

Emerging Trends in Ruthenium (II) – Catalyzed C-H Bond Functionalization

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ABSTRACT

Ruthenium-catalyzed C-H activation has emerged as a powerful tool in modern organic synthesis, offering unique opportunities for selective bond formation. Ruthenium complexes, renowned for their stability and functional group tolerance, enable the activation of inert C-H bonds under mild conditions. This approach has been extensively utilized for the construction of C-C, C-N, C-O, and C-S bonds through processes like olefination, alkylation, arylation, and annulation. Notably, ruthenium catalysis facilitates directed group-assisted transformations, providing site-selective functionalization of aromatic and aliphatic substrates. Mechanistic investigations have unveiled the prevalence of concerted metalation-deprotonation (CMD) pathways and oxidative addition, influenced by substrate and reaction conditions. Recent strides in the field include the development of sustainable and atom-economic strategies utilizing O₂ or air as terminal oxidants, as well as the incorporation of asymmetric catalysis for enantioselective transformations.

Keywords: C-H bond activation, C-H functionalization, Annulations.

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1. Introduction

Ruthenium-catalyzed C-H activation has emerged as a powerful strategy in modern organic synthesis. This approach bypasses the need for pre-functionalized substrates, allowing for the direct functionalization of abundant C-H bonds. Ruthenium catalysts offer several advantages: high thermal and oxidative stability, cost-effectiveness relative to other noble metals, and the ability to operate under mild conditions.¹ These factors, combined with their broad substrate scope and functional group tolerance, have made

ruthenium a preferred choice for C-H activation reactions. The mechanisms of ruthenium-catalyzed C-H activation are diverse, with the concerted metalation-deprotonation (CMD) pathway being particularly prevalent.²⁻⁴ Directing groups such as carboxylates, pyridines, and amides play a crucial role in enabling regioselective C-H bond activation, both in aromatic and aliphatic systems.⁵ These directing groups not only enhance the regioselectivity but also stabilize the reactive intermediates formed during the catalytic cycle.

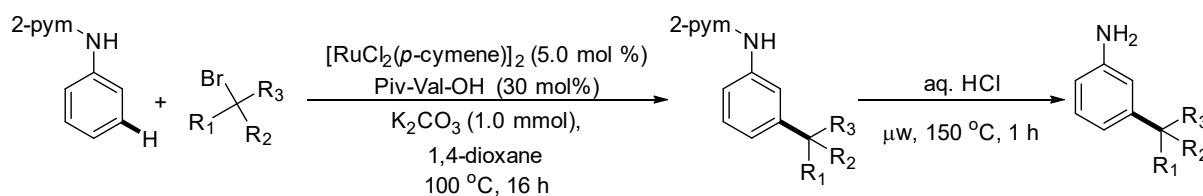
Ruthenium catalysis has been employed to forge a variety of bonds, including C-C, C-N, C-O, and C-S, expanding the synthetic toolbox for constructing pharmaceutically relevant and material-building compounds.⁶ Olefination, arylation, alkylation, and annulation are among the most widely studied transformations.⁷ In particular, olefination reactions, facilitated by the robustness of ruthenium catalysts, have become a benchmark in C-H functionalization. These transformations are not only efficient but also environmentally friendly, especially when employing molecular oxygen or air as terminal oxidants, which generate minimal waste. One of the hallmark advancements in ruthenium-catalyzed C-H activation is its application in asymmetric synthesis.⁸ The development of chiral ruthenium catalysts has enabled enantioselective transformations, providing access to optically active molecules of significant importance in medicinal chemistry. Moreover, late-stage functionalization of complex molecules, including natural products and drug candidates, has been achieved with remarkable precision, showcasing the utility of ruthenium catalysis in the modification of bioactive compounds.⁹

The typical mechanism involves the coordination of the substrate to the ruthenium catalyst via a directing group.¹⁰ Subsequent C-H bond activation leads to the formation of a ruthenium-carbon intermediate. This intermediate can undergo various transformations, such as migratory insertion, reductive elimination, or oxidative coupling, depending on the reaction conditions and desired product. The sustainability of ruthenium-catalyzed C-H activation has also been a focus of recent research.¹¹ The replacement of stoichiometric oxidants like silver and copper salts with greener alternatives has significantly improved the atom economy of these processes. In particular, the use of atmospheric oxygen as the sole oxidant has emerged as a major breakthrough, aligning these reactions with the principles of green chemistry.

Despite its advantages, ruthenium-catalyzed C-H activation is not without challenges. The relatively high cost of ruthenium compared to base metals limits its application on an industrial scale. Additionally, achieving high levels of regioselectivity and enantioselectivity in certain substrates remains a formidable task. However, ongoing research into ligand design, catalyst modification, and reaction engineering continues to address these limitations.

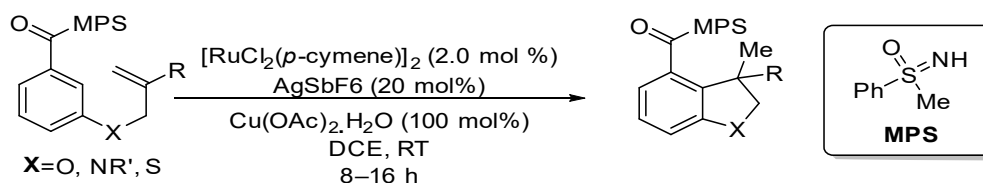
2. Approaches for the Ruthenium(II)-Catalyzed C-H Bond Activation and Functionalization

2.1 N-Acyl Amino Acid Ligands for Ruthenium(II)-Catalyzed meta-C-H tert-Alkylation with Removable Auxiliaries: Jie Li et al., explores a significant advancement in ruthenium-catalyzed C-H functionalization. The work demonstrates the remarkable efficacy of N-acyl amino acid ligands in enabling meta-selective transformations, a challenging frontier in C-H activation chemistry. The authors detail a robust methodology that achieves high meta-selectivity for functionalizing electron-rich anilines and various arenes using removable directing groups. This strategy overcomes limitations associated with traditional chelation-assisted approaches and extends the substrate scope to synthetically valuable, sterically hindered alkyl halides. Furthermore, detailed mechanistic studies provide insights into the reaction's unique characteristics, such as the second-order dependence on catalyst concentration and the homolytic C-Hal cleavage. The findings underscore the versatility and practicality of this catalytic system, paving the way for its broader application in synthetic organic chemistry (Scheme 1).¹²



