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C-H Bond Activation in Five-Membered Oxa- and Aza-Heterocycles: Recent Applications of Rh-Catalysis

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Abstract

This review paper offers an insight into the topic by demonstrating the revolutionary effects and wide range of applications of rhodium chemistry in the carbon-hydrogen bond activation of and aza-heterocycles with 5 ring members. The author hopes to see the scientific community use these works on pyridine and oxazole derivatives to inspire further research and collaboration through an examination of recent developments and future opportunities in various subfields. This will promote a deeper comprehension of the limitless potential of chemistry to shape the world and overcome future challenges.

Keywords: *Aza-Heterocycle; C-H Activation; Oxa-Heterocycle; Rhodium Catalysis*

Introduction

In the scientific community, Chemistry has always played a central role in shaping the understanding of modern scientific advancements globally. It has always pushed the boundaries between the scientific realms to merge into one another and paved the pathway to understanding numerous complex protocols (Blakemore *et al*., 2018). From unveiling the molecular-level understanding of complex biological cycles to developing complex materials of unparalleled properties, chemistry has always emerged as the core subject to set a heavy footprint in that field (Campos *et al*., 2019). Among the various applications, scientific research and technological advancements, the role of transition metals in carbon-hydrogen bond activation has caught the attention of researchers with high level of interest recently (Lam, Wu & Yu, 2021). In this article, the author has highlighted plethora of applications of carbon-hydrogen activation by Rh accelerator in heterocyclic substances and the potential opportunities they offer for the future. The author also dug into the current breakthroughs and significant discoveries in the field of organometalics. Heterocyclic derivatives, especially five-membered oxa- and aza-heterocycles, are widely used in many different fields of science and industry. Whether it's inventing novel drugs to treat illnesses, producing environmentally friendly materials to lessen their influence on the environment, or coming up with energy storage options for a sustainable future. The author's goal is to highlight the last decade's outstanding developments in the array of organometallic chemistry

derivatives, from physical and analytical chemistry to organic and inorganic chemistry. The author anticipates that the present article will provide a thorough understanding of the subject and its possible ramifications by showcasing the most important discoveries and advancements in the area of five-membered oxa- and aza-heterocycles. The potential that these compounds' activation will bring to chemistry in the future is really intriguing. It can be expected that, with the emergence of new materials with remarkable properties, the discovery of more effective catalysts for chemical reactions, and the development of sustainable energy sources, the energy landscape will completely transform as the understanding of transition metal chemical processes continues to advance. Furthermore, there is a good chance that the combination of organometallic chemistry with other scientific disciplines like biology and materials science will result in previously unheard-of breakthroughs in biotechnology, nanotechnology, and medication development.

Recent developments:

I. A direct Bis-cyanation reaction with double C-H activation by Rh-catalysis:

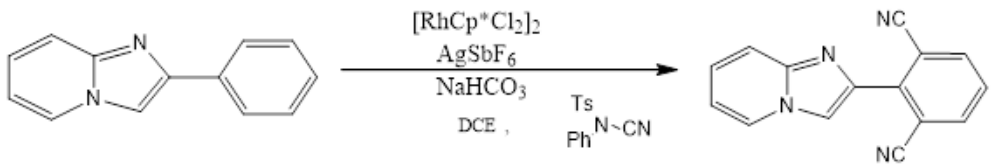

Figure 1: Bis-cyanation reaction with double C-H activation (*Zhu et al., 2017*)

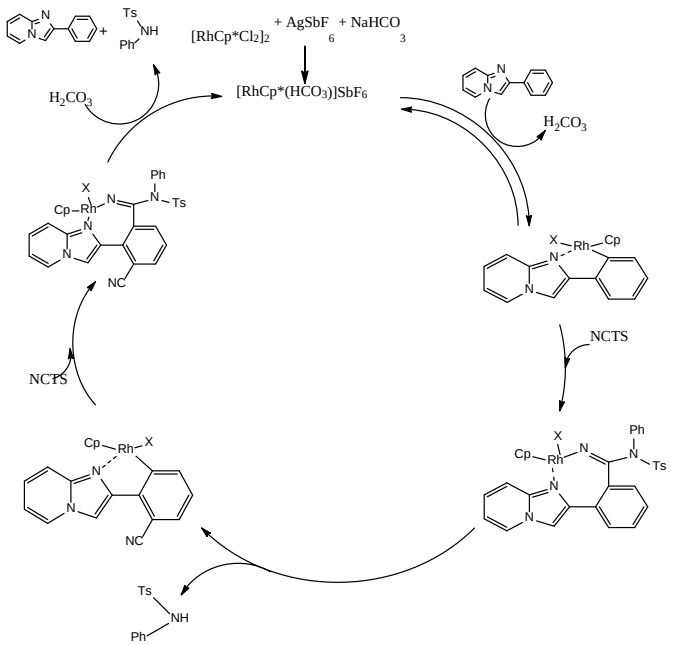

Figure 2: Mechanism of the reaction (Zhu *et al*., 2017)

First, in the presence of $AgSbF_6$ and $NaHCO_3$ the $[RhCp^*Cl_2]_2$ was converted to an active cationic Rh(III) species A. The five-membered rhodacycle B was then formed by chelating N1 at the imidazo[1,2-α]pyridine ring with in situ generated Rh(III) active complex A through a reversible C−H rhodation of 2-phenylimidazo[1,2-α]pyridine. Next, intermediate C was created when the cyano group was coordinated and moved into the C-Rh bond. It then underwent proto-demetalation, roll-over activation, and β-amine elimination to produce mono-cyanated intermediate D. The intended bis-cyanated product was then released and the catalytic cycle got completed (Figure 1, Figure 2). by the regeneration of the active Rh(III) species A when a new NCTS molecule joined with intermediate D to form intermediate E (Zhu *et al*., 2017).

