupankarpaira85@gmail.com*

## Abstract

In this short review article, attempts have been made to provide a concise pathway towards the recent advancements of organometallic chemistry, showcasing the broad spectrum of applications of Rh-catalysis in C-H bond activation and the transformative impact it has on society. By exploring these current developments of the last decade and the future opportunities of various sub-disciplines, it can certainly be hoped that the implementation of these works on other pyridine, oxazole, and aza-heterocycle derivatives will instigate further research and collaborative endeavors, fostering a deeper understanding of the limitless potential of rhodium chemistry. The continuous exploration and application of Rh-catalyzed C-H activation promise to revolutionize synthetic methodologies, driving innovation and progress across multiple scientific domains.

***Keywords:*** *C-H activation; Pyridine; Quinolone; Rhodium-Catalysis*

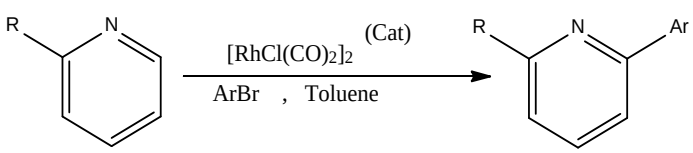
## Introduction

Chemistry, often regarded as the central science, has consistently played a crucial role in shaping humanity's understanding of the surrounding world. From decoding the intricate mechanistic paths of biological processes to engineering novel, newer materials with unparalleled functionalities, the applications of chemical science span a vast spectrum of fields, making it one of the most fundamental disciplines in scientific research and technological achievements (Blakemore *et al*., 2018). In this brief review article, the author will dive into some recent developments and some of the ground-breaking advancements in organometallic chemistry from various C-H activation protocols in pyridine and quinolone-based nitrogen heterocycles through Rh-catalysis (Lam, Wu & Yu, 2021). Through this endeavour, the diverse applications of rhodium catalysis and the potential opportunities they hold for the future. Heterocycles are fundamental components of numerous natural products, agrochemicals, and pharmaceuticals. Nitrogen-containing heterocycles, in particular, are especially significant as a rich source of therapeutic drugs in medicinal chemistry (Mohanty *et al*., 2024). The selection of aza-heterocycles primarily stems from their extensive use in various industries and academic fields (Campos *et al*., 2019). This is mainly because

such motifs exist in numerous fields, such as engendering new pharmaceuticals to fight diseases, designing eco-friendlier materials to minimize environmental impacts, or unveiling energy storage solutions for a sustainable future. The current review article also aims to showcase some of the remarkable advancements in organometallic chemistry, which range from inorganic and organic chemistry to physical and analytical chemistry. This article aims to highlight the key outcomes and breakthroughs from these areas, while also providing readers with a summarized overview of recent developments in the field and their potential implications. C–H bonds are more challenging to utilize than their pre-functionalized counterparts, they are not entirely inert. With the right catalyst, these bonds can be cleaved and used as latent substitutes for various functional groups (Zhang *et al*., 2024). It goes without saying that the future opportunities presented by the C-H activation processes in these compounds are truly exciting. As the understanding of these transition metal chemical pathways continues to evolve, it is fair to anticipate the emergence of newer materials with extraordinary properties along with the discovery of more potent catalysts for such chemical reactions. Additionally, the amalgamation of organometallic chemistry with other scientific streams, such as biological and material sciences, will likely promote unprecedented advancements in the fields of drug discovery, biotechnology, and nanotechnology.

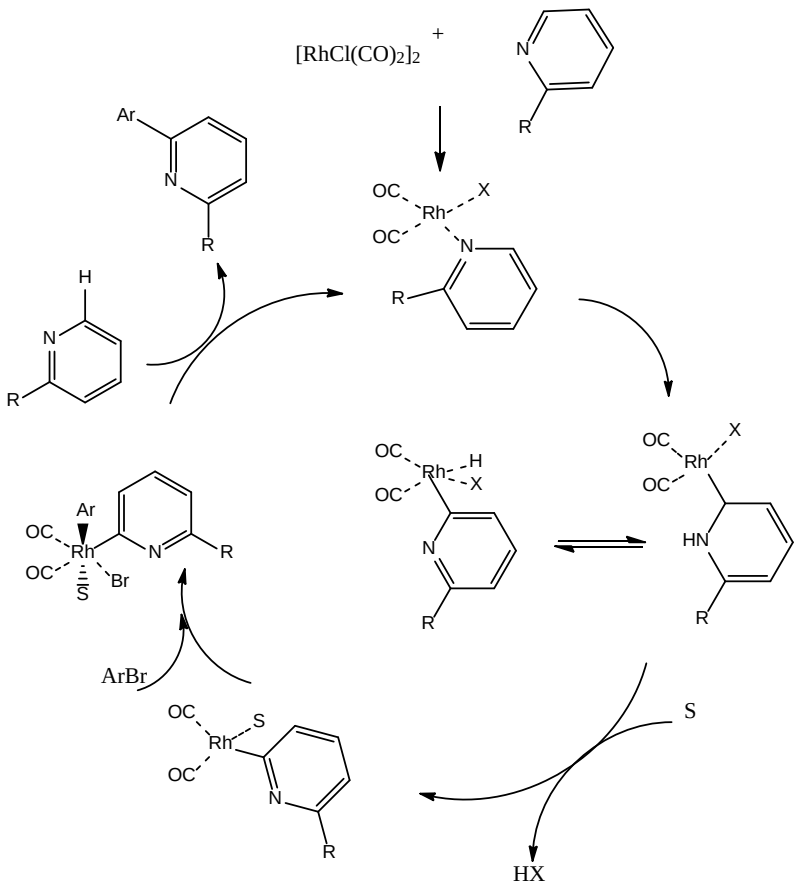
## *Recent developments*

### I. Rhodium(I)-directed Aylation of Azines




**Scheme 1**: Aylation of Azines *(Source: Berman et al., 2010)*

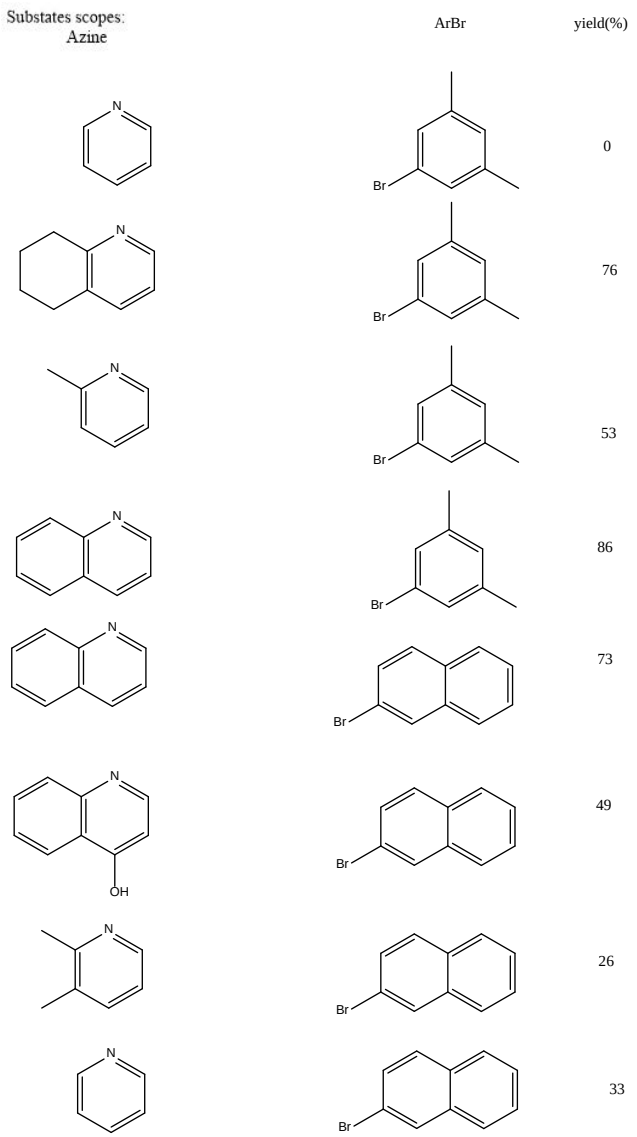
Direct arylation of the azines (scheme-1) can be accomplished with the employment of $[RhCl(CO)_2]_2$. The following diagram illustrates the mechanistic pathway of the arylation reaction between azine compounds and bromoarenes. Initially, a $[RhCl(CO)_2]_2$ molecule forms a bond with the 2-substitute pyridines and transforms into an N-heterocyclic carbene. After the reductive elimination of an HX molecule, A 2-substituted pyridinium Rh-complex is obtained (scheme-2), which readily proceeds along an oxidative addition pathway with the aryl bromide. The subsequent reductive elimination step produces a nitrogen-bound Rh-complex through an exchange with the pyridine starting material, resulting in the formation of the intended product (Berman, Bergman & Ellman, 2010).