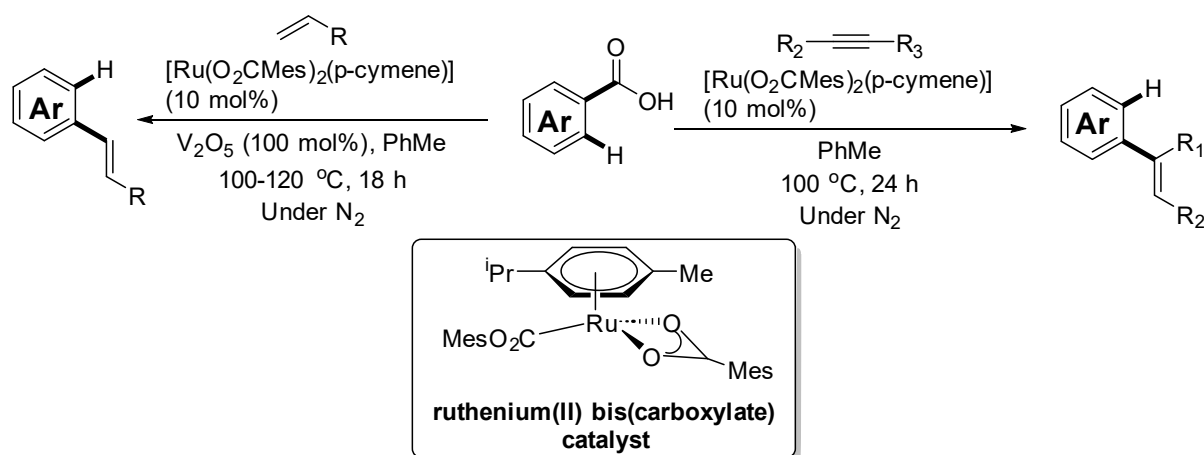
Scheme 1

2.2 Ruthenium-Catalyzed Hydro arylation and One-Pot Twofold Unsymmetrical C-H Functionalization of Arenes: Ghosh et al. highlights an innovative advancement in C-H activation. Using methyl phenyl sulfoximine (MPS) as a directing group, the study demonstrates a ruthenium-catalyzed approach for synthesizing dihydrobenzofurans and indolines via hydroarylation. The research also introduces a novel one-pot strategy for unsymmetrical twofold C-H functionalization, which enables the sequential formation of C-C and C-N or C-C bonds under a single catalytic system. This efficient, atom-economical method allows for the construction of complex heterocyclic frameworks, including isoquinolone-bearing dihydrobenzofurans, under mild conditions. The scalability, broad substrate scope, and mechanistic insights provided in this study underscore its potential for advancing synthetic organic chemistry (Scheme 2).¹³



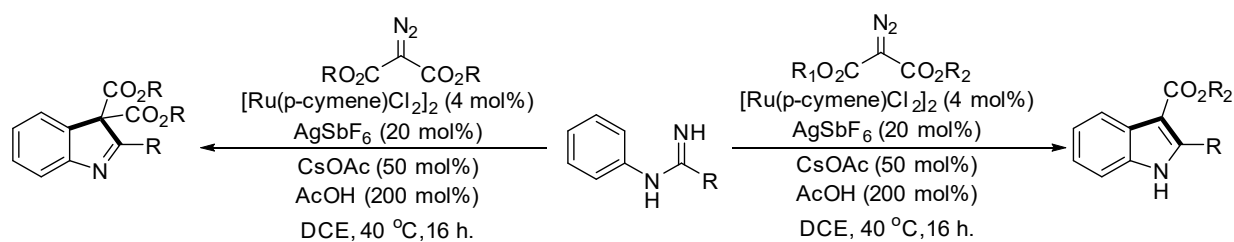
Scheme 2

2.3 Ruthenium(II)-Catalyzed Decarboxylative C-H Activation: Versatile Routes to *meta*-Alkenylated Arenes: Kumar and co-workers, delve into the innovative applications of ruthenium(II) bis(carboxylate) complexes in C-H bond functionalization. This work stands out by achieving decarboxylative C-H alkenylation at low temperatures without the need for copper or silver salts, broadening the substrate scope significantly. Through both oxidative olefination and redox-neutral hydroarylation, the study demonstrates a high degree of chemo-, positional-, and regio-selectivity. The methodology provides efficient access to meta-alkenylated arenes, including those with sensitive substituents, reflecting the robustness and versatility of the catalytic system. By enabling the synthesis of diverse molecular frameworks under mild conditions, this research underscores the transformative potential of ruthenium catalysis in organic synthesis (**Scheme 3**).¹⁴



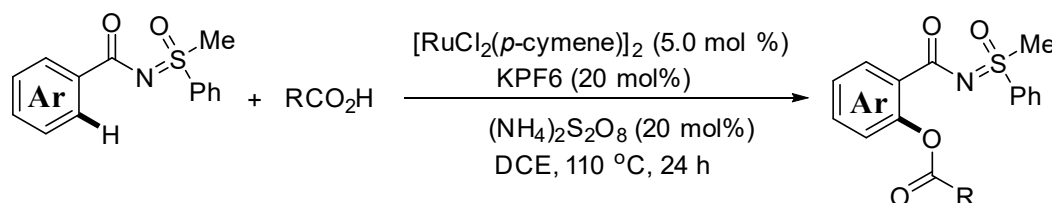
Scheme 3

2.4: Ruthenium(II)-Catalyzed C-H Activation of Imidamides and Divergent Couplings with Diazo Compounds: Substrate-Controlled Synthesis of Indoles and 3*H*-Indoles: Li *et al.* describes a ruthenium-catalyzed C-H activation reaction of imidamides with diazo compounds. The reaction is highly selective for the formation of either indoles or 3*H*-indoles, depending on the substitution pattern of the imidamide. They propose a mechanism for the reaction that involves the formation of a ruthenium carbene intermediate, which undergoes C-H insertion into the imidamide followed by cyclization. This work provides a new method for the synthesis of indoles and 3*H*-indoles, which are important heterocyclic compounds found in many natural products and pharmaceuticals (Scheme 4).¹⁵