In order to achieve lucrative yields of bis-cyanated products, substituents with both electron-donating and electron-withdrawing motifs at the para-, meta-, and ortho-positions were permitted (Figure 3). For the C-H cyanation of meta- and ortho-substituted substrates, only electron-donating groups at the benzene ring are beneficial, whereas substrates with electron-withdrawing groups delivered low yields.

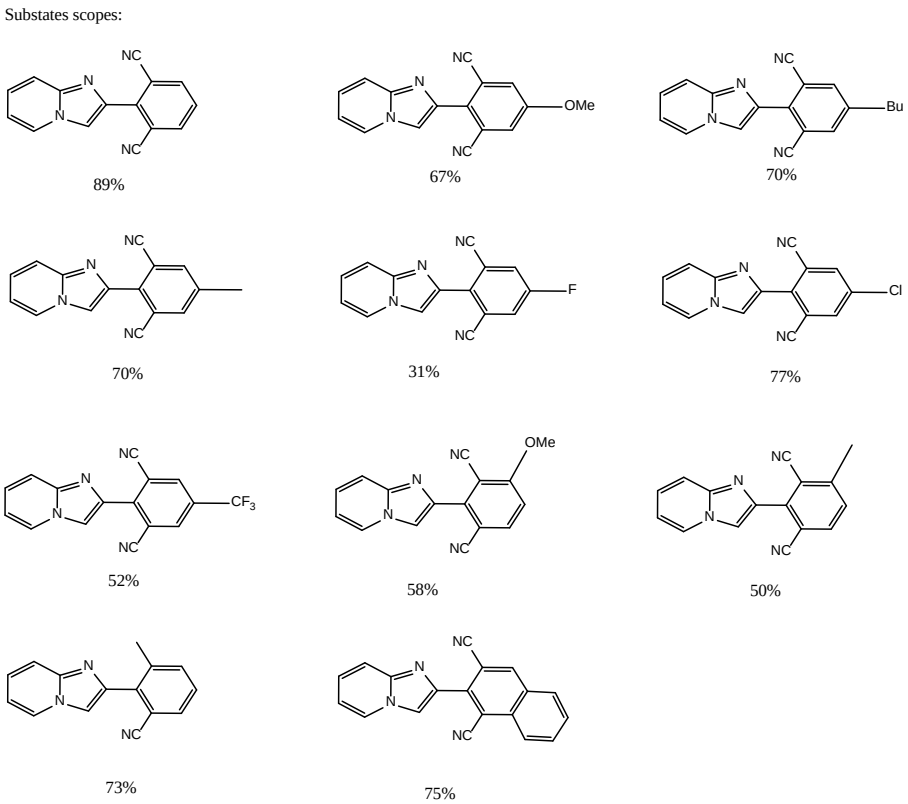

Figure 3: Substarte Scope (Zhu *et al*., 2017)

II. A direct NHC-Driven Cascade C/H bond activation by Rh-catalysis:

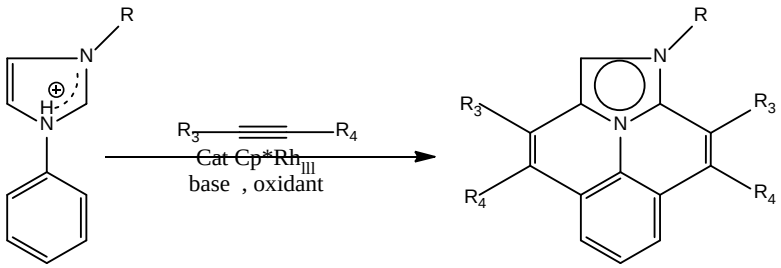

Figure 4: A direct NHC-Driven Cascade C/H bond activation (*Ghorai & Choudhury, 2015*)

The first step is the ortho C-H bond activation of the imidazolium substrate (Figure 4), which forms a five-membered rhodacycle. This activation is controlled by the NHC ligand. The seven-membered rhodacycle intermediate is produced by alkyne insertion into the Rh−aryl bond. In the presence of Ag^{I}, further reductive elimination from alkyl Rh-caryl yields the monoannulated product on one side, which is then repeated to get the other annulated (Figure 5) side product (Ghorai & Choudhury, 2015).