**Scheme 2:** Mechanism of arylation *(Source: Berman et al., 2010)*

Once this protocol is optimized, the authors invoke an electronically deficient catalyst $[RhCl(CO)_2]_2$ in the system, where the limiting reagent is aryl bromide. The authors extensively evaluated the scope of heterocycles and established that many ortho-, meta-, and para-substituted pyridines, as well as an array of heterocycles such as quinolines, effectively participate in this reaction under these sets of optimized reaction conditions. Several straight chain, R-branched, and also aliphatic group-substituted *β*-branched pyridines and quinolines in the C2 position are well tolerated, and all of them undergo efficient C-H activation (scheme-3).

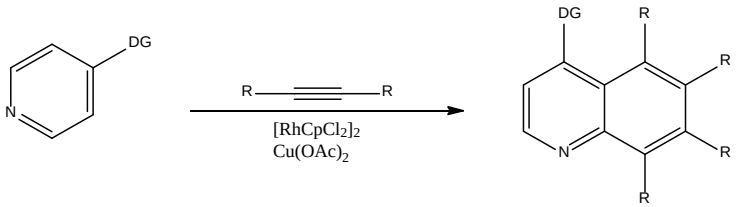
However, in contrast, when the authors used a substrate in which the C2 site was vacant, the arylation reaction didn't proceed. The authors made these observations when they attempted to arylate a pyridine molecule.



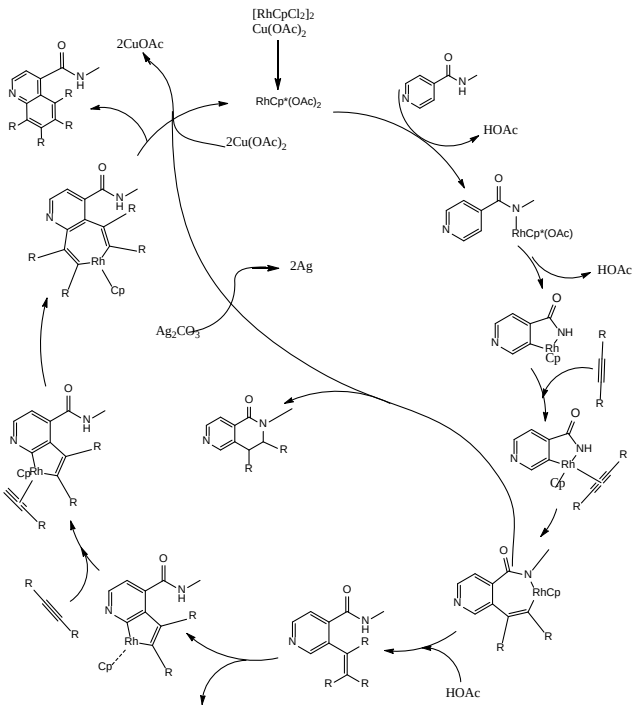

**Scheme 3: Substrate Scope** *(Source: Berman et al., 2010)*

## II. Synthetic protocols of Quinoline systems through Rhodium (III)-promoted Oxidative Annulation reaction of Pyridines

Cupric acetate has been used as the oxidant in Rhodium-catalyzed concomitant C-H activation of pyridines (scheme-4) to create selective synthetic roads to quinolines through oxidative annulation of ortho/meta/para functionalized pyridine moieties and two alkyne counterparts. Nevertheless, the competitive coordination routes (scheme-5) of the pyridine nitrogen atom might block the C-H bond activation of pyridines, leading to a decrease in catalytic efficiency (Song, Gong & Li, 2011).

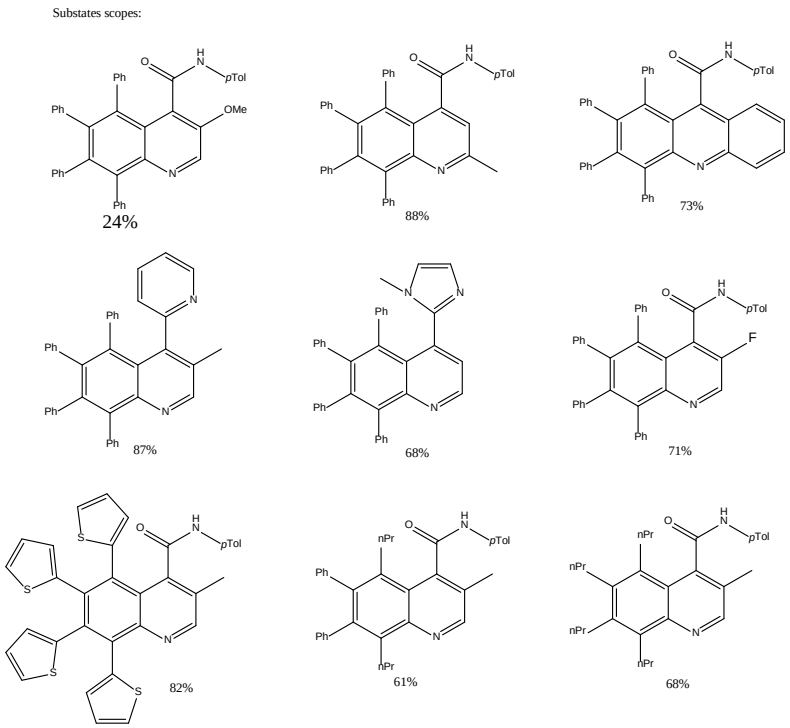



***Scheme 4:*** Oxidative Annulation reaction of Pyridines *(Source: Song et al., 2011)*



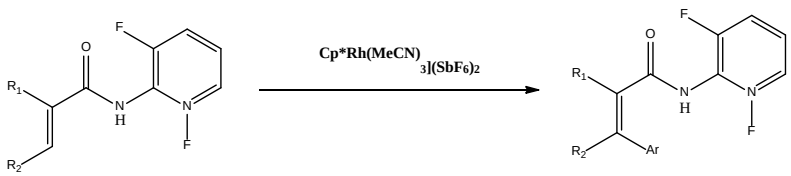

**Scheme 5:** Mechanism of the reaction *(Source: Song et al., 2011)*

Studies reveal that pyridines with an electronically deficient group (scheme-6) participate efficiently to produce the intended quinoline products in good yields. However, adding a methoxy moiety at the 3-position results in a significant reduction in catalytic efficiency. Moreover, a C2-substitution of the pyridines is very well tolerated. Scheme 6 demonstrates that activating a C3 C-H position typically takes place at a less crowded site. Further, the employment of quinoline-4-carboxamide under optimized conditions leads to an acridine with a good yield.