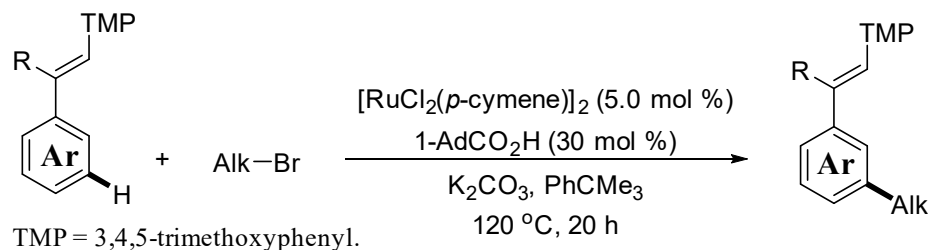
Scheme 4

2.5 Ruthenium(II)-Catalyzed C-H Oxygenations of Reusable Sulfoximine Benzamides: Raghuvanshi et al. reported a novel ruthenium(II)-catalyzed C-H oxygenation of sulfoximine benzamides. This method utilizes a user-friendly ruthenium(II) catalyst to achieve C-H activation with excellent selectivity and functional group tolerance. The oxygenation reaction proceeds *via* a base-assisted intramolecular electrophilic substitution (BIES) mechanism. The resulting oxygenated products are versatile intermediates for further synthetic transformations, and the sulfoximine directing group can be readily removed (**Scheme 5**).¹⁶



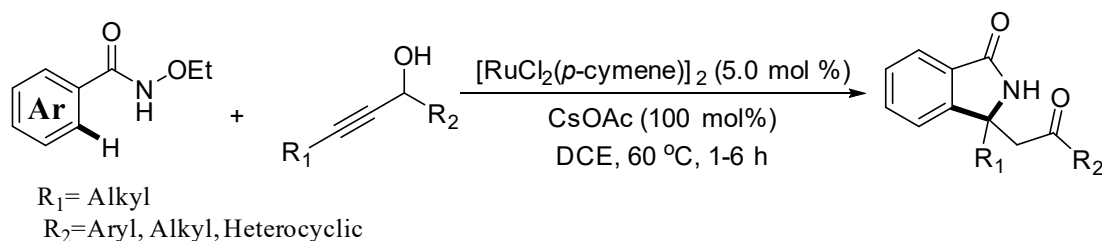
Scheme 5

2.6 Ruthenium(II)-catalysed remote C-H alkylations as a versatile platform to *meta*-decorated arenes: Li *et al.* reported a ground-breaking ruthenium-catalyzed C-H alkylation strategy for the selective functionalization of arenes at the meta-position. This method utilizes a unique arene ligand effect to enable remote C-H activation, providing a versatile platform for the synthesis of diverse *meta*-substituted arenes, including key structural motifs in various fields like pharmaceuticals and materials science (**Scheme 6**).¹⁷



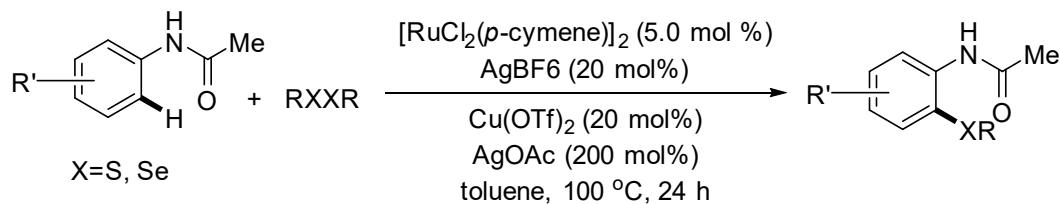
(Scheme 6)

2.7 Ruthenium-Catalyzed Redox-Neutral [4+1] Annulation of Benzamides and Propargyl Alcohols *via* C-H Bond Activation: Liu and co-worker, reported a novel ruthenium-catalyzed annulation reaction between benzamides and propargyl alcohols. This reaction utilizes propargyl alcohols as one-carbon units, leading to the formation of *N*-substituted quaternary isoindolinones. The reaction proceeds under mild conditions and exhibits good functional group tolerance. The authors propose a plausible mechanism for the reaction, highlighting the unique role of ruthenium in activating both the benzamide and propargyl alcohol substrates. This work provides a valuable synthetic tool for the construction of diverse heterocyclic scaffolds (**Scheme 7**).¹⁸



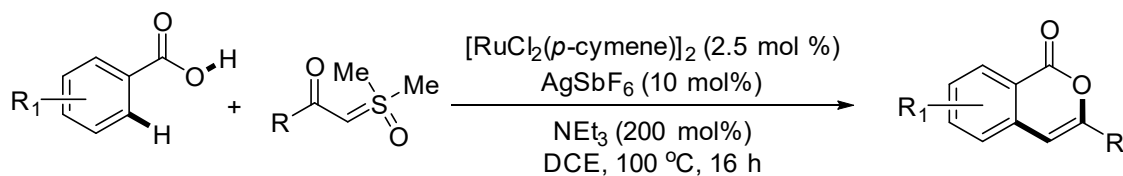
(Scheme 7)

2.8 Ruthenium(II)-Catalyzed C-H Chalcogenation of Anilides: Wenbo Ma and co-worker reported a ruthenium(II)-catalyzed method for C-H chalcogenation of anilides, effectively introducing selenium or sulphur groups using readily available diselenides and disulfides. This approach demonstrates broad substrate scope and excellent site selectivity under mild conditions, emphasizing its utility in synthesizing biologically and synthetically valuable compounds. Mechanistic investigations suggest a base-assisted internal electrophilic substitution (BIES) mechanism. The method offers advantages in environmental sustainability and step economy, positioning it as a promising tool for medicinal chemistry and functional material development (Scheme 8).¹⁹



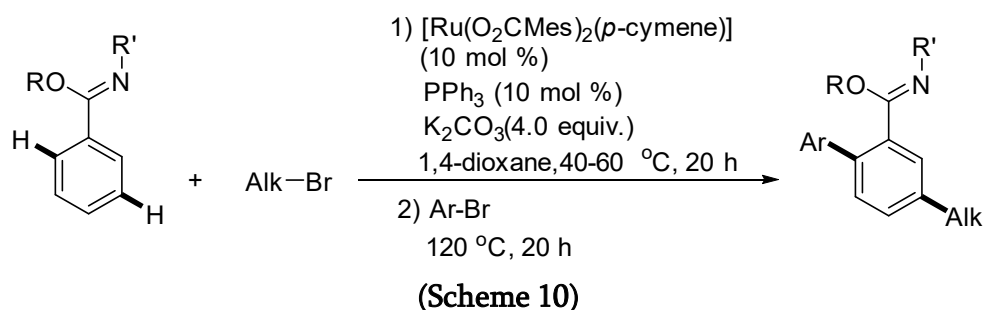
(Scheme 8)