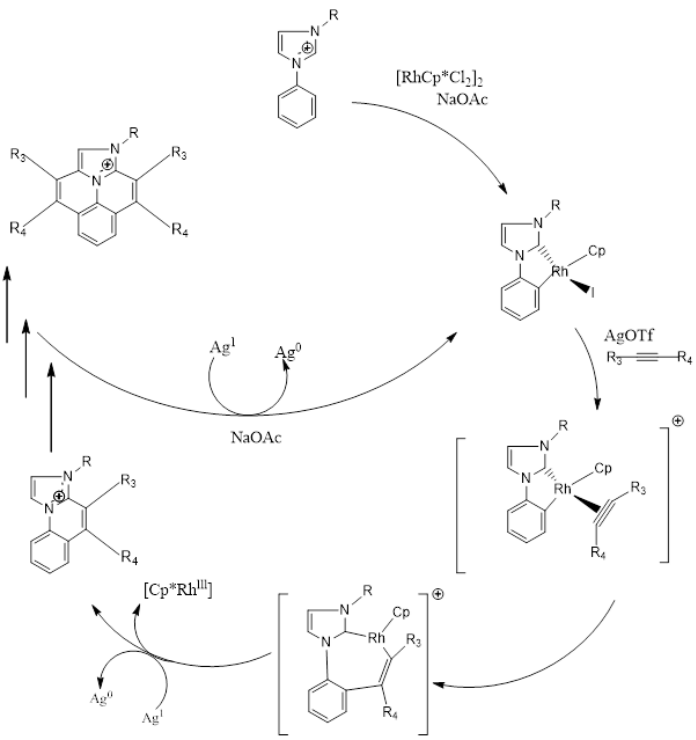

Figure 5: Mechanism of the reaction (*Ghorai & Choudhury, 2015*)

The matching products yielded good results (Figure 6) in this case when the groups on an N-phenyl wingtip that donate and withhold electrons were present. The yield is good when utilizing an alkyne that has a strongly electron withdrawing group, according to the results.

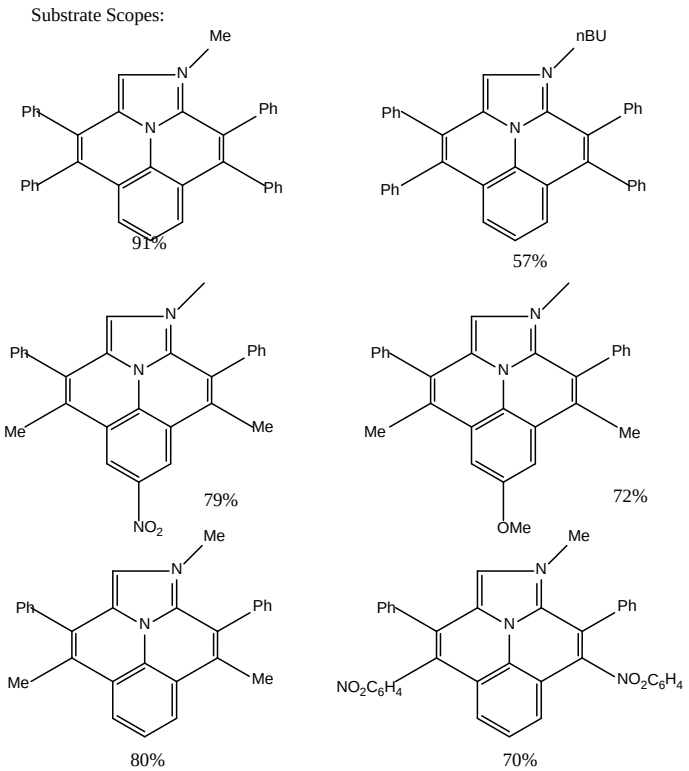

Figure 6: Substarte Scope (*Ghorai & Choudhury, 2015*)

III. An arylation protocol of heterocycles via C/H Bond Activation: Broadened perspective via mechanistic understanding:

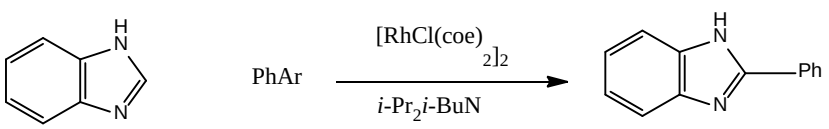

Figure 7: An arylation protocol of heterocycles (*Berman et al., 2008*)

The dimer complex is produced by combining $[RhCl(coe)_2]_2$ with the initial material (see above). The heterocycle complex would be produced by dissociating this complex and coordinating the heterocycle (Figure 7). The mechanism of carbon-hydrogen activation/tautomerization is thought to be responsible for the production of the carbene complex. The (aryl)(carbene)rhodium complex can be produced by oxidatively adding aryl halides to this low-valent, electron-rich Rh complex. Then, an HBr molecule gets removed from this complex, either intramolecularly or with the help of the

additional amine base (Figure 8). Finally, the Rh catalyst was regenerated along with the required product by a reductive elimination step (Berman *et al*., 2008).

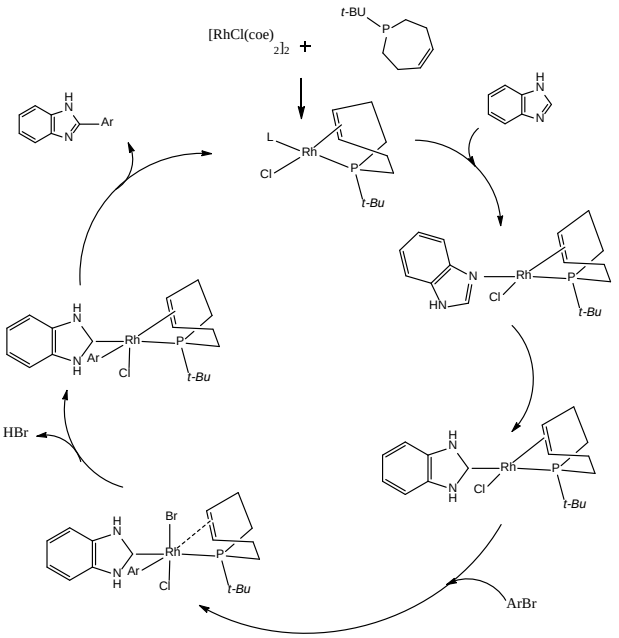

Figure 8: Mechanism of the reaction (*Berman et al., 2008*)