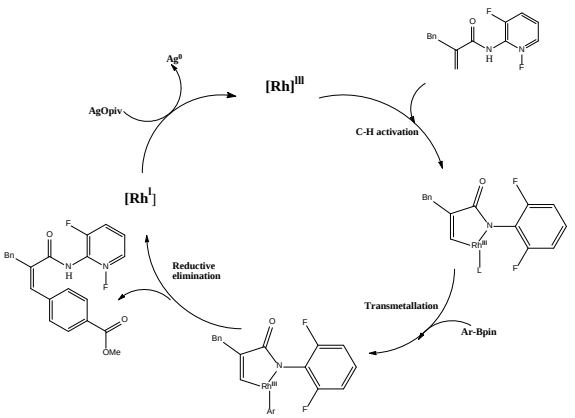

***Scheme 6: Substrate Scope*** (Source: Song *et al.,* 2011)

## III. Rhodium (III)-promoted Heteroarylation/Vinylation Protocol of Some Pyridine 1,6-Difluoroaryl Acrylamides



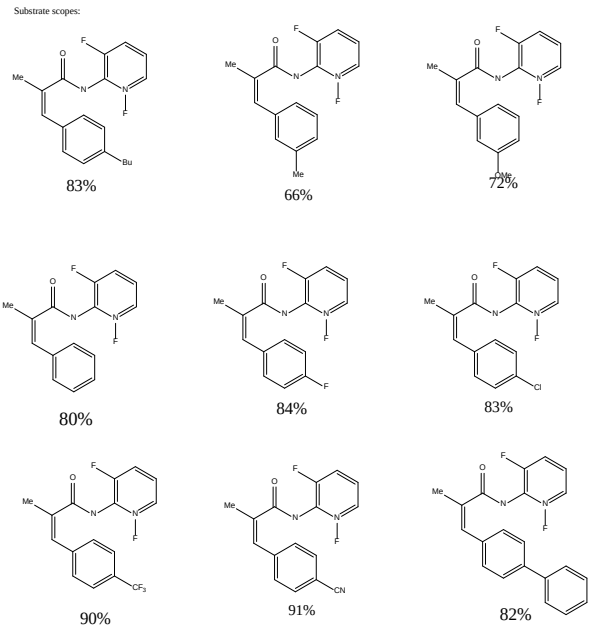

**Scheme 7:** Heteroarylation/Vinylation of Pyridine Acrylamides
*(Source: Wang et al., 2021)*

At the outset (scheme-7), the Rhodium catalyst gets attached with the amide, which gives rise to a five-membered rhodium-plugged cyclic species though a C−H activation reaction. The arylboronic acid pinacol esters then coordinate to the same Rhodium-centre, resulting in the emergence of the Rhodium species 4 (scheme-8). then, a C−C reductive elimination process yields the arylated product and an Iodo-Rhodium species, which can then undergo oxidation to yield Rhodium (III) through AgOPiv (Wang *et al*., 2021).




**Scheme 8:** Mechanism of the reaction *(Source: Wang et al., 2021)*

Generally, the present C−H bond functionalization strategy can be proved to be a nice fit for a vast array of the pinacol esters derived from aryl boronic acid. Also, it is generally applicable to electronically rich or deficient substrates, producing the desired structures with satisfactory yields. Moreover, the meta-substitution as well as the disubstitution with an electron-withdrawing arylboronate can give excellent yields. Additionally, a nice 82% yield could be achieved by employing 2-naphthyl boronates (scheme-9).

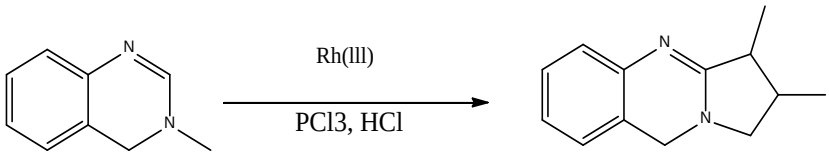



**Scheme 9:** Substrate Scope *(Source: Wang et al., 2021)*

*Exploration of Chemical Complexity*

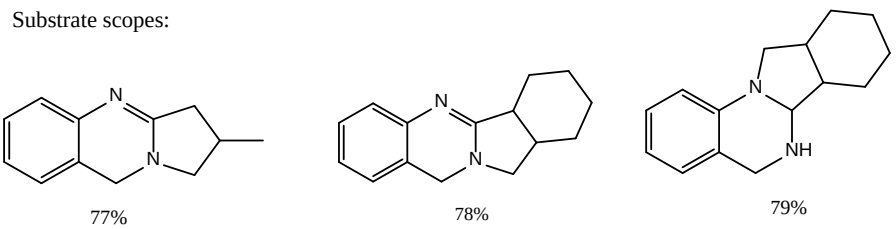
## IV. Rhodium-promoted straightforward C-H Addition reaction of 3,4-Dihydroquinazoline systems with Alkenes and its application in total synthesis of Vasicoline

During the intramolecular couplings of the unactivated alkenes (scheme-10), the 3,4-dihydroquinazolines can be produced, employing a Rh (I) catalyst (Wiedemann, Ellman, & Bergman, 2006).



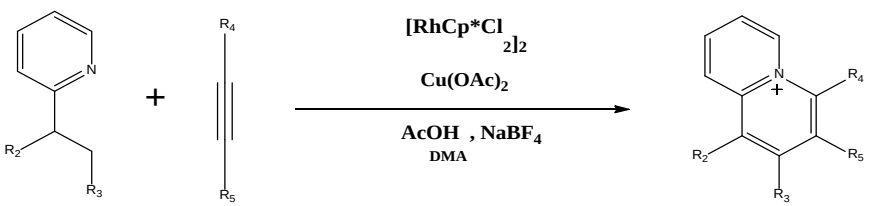

**Scheme 10:** C-H Addition reaction of 3,4-Dihydroquinazoline *(Source: Wiedemann et al., 2006)*

A wide application of this protocol on various motifs (scheme-11), including multisubstituted olefinic substrates, selectively afforded the tetracyclic product (cis-fusion), as desired by the authors. Through this technique, we can efficiently produce quinazoline natural products, which are mainly available from plant and microbial sources, for their antimalarial, antiinflamatory, and antitumor activities.