2.9 Ruthenium(IV) Intermediates in C-H Activation/Annulation by Weak O-Coordination: Liang *et al.* presented a transformative approach to C-H functionalization via ruthenium catalysis. Which uncover the crucial role of ruthenium(IV) intermediates in facilitating efficient annulations of sulfoxonium ylides with benzoic acids. Notably, this method operates under redox-neutral conditions, exhibiting high selectivity and compatibility with a wide range of functional groups, enabling the synthesis of diverse isocoumarins. Through meticulous experimental and computational analyses, the study elucidates a base-assisted internal electrophilic substitution (BIES) mechanism, distinguishing ruthenium catalysis from other metals. This work highlights a sustainable and versatile framework for C-H activation with significant implications for pharmaceutical and natural product synthesis (Scheme 9).²⁰

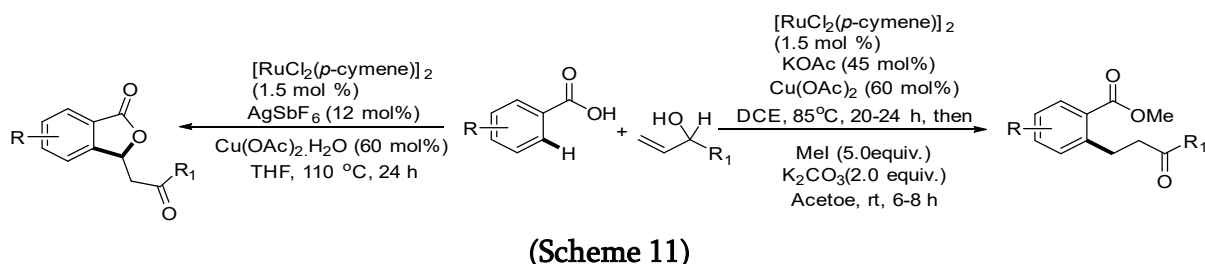


(Scheme 9)

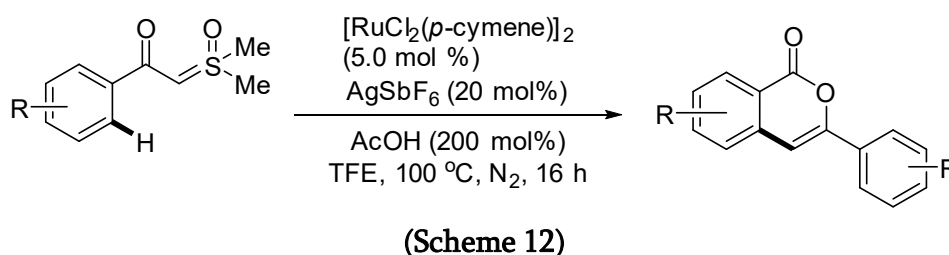
2.10 Sequential *meta*/*ortho*-C-H Functionalizations by One-Pot Ruthenium(II/III) Catalysis: Lutz and co-worker presented a groundbreaking method for site-selective C-H functionalization using a single ruthenium catalyst in a one-pot fashion. The work emphasizes a sequential twofold C-H activation strategy combining *meta*-C-H alkylation and *ortho*-C-H arylation, showcasing exceptional positional selectivity under mild conditions. The study integrates experimental evidence, including electron paramagnetic resonance (EPR) spectroscopy, and computational analyses to elucidate a novel mechanistic pathway involving ruthenium(III) intermediates. The approach's versatility is demonstrated across diverse substrates and functional groups, offering significant implications for sustainable synthesis and late-stage functionalization in organic chemistry. This work sets a benchmark for efficient, selective, and operationally simple C-H functionalization methodologies (Scheme 10).²¹



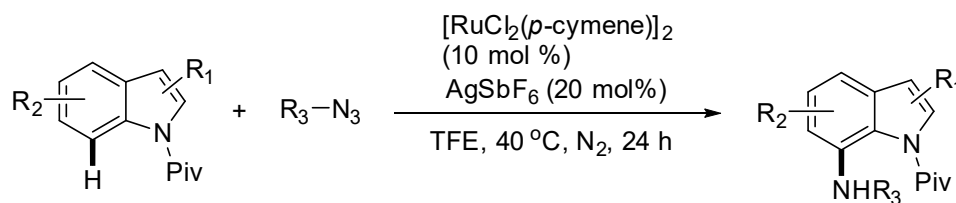
2.11 Ruthenium-Catalyzed C-H Functionalization of Benzoic Acids with Allyl Alcohols: A Controlled Reactivity Switch between C-H Alkenylation and C-H Alkylation Pathways: G. S. Kumar and co-worker highlights an innovative methodology to achieve selective C-H alkylation and C-H alkenylation by employing allyl alcohols as versatile coupling partners. This study presents a controlled switch in reactivity pathways by tuning reaction conditions, allowing access to diverse products such as 2-alkylbenzoic acids and phthalides. The use of carboxylate-directed C-H activation underscores the robustness and sustainability of this approach. Comprehensive mechanistic insights, including kinetic isotope effects and reversibility studies, delineate a pathway involving ruthenacycle intermediates and reactivity control *via* β -hydride elimination or protonolysis. The work not only expands the synthetic toolbox for C-H functionalization but also showcases the utility of allyl alcohols in constructing valuable molecular frameworks (Scheme 11).²²



2.12 Ruthenium(II)-Catalyzed Homocoupling of Weakly Coordinating Sulfoxonium Ylides *via* C-H Activation/Annulations: Synthesis of Functionalized Isocoumarins: Zhou *et al.* developed the ruthenium(II)-catalyzed homocoupling of weakly coordinating sulfoxonium ylides *via* C-H activation represents a significant advancement in synthetic methodology. This process, involving an intramolecular nucleophilic addition and elimination sequence, offers a simple and step-economic route to 3-substituted isocoumarins, compounds with notable synthetic and pharmaceutical importance. The protocol showcases excellent functional group tolerance and efficiency, utilizing sulfoxonium ylides as dual-function reagents serving both as aromatic substrates and acylmethylation reagents. The versatility of the products is further highlighted by their facile transformation into diverse valuable derivatives. This strategy not only emphasizes the utility of ruthenium(II) catalysis in promoting C-H activation but also underscores the potential of sulfoxonium ylides in modern organic synthesis, providing a robust approach for the construction of functionalized isocoumarins (Scheme 12).²³