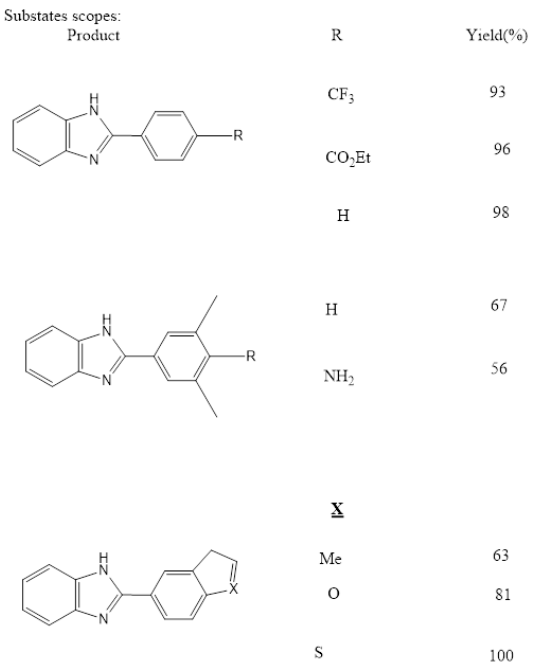

Figure 9: Substarte Scope (*Berman et al., 2008*)

When para and meta substitutions were used, products with high yields were produced (Figure 9). But, ortho-substitution was not fruitful. Additionally, electron-rich compounds paired with good yields. Please note that, in the structures mentioned in Table 9, the “R” groups are referred to as the substituents at the phenyl rings used for the arylation protocol. These findings are highly significant, given that electrophilic metalation occurs at a high yield percentage for these electron-rich heterocycles.

IV. A Hydroformylation reaction of heterocyclic Olefins: A highly selective asymmetric process:

Phosphine-phosphonites are a new class of chiral hybrid diphosphorus ligands that have a novel use in the asymmetric hydroformylation of heterocyclic olefins catalyzed by Rh (Figure 10). The notoriously challenging substrate 2,5-dihydrofuran is enantio selectively converted by the same catalyst under mild reaction conditions, with up to 91% ee contemporaneous with complete regioselectivity to 3-carbaldehydes (Figure11) (Chikkali *et al*., 2012).

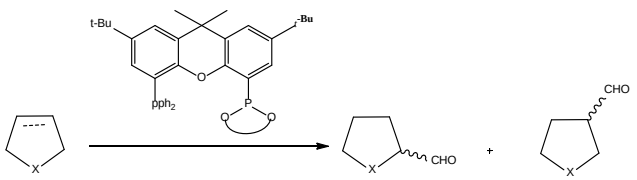

Figure 10: Hydroformylation reaction of heterocyclic Olefins (*Chikkali et al., 2012*)

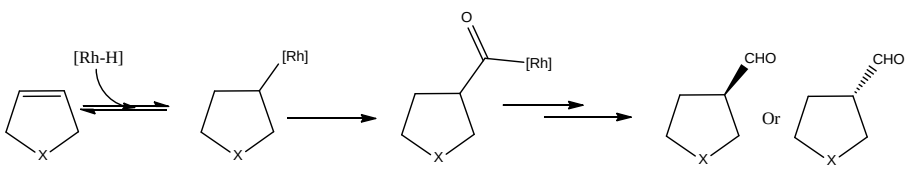

Figure 11: Mechanism of the reaction (*Chikkali et al., 2012*)

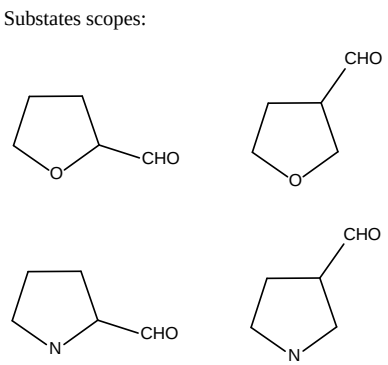

Figure 12: Substarte Scope (*Chikkali et al., 2012*)

Using a sterically more hindered ligand, the 3-carbaldehyde product showed excellent regioselectivity and a promising ee of 89% at room temperature (Figure 12). In product 4, there is a notable reversal of enantio selection from substrate 1 (resulting in (R)-4) to substrate 2 (resulting in (S)-4).

V. Double C-H activation for direct selective C/H oxidative annulations of alkynes and substituted imidazoles with rhodium(III) Catalysis:

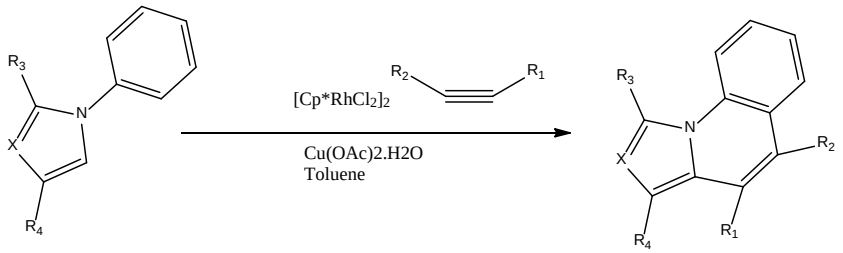

Figure 13: Selective C/H oxidative annulations of alkynes and substituted imidazoles (*Huang et al., 2013*)

Rhodium(III) catalyst was used (Figure 13) to achieve double CH activations of ortho-substituted vinyl/arylimidazoles without the need for a heteroatom-based directing group. Aza-fused heterocycles were effectively and highly yielded by another oxidative annulation with alkynes (Huang *et al*., 2013).