**Scheme 11:** Substrate Scope *(Source: Wiedemann et al., 2006)*

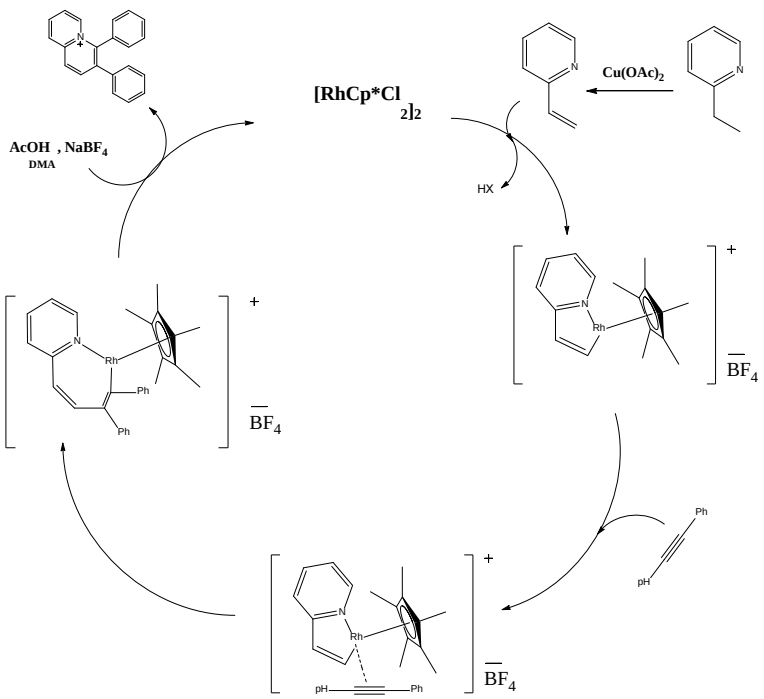
## V. Cooperative $sp^3/sp^2$ C-H Activation protocol of 2-Ethylpyridines by using Copper and Rhodium towards Quinolizinium Salts




**Scheme 12:** C-H Activation of 2-Ethylpyridines *(Source: Luo et al., 2015)*

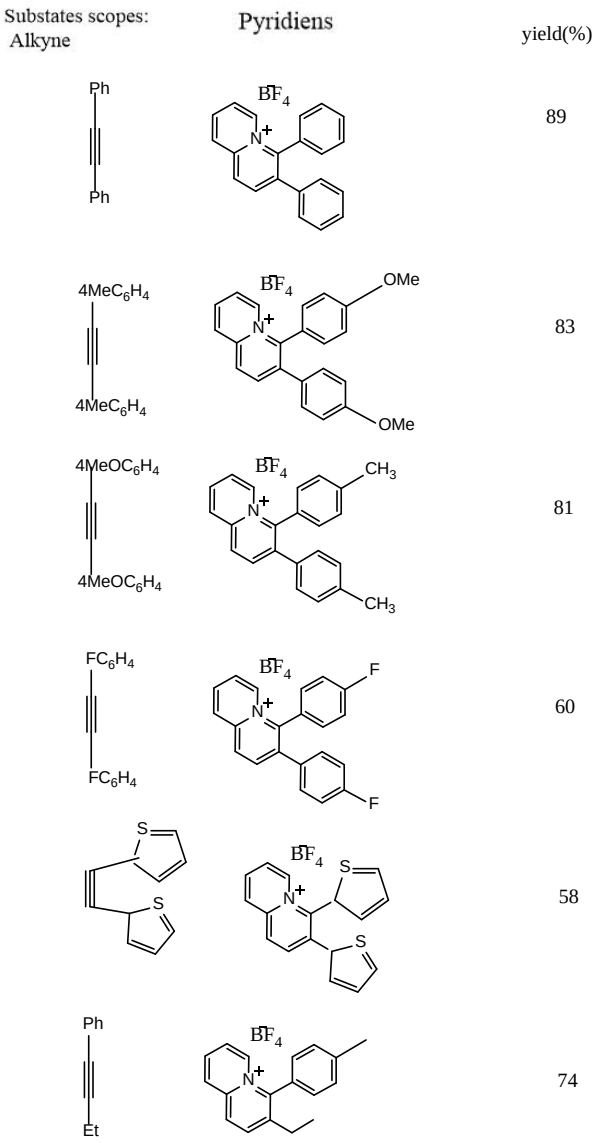
The cooperative $sp^3/sp^2$ C-H activation protocol (scheme-12) commenced with an initial dehydrogenation reaction of 2-ethylpyridine. The reaction is promoted through

cupric acetate to produce 2-vinylpyridine. After that, a coordination reaction takes place between the Rhodium center and the 2-vinylpyridine, which was formed in situ, followed by a cyclometalation reaction via the cleavage of the vinylic C−H linkage (scheme-13). This process led to a rhodium-implanted five-membered metalacycle and easily proceeds through an anion exchange reaction with the $BF_4^-$. Naturally, a cationic metalacycle species with the $BF_4^-$ counteranion, formed in the system, which pushed the species to undergo a reductive elimination step to yield the intended final quinolizinium salt and a monocationic Rh-species. Further oxidation of Rh (I), by cupric acetate, regenerates the Rh (III) reactive catalytic species (Luo *et al*., 2015).




**Scheme 13:** Mechanism of the reaction *(Source: Luo et al., 2015)*

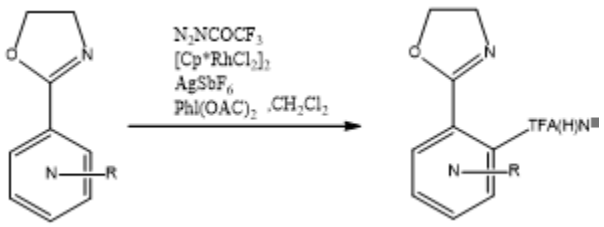
Further studies have shown that the electron-withdrawing groups have a high yield (scheme-14). Alkynes with different terminal moieties were also successfully invoked under this bimetal-mediated cooperative $sp^3/sp^2$ C-H activation protocol to form the intended quinolizinium salts with outstandingly high regioselectivity. But, terminal alkynes and dialkyl alkynes didn't yield the desired quinoliziniums.




**Scheme 14:** Substrate Scope *(Source: Luo et al., 2015)*

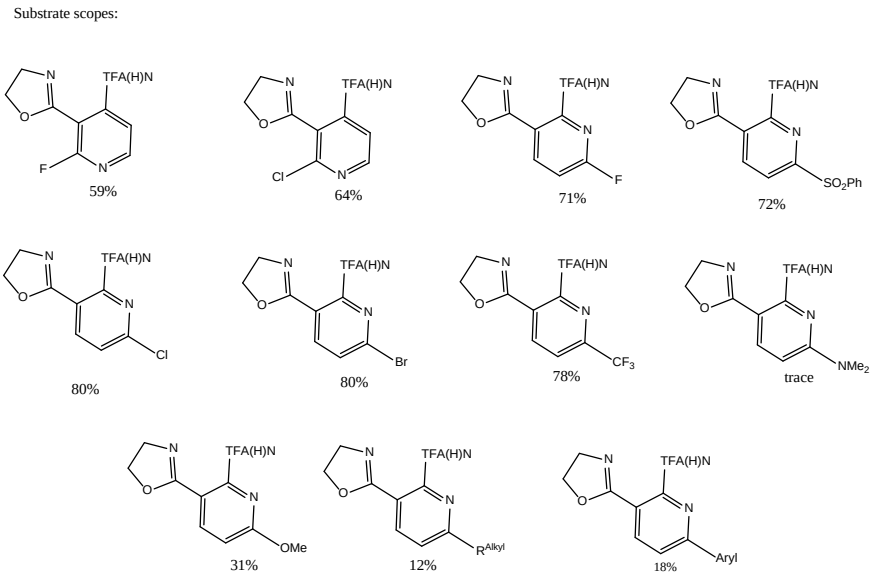
## VI. Synthetic route for the Functionalization of Pyridines through an Oxazoline-guided Regioselective C−H Amination Reaction

Differently functionalized pyridines can be obtained via an oxazoline-promoted regioselective C-H amination reaction (scheme-15). Interestingly, the presence of a C2-substituent is crucial for this transformation to be successful. Furthermore, it allows for extensive embellishment of the finished products. Note that, among these entities, 2-chloropyridines provide access to a wide range of building blocks, for example, a versatile azaquinazoline scaffold (Maiden *et al*., 2016).