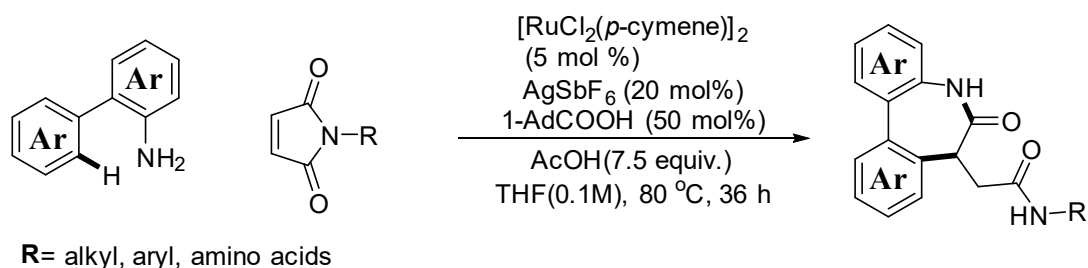


2.13 C7-Indole Amidations and Alkenylations by Ruthenium(II) Catalysis: Lutz Ackermann *et al.* reported a ruthenium(II)-catalyzed site-selective C7-H functionalization of indoles, representing a significant advancement in the selective modification of biologically and pharmaceutically important scaffolds. This strategy addresses the longstanding challenge of activating the C7 position, a key structural motif in antiviral agents targeting SARS-CoV and HIV-1. The methodology employs a ruthenium(II) biscarboxylate catalyst under mild conditions and proceeds *via* a base-assisted internal electrophilic substitution (BIES) pathway facilitated by weak O-coordination, enabling high site selectivity. Notably, this protocol accommodates a broad range of C-N and C-C bond-forming transformations. Furthermore, the approach is characterized by its operational simplicity, scalability to gram-scale synthesis, and the traceless removal of directing groups, thereby enhancing its practicality for pharmaceutical applications. Mechanistic studies, supported by NMR spectroscopy and mass spectrometry, indicate the involvement of ruthenium nitrenoid intermediates, which play a crucial role in achieving the observed site selectivity (Scheme 13).²⁴



(Scheme 13)

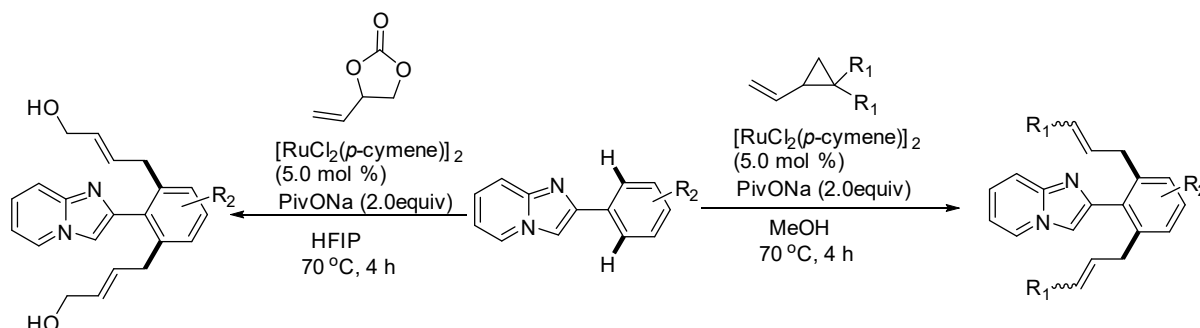
2.14 Ruthenium-Catalyzed Site-Selective C-H Bond Activation/Annulation Cascade toward Dibenzazepinone Skeletons: Chowdhury *et al.* reported a ruthenium(II)-catalyzed free amine-directed hydroarylation and regioselective transamidation cascade between 2-aminobiphenyls and maleimides, representing a significant advancement in the construction of biologically relevant dibenzo[*b,d*]azepinone scaffolds. This methodology effectively addresses the challenge of assembling medium-sized heterocyclic frameworks through a cascade process integrating C-H activation and annulation. The protocol employs a ruthenium(II) catalyst system that enables efficient transformation under mild conditions, delivering the desired products in high yields with excellent functional group tolerance. Notably, the strategy allows structural diversification through the incorporation of amino acid side chains via substrate modification, thereby expanding the scope of accessible dibenzazepinone derivatives. Furthermore, the approach is distinguished by its operational simplicity and synthetic versatility, enhancing its applicability in complex molecule synthesis. Mechanistic investigations indicate that the C-H bond cleavage step is reversible and not rate-determining, highlighting the efficiency of the catalytic system (Scheme 14).²⁵



(Scheme 14)

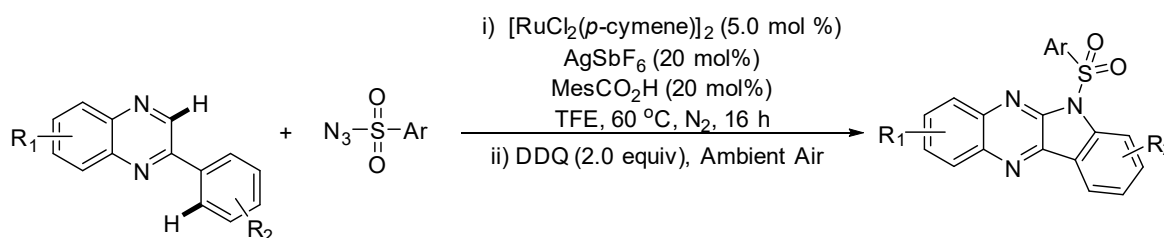
2.15 Ruthenium-Catalyzed C(sp²)-H Bond Bisallylation with Imidazopyridines as Directing Groups: Liu *et al.* reported a ruthenium(II)-catalyzed bis-allylation of imidazopyridines with vinylcyclopropanes (VCPs) and vinyl cyclic carbonates, representing a notable advancement in regioselective C-H activation and functionalization. This strategy exploits the imidazopyridine pharmacophore as an intrinsic directing group, enabling efficient bisallylation through a tandem sequence involving C-H activation and ring cleavage under mild and redox-neutral conditions. The methodology demonstrates a broad substrate scope and excellent functional group tolerance, highlighting its versatility for synthetic applications. Notably, this work represents the first example of direct *o*-

allylation of imidazopyridines, providing a regioselective route to structurally diverse and valuable imidazopyridine derivatives. Furthermore, the protocol is distinguished by its operational simplicity and step-economical nature, facilitating the rapid construction of complex molecular frameworks (Scheme 15).²⁶



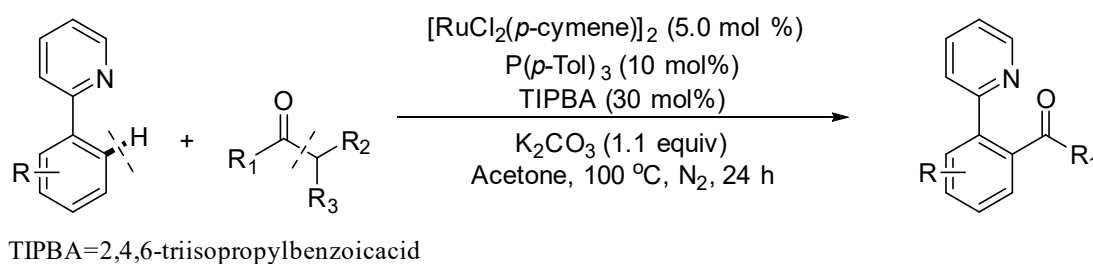
(Scheme 15)