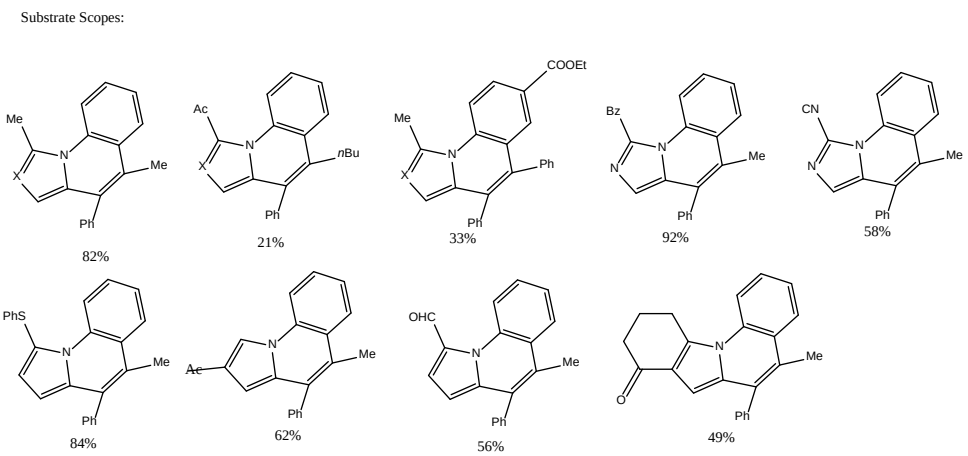

Figure 14: Substarte Scope (*Huang et al., 2013*)

The imidazoles with groups that are either withdrawing or donating electrons at para-position exhibited excellent product yield (Figure 14). Nevertheless, because to steric restriction, an ortho-substituted aryl substrates gave the desired tricycles at much lower yield.

VI. An alternative pathway to Epibatidine for the asymmetric hydroarylation of azabicyles:

A novel rhodium-based chiral NHC-complex, Rh(IBiox[(-)-menthyl](CO)$_2$Cl, has been synthesized and characterized (Figure 15). Furthermore, as a catalyst, this complex's extremely high enantioselectivity was proven and used in the production of epibatidine during an asymmetric hydroarylation reaction of azabicycles (Figure 16) (Bexrud & Lautens, 2010).

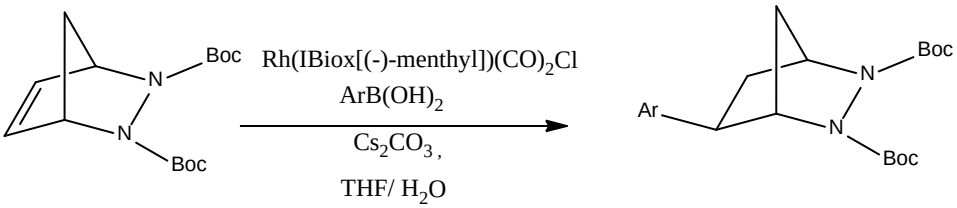

Figure 15: Asymmetric hydroarylation of azabicyles (*Bexrud & Lautens, 2010*)

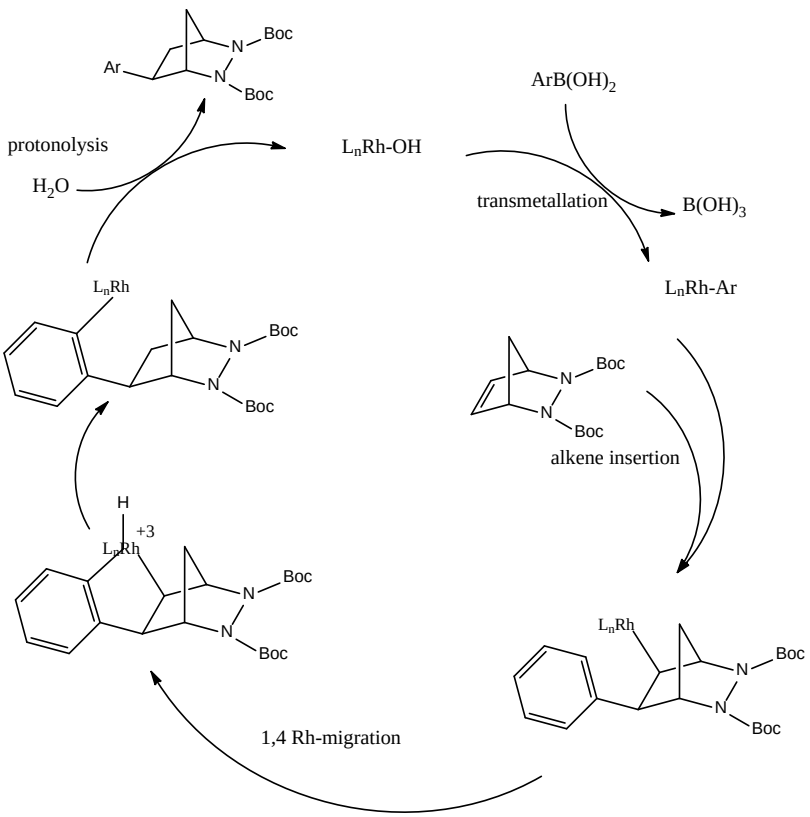

Figure 16: Mechanism of the reaction (*Bexrud & Lautens, 2010*)

Unfavorable steric interactions between the substituents are probably the cause of the low yields found, while electron donating groups can also produce large yields (Figure 17).