**Scheme 15:** Regioselective C−H Amination Reaction *(Source: Maiden et al., 2016)*

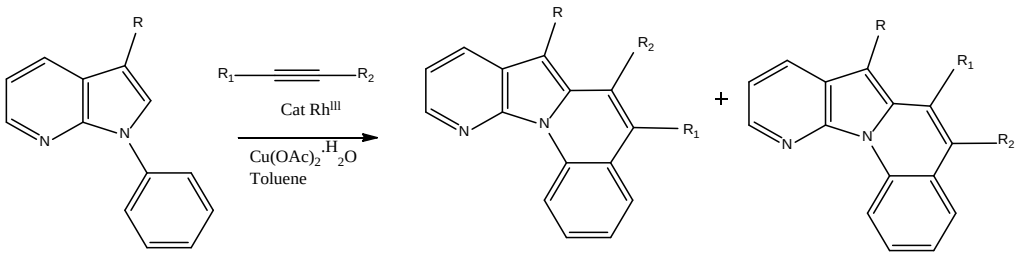
Both 2-halopyridine and 6-halopyridine participated (scheme-16) under the optimized conditions for smooth amidation to produce the aimed products with satisfactory yields. Also, a trifluoromethyl-substituted pyridine has excellent yield and selectivity.




**Scheme 16:** Substrate Scope *(Source: Maiden et al., 2016)*

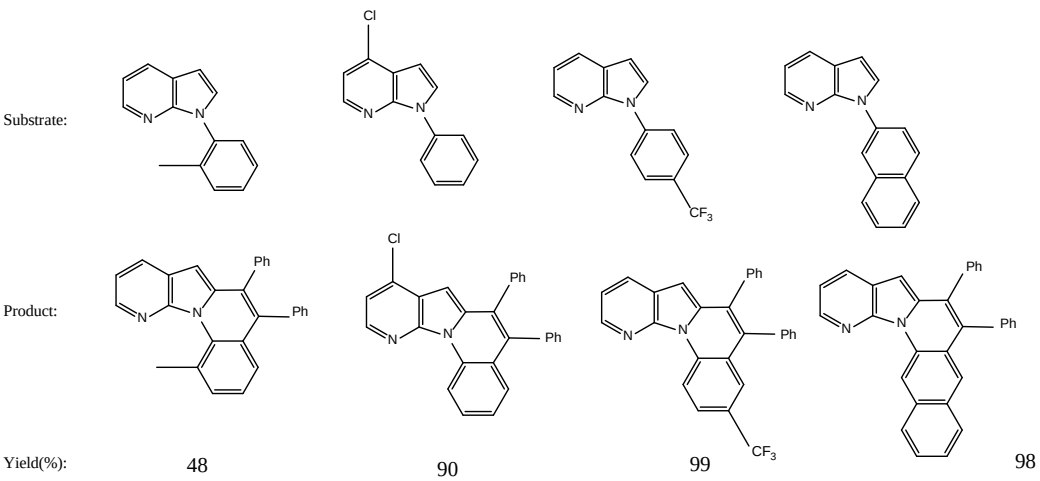
## VII. Rhodium (III)-promoted Oxidative Annulation reaction of 7-Azaindoles with the Alkynes via two consecutive C−H Activation

This Rh (III)-catalyzed double C−H bond functionalization protocol (scheme-17) involves an ortho C−H activation step, which is guided by a nitrogen-based directing group. It is then followed by an ensuing roll-over reaction, which turns into another C−H bond functionalization step of the heterocyclic system. Note that, these 7-azaindole derivatives are generally very difficult to produce. But, under the present protocol, they can be achieved with excellent yields. The scope of the reaction is quite broad. Under the optimized protocol, the 7-azaindoles and also the internal alkynes successfully participated (Li *et al*., 2015).



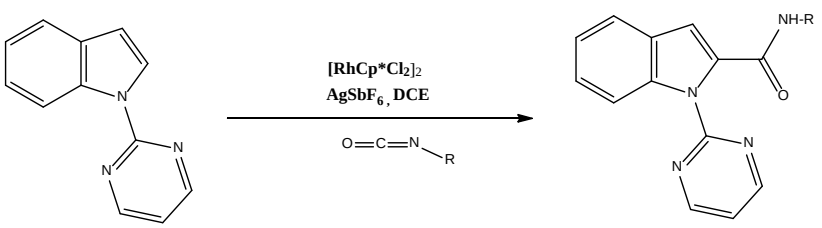

**Scheme 17:** Oxidative Annulation reaction of 7-Azaindoles *(Source: Li et al., 2015)*

The authors have employed both electron donating as well as electron retreating motifs at different sites (scheme-18) of the 7-azaindole species and engaged them under the standardized protocol to afford the desired products with great yields. As expected, an ortho-alkyl substitution on the benzene motif had obstructed the 2nd C-H activation process to produce the product with only 48% yield. Note that, the substrates, having a halogen motif on the pyridine ring were also proved fruitful under the optimized reaction protocol. Even, the alkyl substituted substrates reacted adequately in this coupling process, producing the products with good yields.



