A Short Review of C7 – H Bond Functionalization of Indole/Indoline

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ABSTRACT

Recent progress in transition metal-catalyzed selective C–H functionalization of indoles has attracted significant interest. Indoles functionalized at the C7 position represent key structural frameworks found in numerous bioactive molecules and pharmaceutical agents. Initial advancements in C7 modifications were achieved via directed ortho metalation (DOM), followed by quenching with appropriate electrophiles or through halogenation using Cu (II) halides. Direct functionalization at the C-7 position of indoles is relatively challenging due to the intrinsic reactivity pattern of the pyrrole-type ring, which favors modifications at the C-2 and C-3 positions. Nonetheless, recent advancements in transition-metal-catalyzed, auxiliary-assisted strategies have enabled site-selective C-7 functionalization. These methods have proven to be powerful tools for forming carbon–carbon and carbon–heteroatom bonds, thereby expanding the structural diversity of indole derivatives. This review underscores the progress and applications of recent advancements in the transformation of the otherwise inert C7–H bond.

Keywords: Metalation, site selective, C-H Activation

INTRODUCTION

Indole and its derivatives frequently serve as fundamental structural units in natural products and a broad spectrum of biologically active compounds [1]. The wide range of valuable properties exhibited by molecules containing the indole core continues to drive the development of new synthetic methods for their construction [2]. Traditionally, the synthesis of substituted indoles is categorized into two main approaches: (a) building the indole ring from non-indole starting materials [3], and (b) directly modifying an already-formed indole structure. Indole synthesis and functionalization have been extensively studied for over a century, leading to the development of numerous well-established classical methods. In recent decades, C–H activation has emerged as a promising and efficient approach for modifying indoles and their derivatives. While Sandtorv's review provides extensive coverage of C2 and C3 functionalization [4], the modification of benzenoid positions remains largely underexplored. Recent reviews by the Ackermann and Shi research groups focus on different aspects of benzenoid functionalization: the Ackermann group highlights advancements in C4-position functionalization [5], while the Shi group emphasizes strategies for achieving regioselective arylation of the benzenoid ring [6].

As a continuation of our investigations into directed C–H functionalization, with a focused interest in transforming the indole framework, we present this feature article highlighting transition-metal-catalyzed, site-selective C7-functionalization of indoles. Indoles naturally favor C3 metalation during C–H activation [7]. To override this preference and enable site-selective C–H functionalization, various heteroatom-containing groups are introduced at the nitrogen (N) position of the indole. To achieve site-selective C–H functionalization, commonly used directing groups like acetyl [8], pivaloyl [9], N, N-dimethylcarbamoyl[10], and pyrimidyl[11] are employed to promote C2 selectivity, whereas bulkier groups such as phosphinoyl and hydrosilyl shift selectivity towards the C7 position. Sterically demanding groups like di-tert-butyl substituents enhance C7 selectivity by restricting N–P bond rotation and favorably orienting the molecule for C–H activation at the C7 position. Selective functionalization at the C7 position remains rare; however, several elegant transition-metal-catalyzed methods have been developed to address this challenge. This article aims to explore strategies for achieving reactivity at the relatively less reactive C7 position.