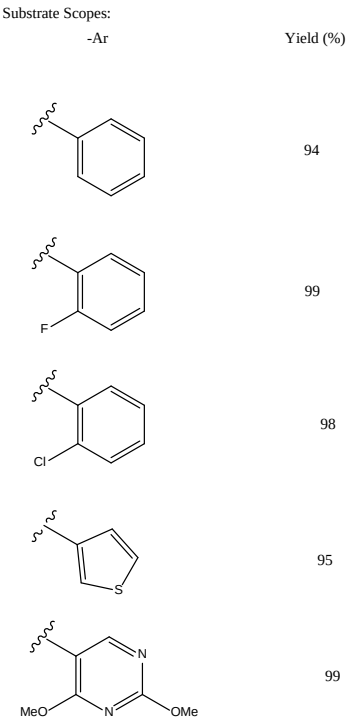

Figure 17: Substarte Scope (*Bexrud & Lautens, 2010*)

VII. Divergent synthesis of indoles and pyrroles by Rh(III)-catalyzed C/H activation:

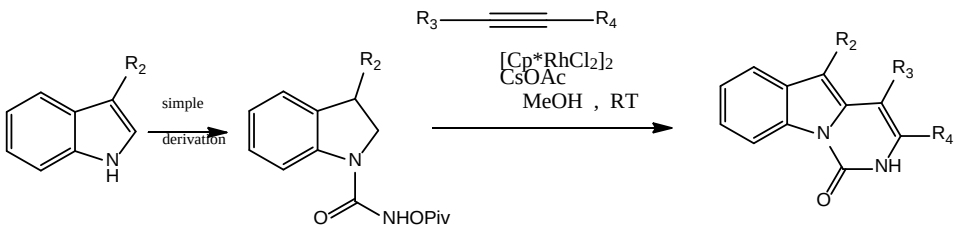

Figure 18: Divergent synthesis of indoles and pyrroles (*Zhang, Zheng & Cui, 2014*)

In this protocol (Figure 187), in presence of CsOAc, a carboxylate was produced from $[Cp^*RhCl_2]_2$, which promoted the C-H activation of indole/pyrrole-N-carboxamides through an initial metalation, followed by a deprotonation pathway (Figure 19), resulting in the formation of rhodacycle (Zhang, Zheng & Cui, 2014).

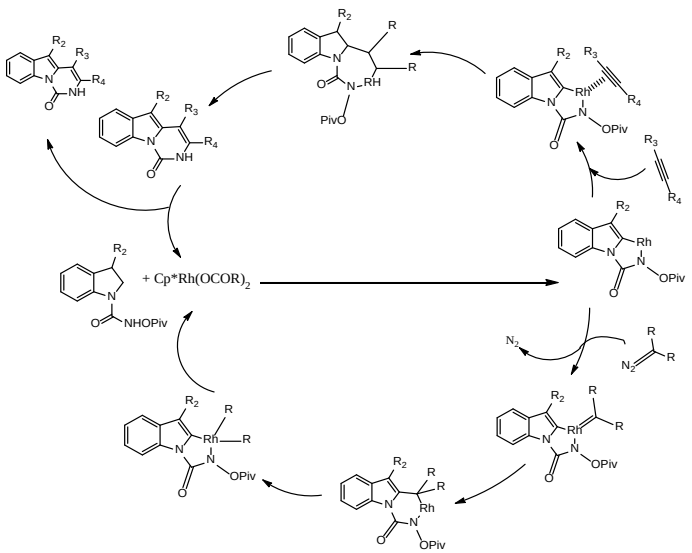

Figure 19: Mechanism of the reaction (*Zhang, Zheng & Cui, 2014*)

The scope of this protocol was expanded by examining the usage of the alkenes under the typical reaction conditions, since these are another excellent coupling partner in this C-H activation/cyclization protocol. The product yield is decreased by the electron-withdrawing group (Figure 20).