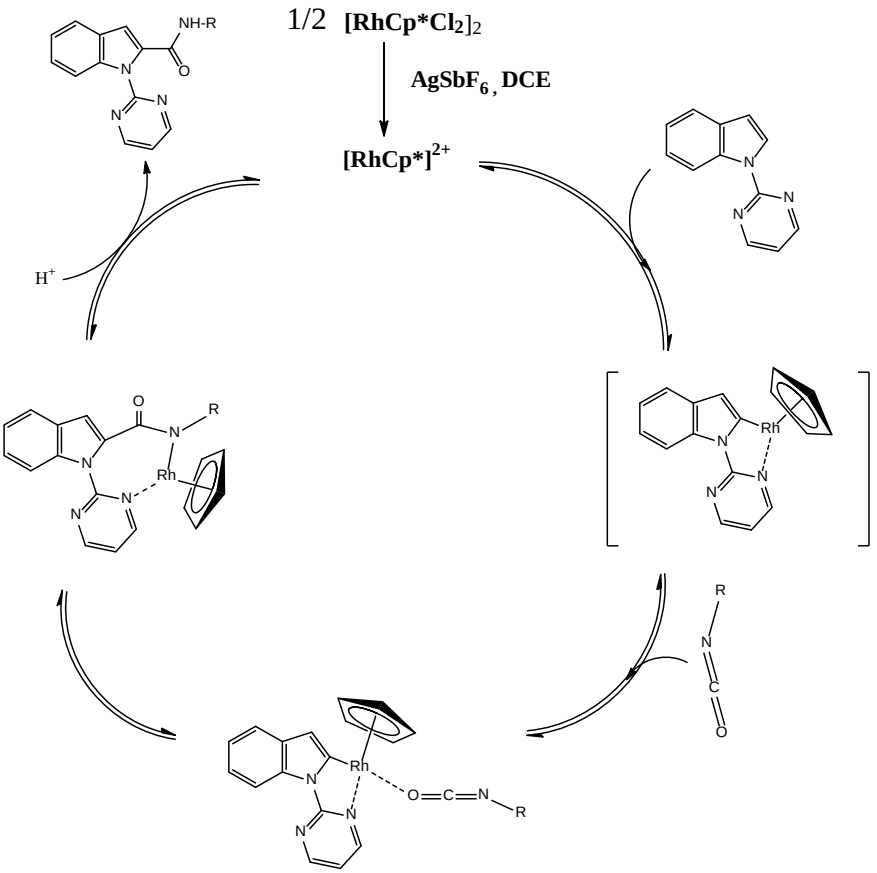

**Scheme 18:** Substrate Scope *(Source: Li et al., 2015)*

## VIII. Rhodium (III)-promoted C-H Amidation Reaction on Indoles with Isocyanates



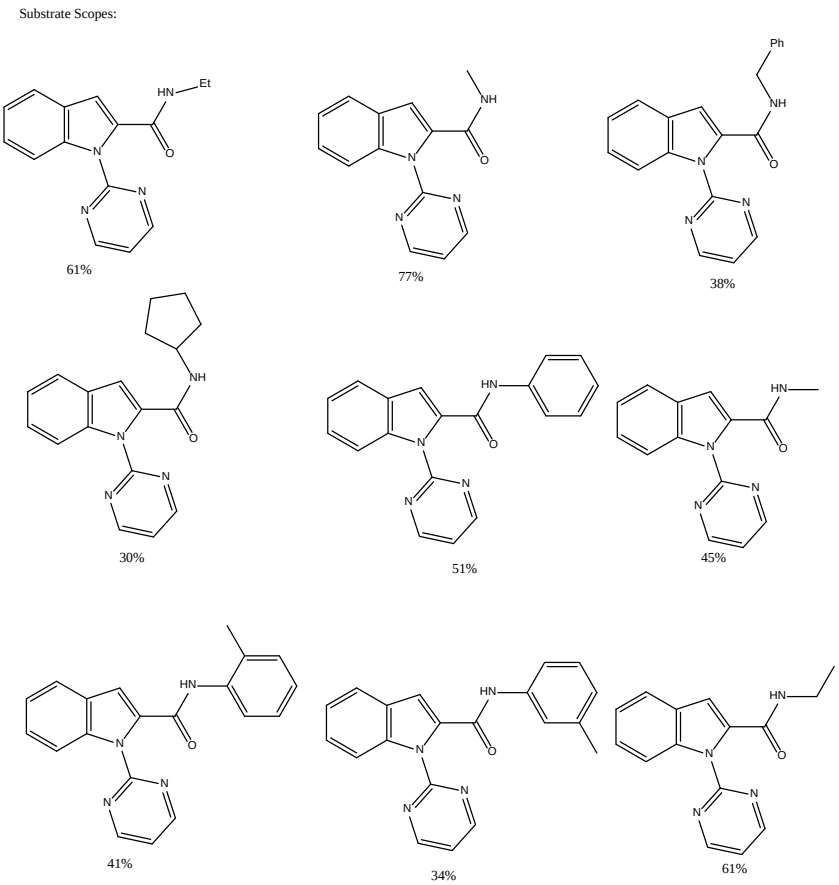

**Scheme 19:** C-H Amidation Reaction on Indoles *(Source: Jeong et al., 2015)*

When $[RhCp^*Cl_2]_2$ and $AgSbF_6$ react, a cationic Rh (III)-catalyst is formed, where the silver salt easily coupled with the pyrimidinyl nitrogen. Such catalysts can readily promote the C-H activation reversibly at the indole C2-site, thereby providing a rhodium-based metalacycle intermediate along with the release of a proton ($H^+$). The subsequent synchronization of the isocyanate then shaped an intermediate compound, which, on an additional drifting insertion into the Rhodium-Carbon bond, formed a complex that, upon accepting a proton, yielded the intended product (schemes-19 & 20) and also regenerated the active Rhodium (III) catalyst (Jeong *et al*., 2015).



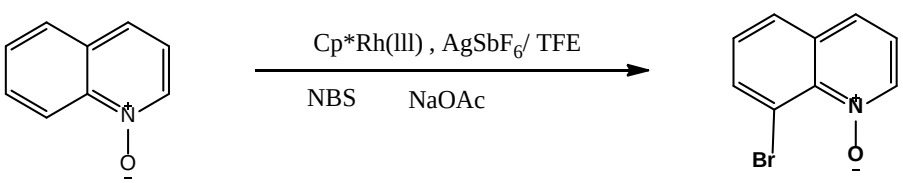

**Scheme 20:** Mechanism of the reaction *(Source: Jeong et al., 2015)*

The authors screened a variety of aryl isocyanates, both having electronically poor as well as electronically wealthy substituents (Me, Br, and $CF_3$) and they found that all were well endured under the given conditions and afforded the resultant products (scheme-21). But highly electronically scarce phenylsulfonyl isocynates tend to give low yields, possibly ascribed to the reversible nature of the amidation process.




**Scheme 21:** Substrate Scope *(Source: Jeong et al., 2015)*

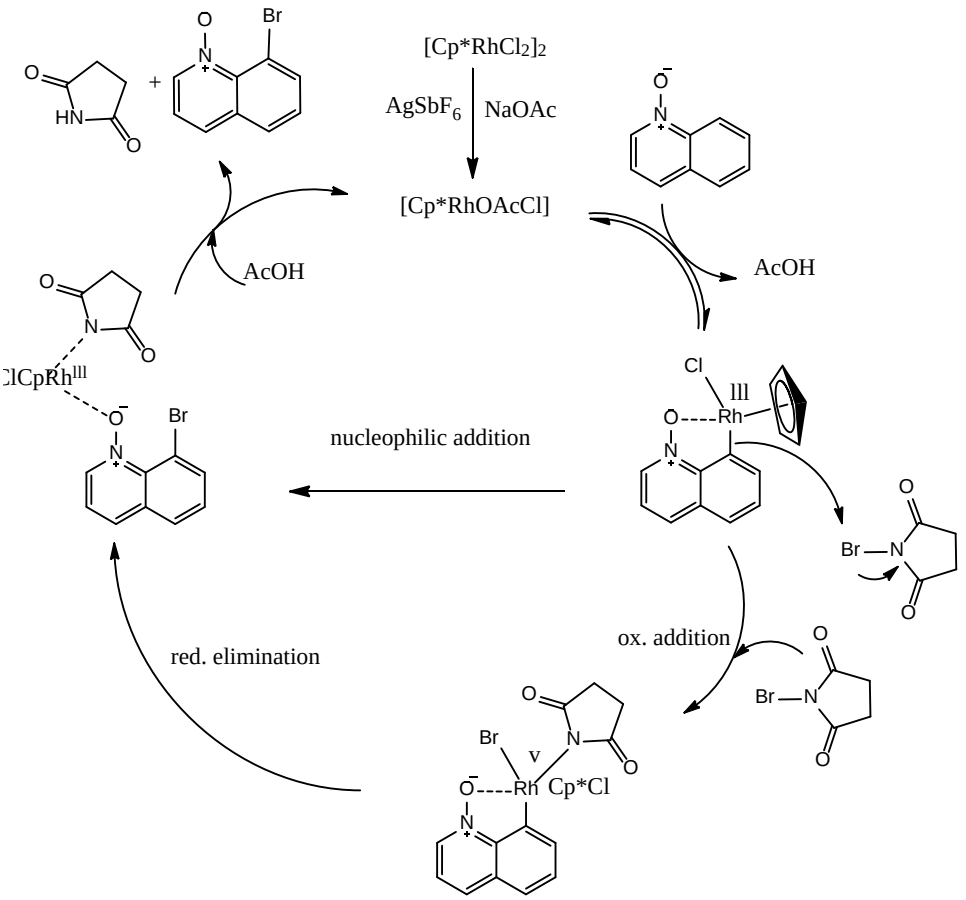
## IX. Rhodium (III)-promoted C−H Activation reaction of Quinoline N-Oxides