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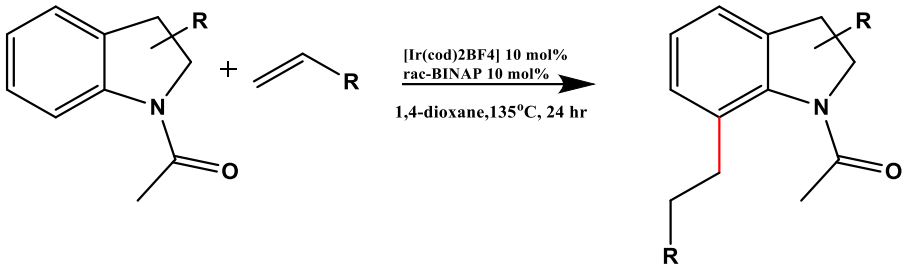
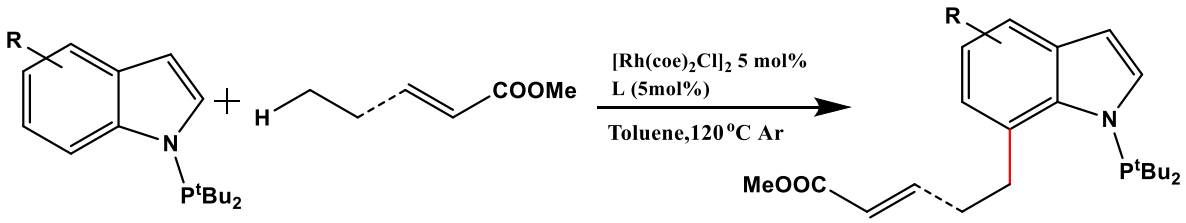
Different strategies developed for the of C7 – H bond functionalization of Indole /indoline

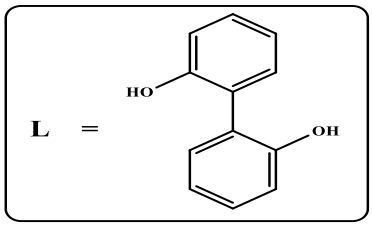
Shibata et al. developed an Ir(I)-catalyzed alkylation method for indolines using alkenes as coupling partners [12]. The reaction employed BINAP as a ligand, which significantly enhanced the catalytic efficiency, and BF_4^- served as the counter anion to the Ir-catalyst, delivering excellent product yields shown in Scheme 1.



Scheme 1

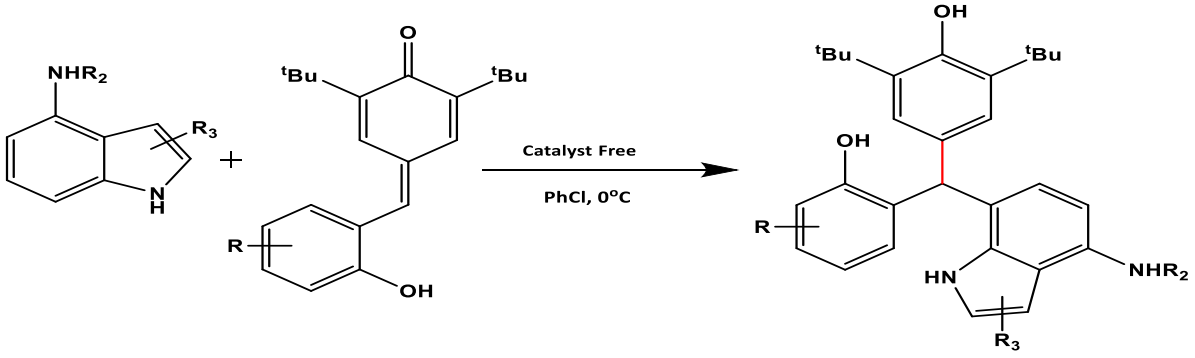
Shi et al. achieved a significant breakthrough in C7-alkylation of indoles by utilizing a sterically bulky N-$PtBu_2$ directing group under Rh(I) catalysis [13]. By employing conjugate-active olefins as coupling partners, they successfully overcame the inherent electronic preference for the C3-position of indole. Notably, this transformation proceeds through a long-range deconjugative isomerization initiated by hydrometalation, diverging from the conventional Michael addition pathway shown in Scheme 2.





Scheme 2

Lu Cai et al. reported a catalyst-free Friedel–Crafts alkylation of indoles at the C7 position using para-quinone methide derivatives and 4-alkylaminoindoles as nucleophiles[14]. This mild and efficient protocol enables the synthesis of 7-indolyl-substituted triarylmethane derivatives, offering broad substrate scope, operational simplicity, and potential applicability in the preparation of biologically active molecules shown in Scheme 3.