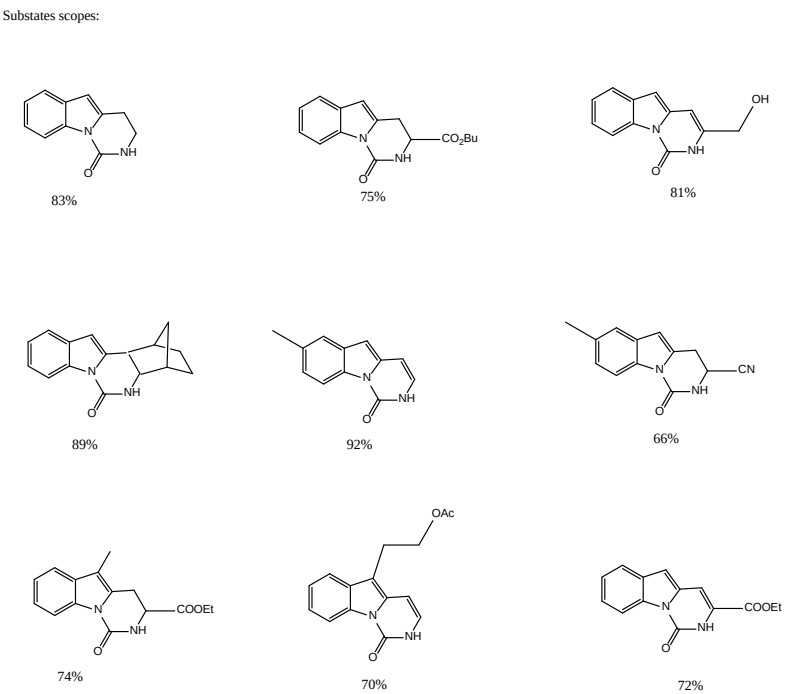

Figure 20: Substarte Scope (*Zhang, Zheng & Cui, 2014*)

VIII. C-H activation at the indole C4-position with allyl alcohols: An example of Rh-carbonyl directed reaction

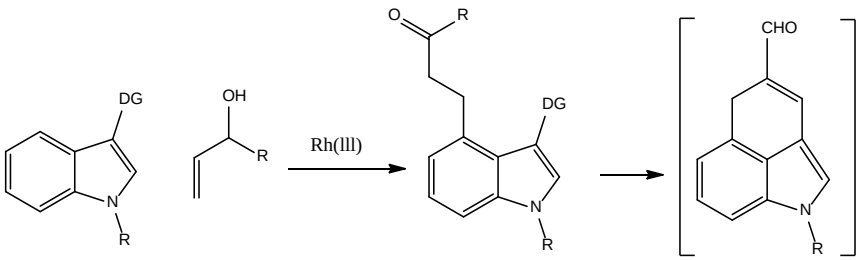

Figure 21: Rh-carbonyl directed reaction (*Sherikar, Devarajappa & Prabhu, 2020*)

In this reaction (Figure 21), the authors report that, a weak coordination of the carbonyl group with the Rh(III) center, directs the coupling of allyl alcohols at the C-4 site of indole derivatives under the optimized activation condition (Figure 22). As a result, indole derivatives only experience alkylation at C–4 site. Under aldol reaction conditions, the resultant product creates a tricyclic derivative as a synthetic precursor to construct certain alkaloid molecules, including hapalindole or ergot alkaloids and similar heterocycles (Sherikar, Devarajappa & Prabhu, 2020).

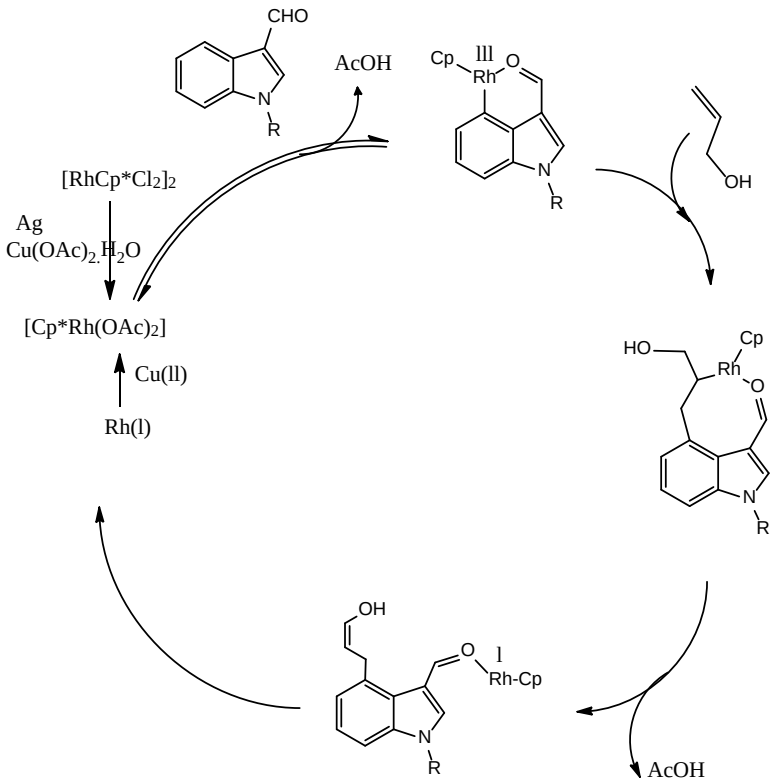

Figure 22: Mechanism of the reaction (*Sherikar, Devarajappa & Prabhu, 2020*)

The intended products were not produced by the substituted indole derivatives that withdrew electrons or by various carbonyl directing such at the indole's C3-position (Figure 23). N-protected derivatives and indole-3-carbaldehyde derivatives with a free NH group failed to create the intended product.