2.16 One-Pot Construction of Indolo[2,3-*b*]quinoxalines through Ruthenium-Catalyzed *Ortho* C-H Bond Functionalization of 2-Arylquinoxalines with Sulfonyl Azides: Laru *et al.* reported a ruthenium(II)-catalyzed synthesis of N-substituted indolo[2,3-*b*]quinoxalines via *ortho*-C-H functionalization of 2-arylquinoxalines with sulfonyl azides, followed by DDQ-mediated oxidation, representing an efficient one-pot strategy for double C-N bond formation. This methodology provides rapid access to structurally complex heterocycles in high yields (up to 94%) with broad substrate scope and excellent functional group tolerance. The reaction proceeds through a five-membered ruthenacyclic intermediate during the initial amination step, followed by a radical-mediated oxidative amination process, highlighting a unique combination of organometallic and radical pathways. Notably, the protocol enables the synthesis of diverse bioactive indolo[2,3-*b*]quinoxaline derivatives, including unprotected and 9-bromo-substituted scaffolds. Furthermore, the approach is distinguished by its operational simplicity and synthetic versatility, enhancing its applicability in complex molecule synthesis. This strategy underscores the potential of ruthenium(II) catalysis in constructing fused heterocyclic frameworks and provides a robust platform for accessing biologically relevant molecules with diverse functionalization patterns, offering promising prospects for medicinal chemistry and pharmaceutical research (Scheme 16).²⁷



(Scheme 16)

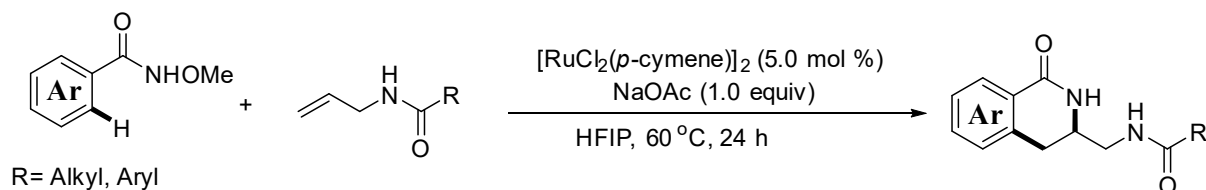
2.17 A Strategy for Amide C-N Bond Activation with Ruthenium Catalyst: Selective Aromatic Acylation: W. Li *et al.* reported a ruthenium(II)-catalyzed strategy for amide C-N bond activation, representing a significant advancement in tandem C-H and C-N bond functionalization. This approach utilizes *in situ*-generated bis-cycloruthenated complexes, which exhibit enhanced oxidative addition capability, enabling the activation of otherwise inert amide C-N bonds under mild conditions. The methodology proceeds with high selectivity to afford monoacylated products in moderate to good yields, while demonstrating broad functional group tolerance, including halogens, esters, acetyl, and vinyl substituents. Notably, the protocol avoids undesired alkylation, ensuring selective monoacylation. Furthermore, the use of an air-stable and cost-effective Ru(II) catalyst, combined with operational simplicity and a wide substrate scope, enhances the practical applicability of this transformation. This tandem strategy highlights the potential of ruthenium catalysis in enabling challenging bond activations and provides an efficient platform for the synthesis of valuable monoacylated compounds, with promising implications for advanced organic synthesis (Scheme 17).²⁸



(Scheme 17)

2.18 Ruthenium(II)-catalyzed C-H activation and (4+2) annulation of aromatic hydroxamic acid esters with allylic amides: Giri *et al.* reported a ruthenium(II)-catalyzed (4+2) annulation of aromatic hydroxamic acid esters with allylic amides, representing an efficient strategy for the construction of aminomethyl isoquinolinone frameworks. This transformation proceeds *via ortho*-C-H bond activation under mild conditions, affording a diverse range of isoquinolinones in good to excellent yields. Notably, the reaction exhibits unique reactivity by favoring annulation over the commonly observed allylation pathway associated with allylic coupling partners, highlighting the distinct reactivity profile of the ruthenium catalyst system. The methodology also demonstrates broad substrate scope and excellent functional group tolerance. Furthermore, the protocol enables late-stage functionalization of complex bioactive molecules, including steroid derivatives and amino acid analogues, underscoring its synthetic utility. This unprecedented strategy expands the scope of ruthenium(II)-catalyzed annulation reactions and provides a practical platform for accessing structurally complex heterocycles, with promising applications in medicinal chemistry and related fields

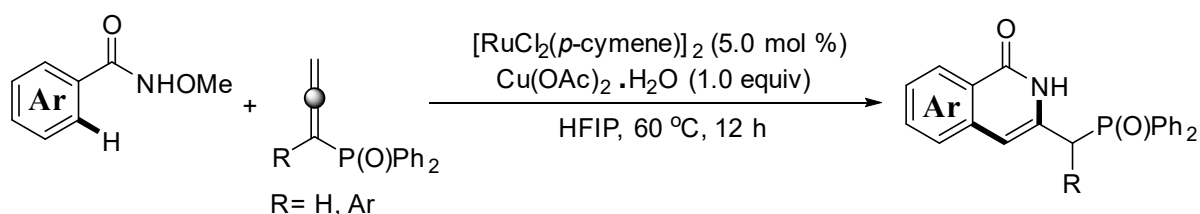
(Scheme 18).²⁹



(Scheme 18)

2.19 Regioselective Annulation of Allenylphosphine Oxides with Aromatic Amides under Ruthenium(II) Catalysis: Chowdhury *et al.* reported a ruthenium(II)-catalyzed (4+2) annulation between aromatic amides and allenylphosphine oxides, representing an innovative approach for the synthesis of NH-free isoquinolinone frameworks. This unprecedented transformation proceeds under mild conditions via weak coordination assistance, enabling regioselective allene insertion into the Ru-C bond to afford a diverse range of isoquinolinone derivatives. The methodology exhibits excellent functional group tolerance and high selectivity, making it particularly suitable for late-stage functionalization of biologically relevant molecules, including complex substrates such as cholesterol, tocopherol, ibuprofen, probenecid, and amino acid derivatives. Furthermore, the phosphine oxide moiety serves as a versatile synthetic handle for subsequent transformations, facilitating the synthesis of 2-alkyl and 2-alkenyl NH-free isoquinolinones.