Scheme 3

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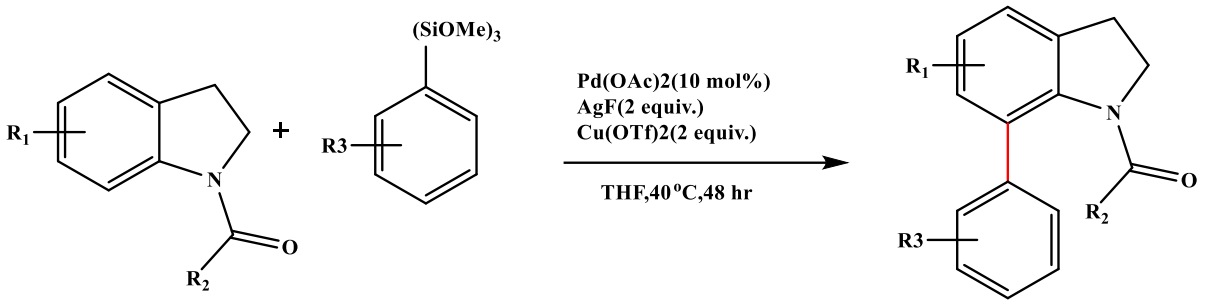
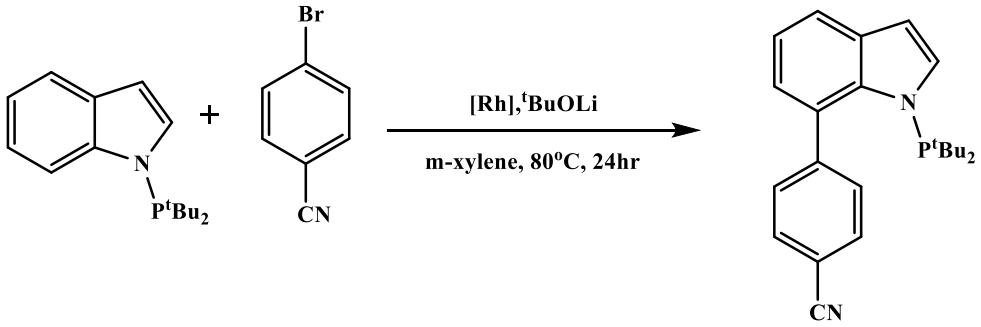
Pinaki Bhusan et al. reported a Co(II)-PCy_3-catalyzed site-selective C7-arylation of indolines using arylboronic acids as coupling partners[15]. The presence of the PCy_3 ligand and molecular oxygen significantly enhanced the reaction yield. Furthermore, radical scavenger experiments supported the involvement of a radical intermediate in the reaction pathway shown in Scheme 4.