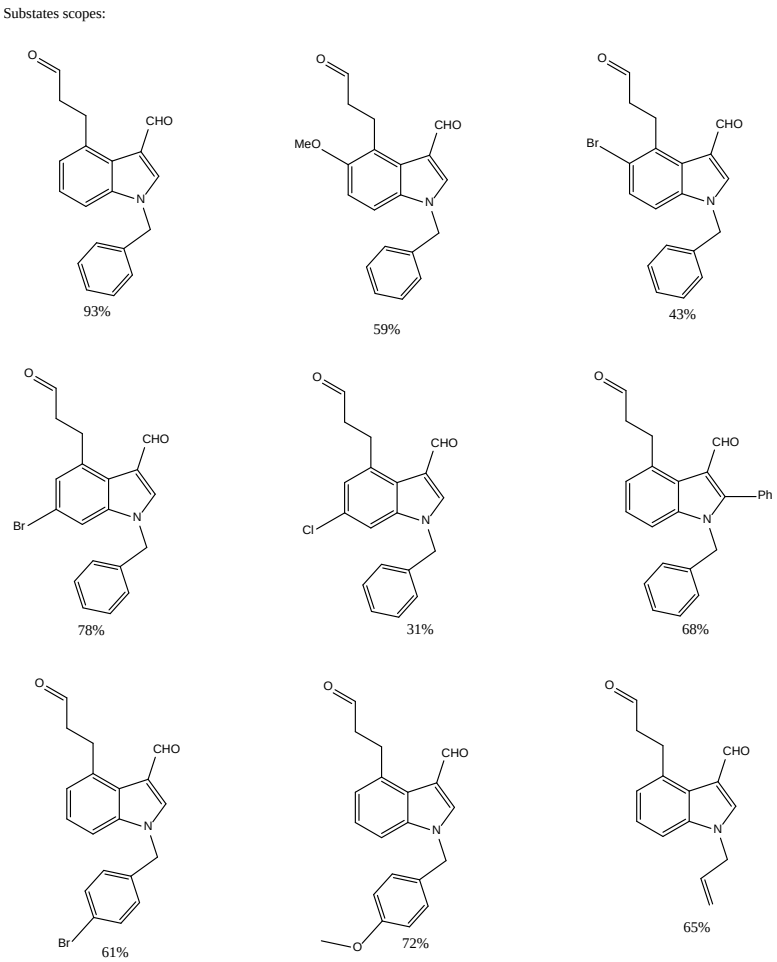

Figure 23: Substarte Scope (*Sherikar, Devarajappa & Prabhu, 2020*)

IX. Rh(III)-catalyst's dual function in the regioselective halogenation of heterocycles:

It is reported (Figure 24) that electron-rich heterocycles can be selectively brominated and iodinated with Rh(III). According to kinetic studies, rhodium has two functions in the bromination process: first, it catalyzes the directed halogenation, and second, it stops these substrates from naturally halogenating. It is possible to use furans, thiophenes, benzothiophenes, pyrazoles, quinolones, and chromones (Schröder, Lied & Glorius, 2015).

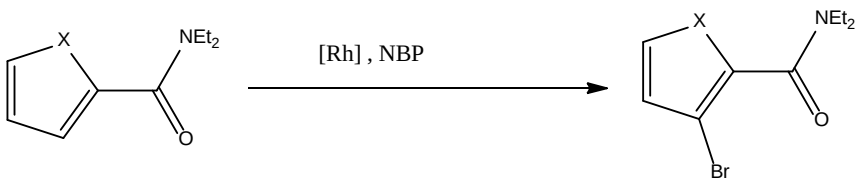

Figure 24: Regioselective halogenation of heterocycles (*Schröder, Lied & Glorius, 2015*)

In order to guarantee high levels of regioselectivity, the rhodium catalyst plays two functions in facilitating the halogenation of substrates, where both the 3- and 5-positions are free (Figure 25). Here, the 5-position becomes less reactive, as rhodium inhibits the intrinsic reaction by delaying the generation of Br_2. Consequently, the directing effect on the halogenation reaction at C3-site was also catalysed, having NBP as the bromine source.

Substates scopes:

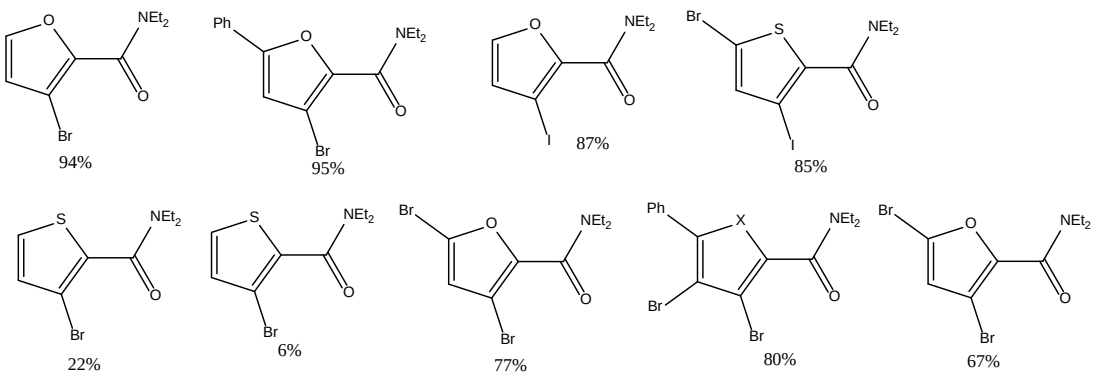

Figure 25: Substarte Scope (*Schröder, Lied & Glorius, 2015*)

Conclusion:

The wide range of applications and revolutionary effects of Rhodium chemistry in the carbon-hydrogen bond activation of oxa- and aza-heterocycles, having 5 ring members, are demonstrated in this review article, which provides an insight into the field. Through an examination of current advancements and forthcoming prospects in diverse subfields, the scientific community now aims to apply these works on pyridine and oxazole derivatives to stimulate additional investigation and cooperation, cultivating a more profound understanding of the infinite capacity of chemistry to mould the world and confront the obstacles that lie ahead.

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