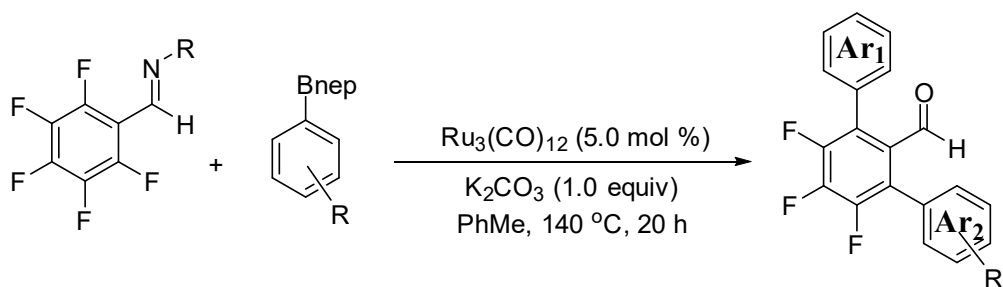
Mechanistic studies suggest a reversible C-H ruthenation step proceeding *via* a concerted metalation-deprotonation (CMD) pathway, which is not rate-limiting in the catalytic cycle. Overall, this strategy expands the scope of ruthenium(II)-catalyzed annulation reactions and provides an efficient platform for accessing structurally diverse heterocycles, with promising applications in medicinal chemistry and chemical biology (Scheme 19).³⁰



(Scheme 19)

2.20 Ruthenium-Catalyzed C-F Bond Arylation of Polyfluoroarenes: Polyfluorinated Biaryls by Integrated C-F/C-H Functionalization: Michal group has developed a site-selective arylation of C-F bonds in polyfluoroarenes enabled by a ruthenium catalyst system, providing a robust and efficient approach for the synthesis of polyfluorinated

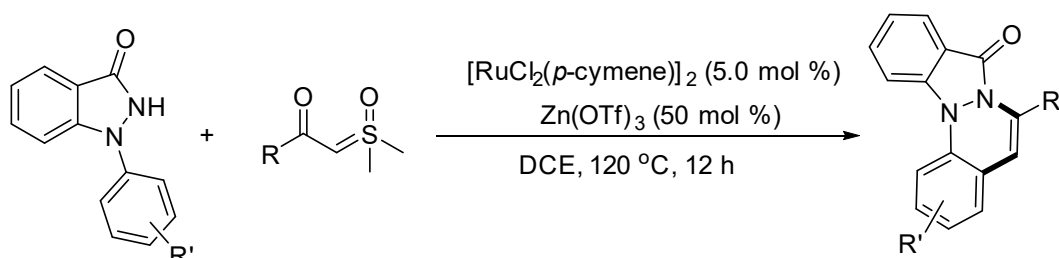
biaryls, which are crucial in pharmaceuticals, agrochemicals, and functional materials. This methodology is distinguished by its exclusive reactivity at the ortho-position of polyfluorinated arenes, facilitated by ruthenium(0) chelation to a readily modifiable directing group. The approach accommodates a wide range of polyfluoroarenes and organoboranes, delivering biaryls with a versatile aldehyde functional group, which is easily removable. A unique feature of this method is its ability to integrate C-F and C-H functionalization using the same ruthenium catalyst, enabling programmed access to multifluorinated biaryls. The reaction displays exceptional functional group tolerance and broad applicability, exemplified by the synthesis of polyfluorinated ligands, heterocycles, pharmaceuticals, and porphyrin analogues. Density functional theory (DFT) studies offer insights into the selectivity of C-F bond activation, highlighting the key role of ruthenium(0) catalysis in this transformation. Given the scarcity of methods for selective C-F activation in polyfluorinated molecules, this approach is poised to make significant contributions to the development of fluorinated chemical space. Ongoing research aims to further expand the scope of $\text{Ru}_3(\text{CO})_{12}$ catalyzed C-X functionalizations, including photochemical methods (Scheme 20).³¹



(Scheme 20)

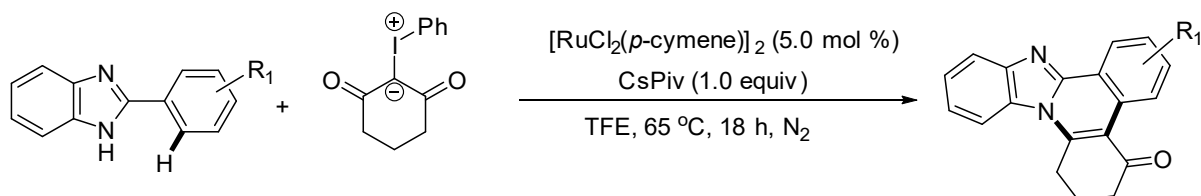
2.21 Ruthenium-catalyzed C-H Functionalization/Annulation of *N*-Aryl Indazoles/Phthalazines with Sulfoxonium Ylides to access Tetracyclic-fused Cinnolines

Yu *et al.* has developed a ruthenium-catalyzed cascade C-H functionalization/intramolecular annulation of *N*-phenylindazoles with sulfoxonium ylides for the efficient synthesis of indazolo[1,2-*a*]cinnolinones. This transformation offers several advantages, including one-pot C-H/N-H functionalization, the use of a cost-effective ruthenium catalyst, and broad substrate scope with good functional group tolerance. Notably, this reaction does not require external oxidants, making it more efficient and sustainable. In addition, the reaction of 2-arylphthalazine-1,4-diones with sulfoxonium ylides successfully yields phthalazino[2,3-*a*]cinnolindiones under standard conditions, further demonstrating the versatility of the method. This work represents a **straightforward** and cost-effective protocol for the synthesis of cinnoline derivatives, making it a valuable addition to the synthetic toolbox for producing complex heterocyclic structures (Scheme 21).³²



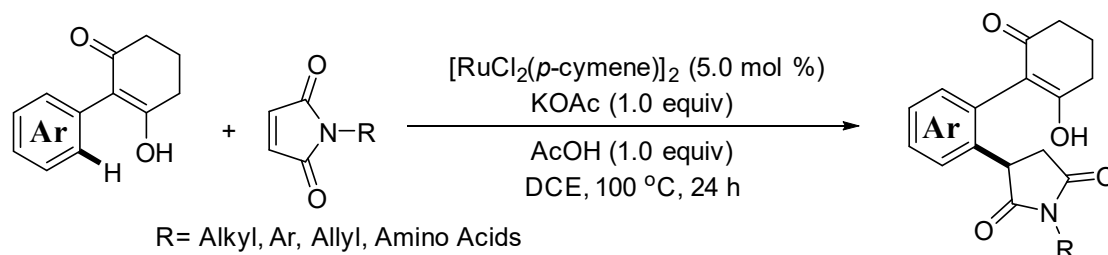
(Scheme 21)