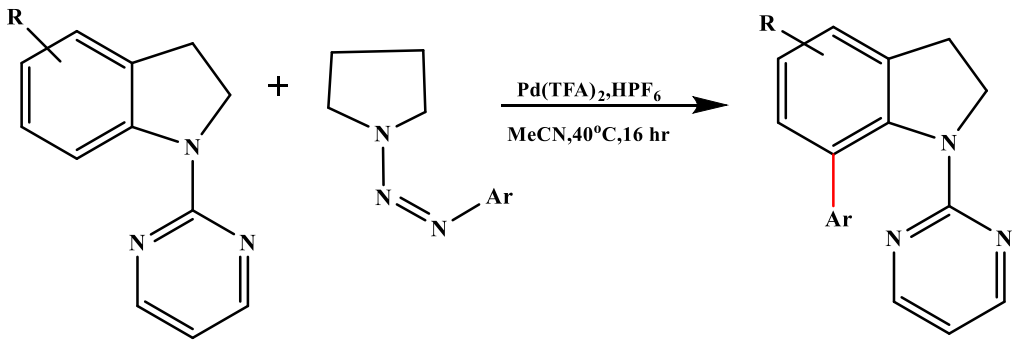
Scheme 4

Mu et al. reported a Rh(I)-catalyzed site-selective C7-arylation of indoles using aryl halides as coupling partners[16]. The study indicates that the catalytically active species, $Rh(PPh_3)_2OtBu$, preferentially initiates the reaction via C–H activation of the indole to form a five-membered rhodacycle intermediate, rather than through oxidative addition of the aryl halide to generate a Rh(III) species. This pathway is energetically more favorable. The reaction proceeds through subsequent C(aryl)–C(aryl) reductive elimination and catalyst regeneration, ultimately yielding the desired 7-arylindole product shown in Scheme 5.



Scheme 5

Gao et al. developed a palladium-catalyzed method for the direct C–H arylation of indolines at the C7 position, carried out at near-ambient temperature[17]. The reaction employed aryltriazene as a stable aryl source and electron shuttle, enabling the in situ generation of aryl radicals with the help of a promoter. A pyrimidine group served as a removable directing group, and the transformation proceeded efficiently under oxidant- and ligand-free conditions, affording 7-arylindolines shown in Scheme 6.



Scheme 6

Ma et al. developed an efficient rhodium-catalyzed strategy for direct C–H alkenylation at the C7 position of various indoles[18]. The method delivered good to excellent yields with coupling partners such as acrylates,

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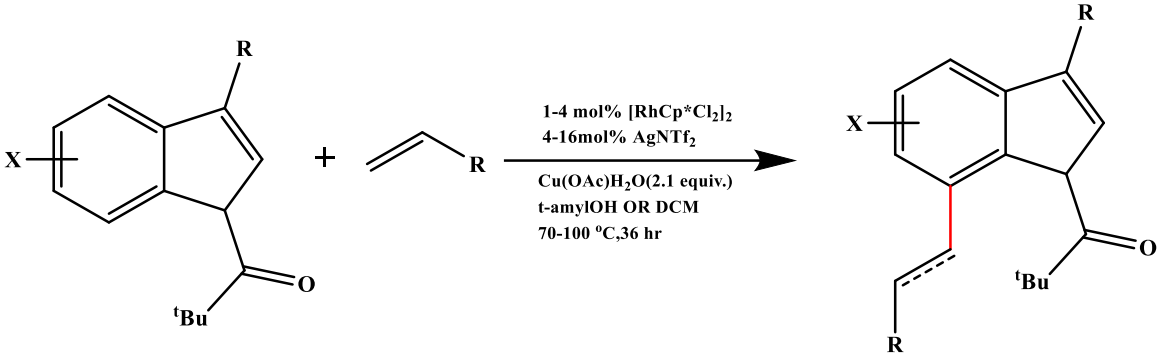
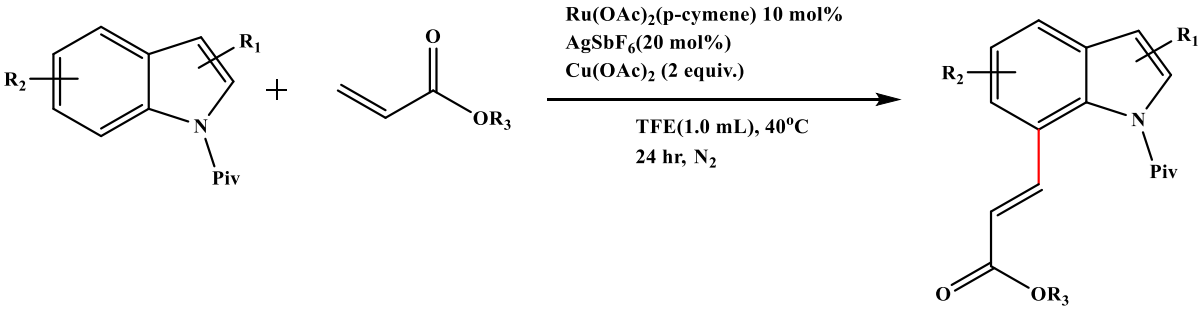
styrenes, and vinyl phenyl sulfones. High regioselectivity and reaction efficiency were achieved through the combined use of an N-pivaloyl directing group and the rhodium catalyst shown in Scheme 7.