**Scheme 22:** C−H Activation of Quinoline N-Oxides *(Source: Dhiman et al., 2019)*

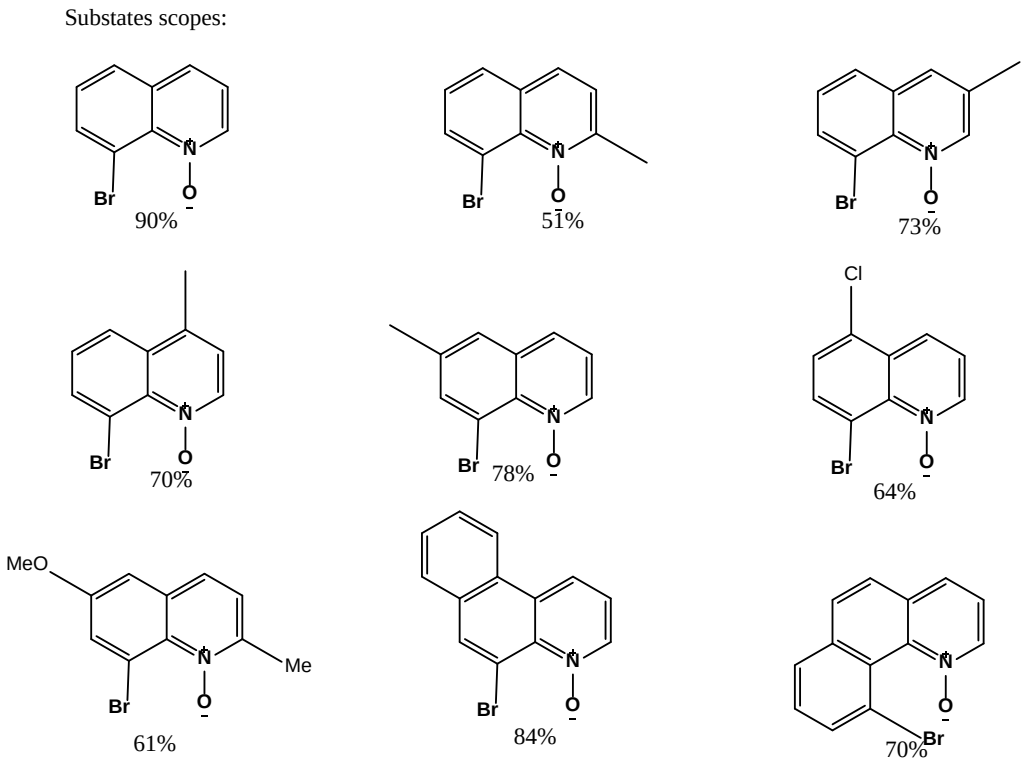
intermediate for such C8-functionalization (scheme-22) is a five-membered rhodacycle, formed in situ on reaction with the quinoline N-oxide. Dhiman *et al*. (2019) also used N-fluorobis-(phenylsulfonyl)-imide as the reagent for this C8-amidation technique of quinoline N-oxide unveiled by the authors. Both the bromination and amidation steps at the C8-site of the quinoline N-oxide systems were routed through this technique (scheme-23). This transformation has also been successfully

implemented, scaling up to a few-gram scale level. Such a scaled-up protocol also showed satisfactory functional group tolerance on a wide variety of substrates. A thorough mechanistic study revealed that the core intermediate for such C8-functionalization is a five-membered rhodacycle, formed in situ on reaction with the quinoline N-oxide. Dhiman *et al*. (2019) also used N-fluorobis-(phenylsulfonyl)-imide as the reagent for this C8-amidation technique of quinoline N-oxide.



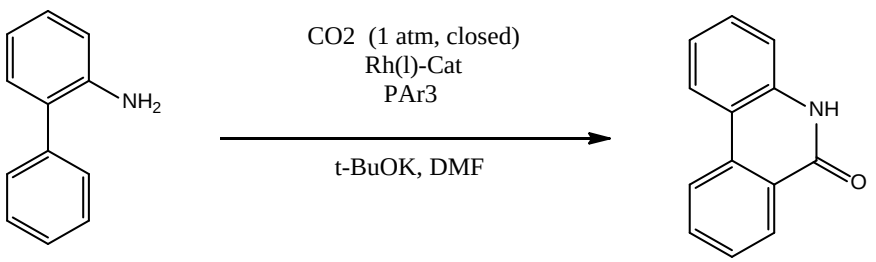

**Scheme 23:** Mechanism of the reaction *(Source: Dhiman et al., 2019)*

The authors screened various quinoline N-oxides to structure the substrate scope, and found that substituting OMe, iPr, t Bu, Br, Cl, and NH(Boc) at the C6 position of the system produced the intended product with moderate to high yields. Additionally, the authors observed a similar reactivity with 5-chloroquinoline N-oxide (scheme-24). However, when the substituent is situated at the C2-site, it was found that the yield is quite low, probably due to substantial steric hindrance at the site.