2.22 Ru(II)-Catalyzed C-H Functionalization of 2-Arylbenzimidazoles with Iodonium Ylides: A Straightforward Access to Bridgehead Polycyclic *N*-Heterocycles: Saiprasad and co-worker has disclosed an efficient ruthenium-catalyzed C-H functionalization of 2-arylbenzimidazoles and 2-arylimidazoles with iodonium ylides, leading to the synthesis of substituted tetracyclic and pentacyclic bridgehead *N*-heterocycles. In this groundbreaking approach, iodonium ylides serve as carbene precursors, proceeding *via* a Ru-carbenoid intermediate for the first time. This protocol operates under mild conditions, showcases a broad substrate scope, and enables the gram-scale synthesis of high-value bridgehead polycyclic *N*-heterocycles with diverse functional groups. Furthermore, its synthetic utility was demonstrated through the concise synthesis of the core structure of the natural product zephycandidine A. Ongoing studies in the laboratory aim to explore the biological applications of this methodology, underscoring its potential in medicinal chemistry and drug discovery (Scheme 22).³³



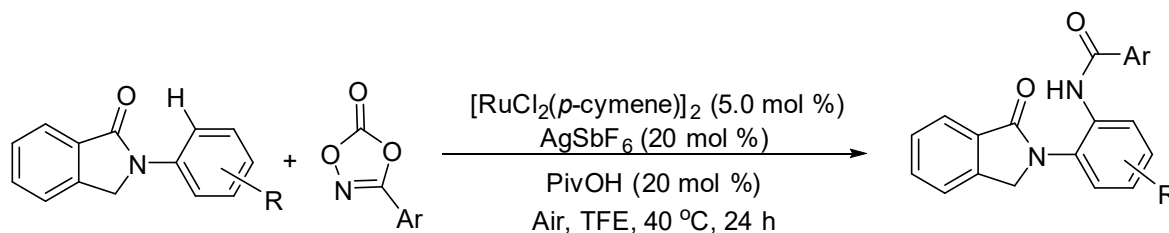
(Scheme 22)

2.23 Redox-Neutral Ruthenium(II)-Catalyzed Enol-Directed Arene C-H Alkylation with Maleimides: Mondal *et al.* has developed an enol-directed regioselective arene C-H alkylation with maleimides under redox-neutral Ru(II) catalysis, providing diverse 3-aryl succinimides, including amino acid-derived frameworks, in good to excellent yields. The products can be further transformed into resorcinol-based biaryls *via* oxidative aromatization. Mechanistic studies indicate a reversible C-H ruthenation step in the reaction pathway. This operationally simple method showcases broad substrate compatibility and functional group tolerance, offering valuable applications in synthetic chemistry. Further exploration of enol-directed C-H activation reactions is ongoing (Scheme 23).³⁴



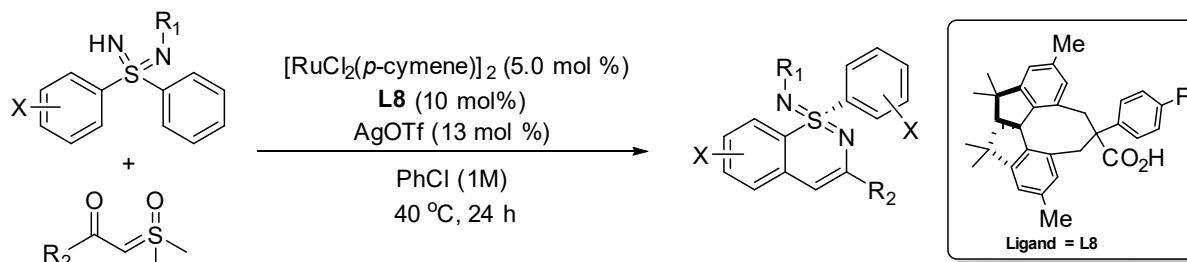
(Scheme 23)

2.24 Precise control of the site selectivity in ruthenium catalyzed C-H bond amidations using cyclic amides as powerful directing groups: Yuan and workers have developed a ruthenium-catalyzed method for selective C-H bond amidation using cyclic amides as weak directing groups and dioxazolone derivatives as safe amidating agents. This protocol offers high mono-, regio-, and site-selectivity under mild conditions (air, 40 °C) with broad functional group compatibility across upto20 examples. Mechanistic insights, supported by DFT calculations, reveal that six-membered cycloruthenate intermediates drive selectivity, with CO₂ extrusion as the rate-determining step. This efficient and versatile methodology advances C-N bond formation, providing valuable applications in organic synthesis and medicinal chemistry (Scheme 24).³⁵



(Scheme 24)

2.25 Enantioselective Synthesis of 1,2-Benzothiazine 1-Imines *via* Ru^{II}/ Chiral Carboxylic Acid-Catalyzed C-H Alkylation/Cyclization: Tao group has developed an enantioselective synthesis of 1,2-benzothiazine 1-imines, cyclic sulfondiimine derivatives, via C-H alkylation/cyclization of sulfondiimines with sulfoxonium ylides. This transformation leverages a combination of [Ru(*p*-cymene)Cl₂]₂ and a newly developed chiral spiro carboxylic acid, achieving high enantioselectivity. The methodology expands the accessible chemical space of chiral S⁶ compounds and demonstrates a broad substrate scope. This study highlights the potential of the metal/chiral carboxylic acid system for enantioselective C-H functionalization reactions (Scheme 25).³⁶



(Scheme 25)

6. Conclusion

In conclusion, ruthenium-catalyzed C-H activation represents a transformative approach in organic synthesis, offering unparalleled opportunities for innovation in bond formation and molecular complexity. Its combination of efficiency, selectivity, and sustainability underscores its critical role in addressing contemporary challenges in synthetic chemistry. This review aims to provide a comprehensive overview of recent advancements, focusing on mechanistic insights, synthetic applications, and emerging trends in ruthenium-catalyzed C-H activation.

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Dr. Ashish Joshi - Formal Analysis and Writing

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Statement of Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this review article. The authors have no financial, commercial, or personal relationships that could be perceived to influence the work reported in this paper.

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