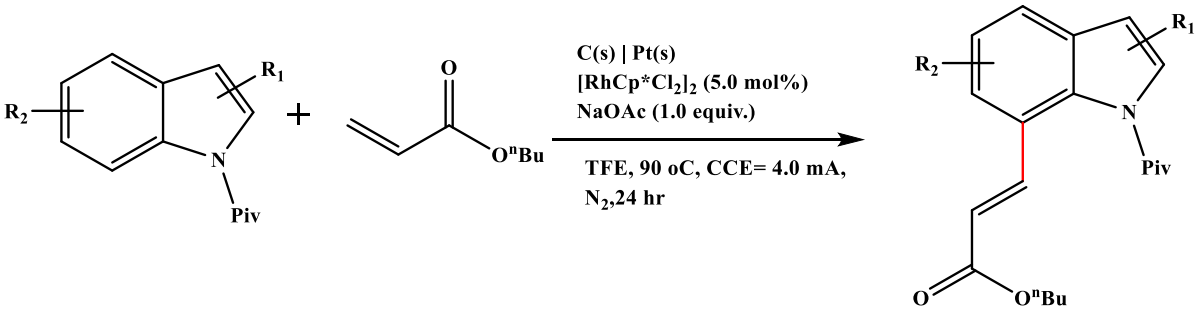
Scheme 7

Ackermann et al. developed a ruthenium (II) biscarboxylate-catalyzed method for site-selective C7–H activation of indoles under mild reaction conditions[19]. Base-assisted internal electrophilic-type substitution via weak O-coordination enabled selective C7–H ruthenation of indoles, providing a versatile platform for C–N and C–C bond formation with broad substrate scope shown in Scheme 8.



Scheme 8

Ackermann et al. introduced the first electrochemically driven C7-alkenylation of indoles, offering a novel and sustainable approach that avoids the use of toxic and costly chemical oxidants[20]. This method enables highly selective functionalization at the C7-position, and a wide range of substrates underwent successful alkenylation with potential for diverse product derivatization shown in Scheme 9.



Scheme 9

CONCLUSION

Given the widespread presence of indole motifs in numerous organic compounds, highly efficient and practical methods for site-selective C–H functionalization of indoles have been extensively developed. Several alternative strategies have been developed to override the inherent reactivity at the C2 and C3 positions, enabling selective functionalization on the less reactive benzenoid ring of indoles. The current body of work highlights the

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advancement of transition metal-catalyzed C7 functionalization of indoles and indolines, achieved through the careful selection of catalytic systems and coupling partners.

Reported methodologies predominantly rely on noble transition-metal catalysts and necessitate the installation and subsequent removal of directing groups (DGs), thereby raising concerns regarding step economy and overall sustainability. In this synthetic realm, the development of streamlined strategies, such as the use of traceless directing groups and the integration of electrochemical as well as non-covalent interactions with first-row transition metals will significantly enrich the modern landscape of organometallic research. Undoubtedly, these pioneering methods will serve as a foundation for exploring new directions in both synthetic and materials chemistry.