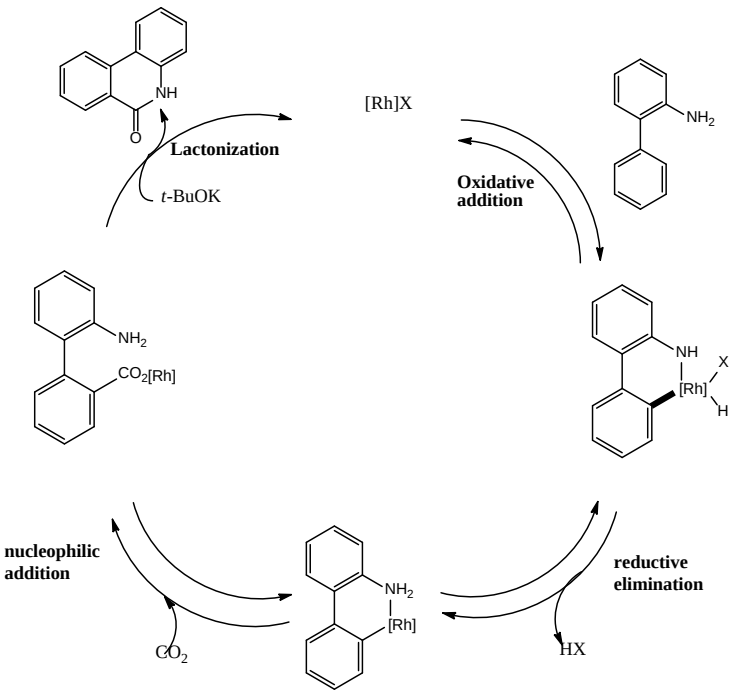

**Scheme 24:** Substrate Scope *(Source: Dhiman et al., 2019)*

## X. Rhodium (I)-promoted Aryl C−H Carboxylation reaction of 2-Arylanilines with gaseous carbon dioxide



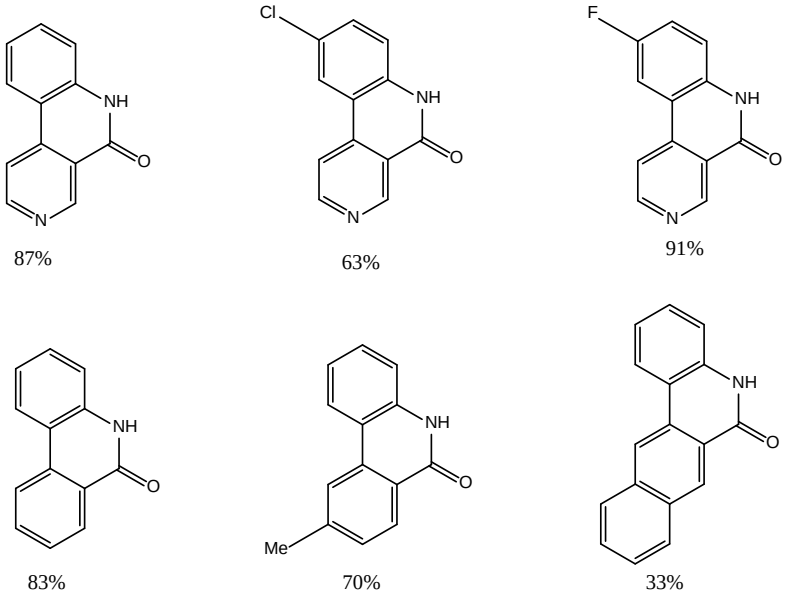

**Scheme 25:** Carboxylation reaction of 2-Arylanilines *(Source: Gao et al., 2019)*

This reaction (scheme-25) is an example of the oxidative addition process of an Iodo-rhodium species, which is reversible in nature. Subsequently, HX undergoes a clear reductive elimination. The process generates a rhodium-implanted metalacycle, subsequently undergoing a nucleophilic carboxylation step with carbon dioxide to form the rhodium carboxylate (scheme-26). The concluding lactamization reaction of rhodium carboxylate, promoted by potassium butoxide, eventually generated the product and reproduced the Rh (I) catalyst (Gao *et al*., 2019).




**Scheme 26:** Mechanism of the reaction *(Source: Gao et al., 2019)*

Substrate scopes:




**Scheme 27:** Substrate Scope *(Source: Gao et al., 2019)*

*Exploration of Chemical Complexity*

In order to explore the substrate scope (scheme-27) with several electronically scarce as well as electronically rich substituents, the authors placed various substituents at the meta-position and para-position, and they were found to be fruitful under the optimized protocol. The yields of desired phenanthridinones are generally outstanding to excellent. Note that the electron-poor motifs like trifluoromethyl, amide, and cyanides were quite well tolerated with this reaction and smoothly led to a high-yielding synthetic protocol without the hydrolytic cleavage of these base-sensitive substituents.

## Conclusion

This review article may be used as a window into the most recent developments in organometallic chemistry, highlighting the wide range of uses for Rh-catalysis in C-H bond activation procedures as well as the revolutionary effects it has had on society. One can definitely apply these works to other pyridine, oxazole, and aza-heterocycle derivatives to incite further research and collaborative endeavors, fostering a deeper understanding of the boundless potential of Rhodium chemistry. This can be achieved by exploring the current developments of the last ten years and the future opportunities of various sub-disciplines.

## Acknowledgment

The author would like to thank the teacher in charge of Maharaja Manindra Chandra College, India for providing office space and internet facilities. The author also acknowledges the constant support extended by his colleagues in the Department of Chemistry at Maharaja Manindra Chandra College.

## References

Berman, A. M., Bergman, R. G., & Ellman, J. A. (2010). Rh (I)-catalyzed direct arylation of azines. *The Journal of organic chemistry*, *75*(22), 7863-7868. https://doi.org/10.1021/jo101793r

Blakemore, D. C., Castro, L., Churcher, I., Rees, D. C., Thomas, A. W., Wilson, D. M., & Wood, A. (2018). Organic synthesis provides opportunities to transform drug discovery. *Nature chemistry*, *10*(4), 383-394. https://doi.org/10.1038/s41557-018-0021-z

Campos, K. R., Coleman, P. J., Alvarez, J. C., Dreher, S. D., Garbaccio, R. M., Terrett, N. K., ... & Parmee, E. R. (2019). The importance of synthetic chemistry in the pharmaceutical industry. *Science*, *363*(6424), eaat0805. https://doi.org/10.1126/science.aat0

Dhiman, A. K., Gupta, S. S., Sharma, R., Kumar, R., & Sharma, U. (2019). Rh (III)-catalyzed C (8)–H activation of quinoline N-Oxides: regioselective C–Br and C–N bond formation. *The Journal of Organic Chemistry*, *84*(20), 12871-12880. https://doi.org/10.1021/acs.joc.9b01538

Gao, Y., Cai, Z., Li, S., & Li, G. (2019). Rhodium (I)-catalyzed aryl C–H carboxylation of 2-arylanilines with CO2. *Organic letters*, *21*(10), 3663-3669. https://doi.org/10.1021/acs.orglett.9b01105

Jeong, T., Han, S., Mishra, N. K., Sharma, S., Lee, S. Y., Oh, J. S., ... & Kim, I. S. (2015). Rh (III)-Catalyzed C–H Amidation of Indoles with Isocyanates. *The Journal of Organic Chemistry*, *80*(14), 7243-7250. https://doi.org/10.1021/acs.joc.5b00763

Lam, N. Y., Wu, K., & Yu, J. Q. (2021). Advancing the logic of chemical synthesis: C− H activation as strategic and tactical disconnections for C− C bond construction. *Angewandte Chemie*, *133*(29), 15901-15924. https://doi.org/10.1002/ange.202011901

Li, S. S., Wang, C. Q., Lin, H., Zhang, X. M., & Dong, L. (2015). Rhodium (III)-catalyzed oxidative annulation of 7-azaindoles and alkynes via double C–H activation. *Organic letters*, *17*(12), 3018-3021. https://doi.org/10.1021/acs.orglett.5b01228

Luo, C. Z., Gandeepan, P., Wu, Y. C., Tsai, C. H., & Cheng, C. H. (2015). Cooperative C (sp3)–H and C (sp2)–H Activation of 2-Ethylpyridines by Copper and Rhodium: A Route toward Quinolizinium Salts. *ACS Catalysis*, *5*(8), 4837-4841. https://doi.org/10.1021/acscatal.5b01244

Maiden, T. M., Swanson, S., Procopiou, P. A., & Harrity, J. P. (2016). Synthesis of Functionalized Pyridines via a Regioselective Oxazoline Promoted C–H Amidation Reaction. *Organic letters*, *18*(14), 3434-3437. https://doi.org/10.1021/acs.orglett.6b01612

Mohanty, S. R., Prusty, N., Nanda, T., Mahulkar, P. S., & Ravikumar, P. C. (2024). Directing group-assisted selective C–H activation of six-membered N-heterocycles and benzo-fused N-heterocycles. *Organic Chemistry Frontiers*, *11*(2), 540-575. https://doi.org/10.1039/D3QO01396K

Song, G., Gong, X., & Li, X. (2011). Synthesis of quinolines via Rh (III)-catalyzed oxidative annulation of pyridines. *The Journal of Organic Chemistry*, *76*(18), 7583-7589. https://doi.org/10.1021/jo201266u

Wang, H. W., Qiao, Y. H., Wu, J. X., Wang, Q. P., Tian, M. X., Li, Y. F., ... & Lu, Y. (2021). RhIII-Catalyzed C–H (Het) arylation/Vinylation of N-2, 6-Difluoroaryl Acrylamides. *Organic Letters*, *23*(3), 656-662. https://doi.org/10.1021/acs.orglett.0c03688

Wiedemann, S. H., Ellman, J. A., & Bergman, R. G. (2006). Rhodium-Catalyzed Direct C− H Addition of 3, 4-Dihydroquinazolines to Alkenes and Their Use in the Total Synthesis of Vasicoline. *The Journal of Organic Chemistry*, *71*(5), 1969-1976. https://doi.org/10.1021/jo052345b

Zhang, Y., Zhang, J. J., Lou, L., Lin, R., Cramer, N., Wang, S. G., & Chen, Z. (2024). Recent advances in Rh (I)-catalyzed enantioselective C–H functionalization. *Chemical Society Reviews*. https://doi.org/10.1039/D3CS00762F