REFERENCES

1. Yang, Youqing, and Zhuangzhi Shi. "Regioselective direct arylation of indoles on the benzenoid moiety." Chemical Communications 54.14 (2018): 1676-1685.
2. Bugaenko, Dmitry I., Alexander V. Karchava, and Marina A. Yurovskaya. "Synthesis of indoles: recent advances." Russian Chemical Reviews 88.2 (2019): 99.
3. Cacchi, Sandro, and Giancarlo Fabrizi. "Synthesis and functionalization of indoles through palladium-catalyzed reactions." Chemical reviews 105.7 (2005): 2873-2920.
4. Sandtorv, Alexander H. "Transition Metal-Catalyzed C- H Activation of Indoles." Advanced Synthesis & Catalysis 357.11 (2015): 2403-2435.
5. Kalepu, Jagadeesh, et al. "C4–H indole functionalisation: precedent and prospects." Chemical Science 9.18 (2018): 4203-4216.
6. Yang, Youqing, and Zhuangzhi Shi. "Regioselective direct arylation of indoles on the benzenoid moiety." Chemical Communications 54.14 (2018): 1676-1685.
7. Pelkey, Erin T. "Metalation of indole." Heterocyclic Scaffolds II: Reactions and Applications of Indoles. Berlin, Heidelberg: Springer Berlin Heidelberg, 2010. 141-191.
8. Potavathri, Shathaverdhan, et al. "Oxidant-controlled regioselectivity in the oxidative arylation of N-acetylindoles." Tetrahedron letters 49.25 (2008): 4050-4053.
9. Stuart, David R., Elisia Villemure, and Keith Fagnou. "Elements of regiocontrol in palladium-catalyzed oxidative arene cross-coupling." Journal of the American Chemical Society 129.40 (2007): 12072-12073.
10. Ikemoto, Hideya, et al. "Pyrroloindolone synthesis via a Cp* CoIII-catalyzed redox-neutral directed C–H alkenylation/annulation sequence." Journal of the American Chemical Society 136.14 (2014): 5424-5431.
11. Ding, Zhenhua, and Naohiko Yoshikai. "Mild and efficient C2-alkenylation of indoles with alkynes catalyzed by a cobalt complex." Angewandte Chemie-International Edition 51.19 (2012): 4698-4701.
12. Pan, Shiguang, Naoto Ryu, and Takanori Shibata. "Iridium (I)-Catalyzed Direct C□ H Bond Alkylation of the C-7 Position of Indolines with Alkenes." Advanced Synthesis & Catalysis 356.5 (2014): 929-933.
13. Borah, Arun Jyoti, and Zhuangzhi Shi. "Rhodium-catalyzed, remote terminal hydroarylation of activated olefins through a long-range deconjugative isomerization." Journal of the American Chemical Society 140.19 (2018): 6062-6066.
14. Cai, Lu, Xian Jia, and Junling Zhao. "C7-Friedel–Crafts alkylation of 4-aminoindoles with para-quinone methide derivatives under catalyst-free conditions." Synthetic Communications 50.11 (2020): 1679-1686.
15. De, Pinaki Bhusan, et al. "Expedient cobalt (II)-catalyzed site-selective C7-arylation of indolines with arylboronic acids." Chemical Communications 54.20 (2018): 2494-2497.
16. Mu, Xueli, et al. "Mechanistic insight into the rhodium-catalyzed, P-directed selective C7 arylation of indoles: a DFT study." Molecular Catalysis 495 (2020): 111147.
17. Gao, Jianan, et al. "Pd-Catalyzed C-7 Arylation of Indolines with Aryltriazenes under Mild Conditions." The Journal of Organic Chemistry 88.15 (2023): 11056-11068.
18. Xu, Lanting, et al. "Rhodium-catalyzed regioselective C7-functionalization of N-pivaloylindoles." Angewandte Chemie International Edition 55.1 (2016): 321-325.

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue VIII August 2025

19. Choi, Isaac, Antonis M. Messinis, and Lutz Ackermann. "C7-indole amidations and alkenylations by ruthenium (II) catalysis." Angewandte Chemie International Edition 59.30 (2020): 12534-12540.
20. Zangarelli, Agnese, Binbin Yuan, and Lutz Ackermann. "Electrochemical C7-Indole Alkenylation via Rhodium Catalysis." Israel Journal of Chemistry 64.1-2 (2024): e202300103.