

Synthesis and Site-Selective C–H Functionalization of Indoles through Iridium Catalysis

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Site-selective C–H functionalization is a formidable challenge in homogeneous transition-metal catalysis. In this context, I present a physical organic approach to elucidate the factors governing the regioselective amidation of N-acylindoles via Ir(III) catalysis. The bulkiness of N-directing groups in indole substrates and the electronic properties of carboxylate additives emerged as pivotal factors influencing C2 and C7 selectivity. The microscopic mechanisms underlying these selectivities were investigated through DFT-based transition state analysis. Computational insights prompted an exploration of a linear free energy relationship, and the parametrization of molecular determinants facilitated the development of an intuitive yet robust statistical model. This model demonstrates high accuracy and successfully correlates with an extensive set of validation data points. This mechanistic investigation ultimately led to the development of a novel C2 amidation and alkenylation protocol for indoles, achieving exclusive functionalization at the C2 position with selectivity exceeding 70:1. Additionally, I present an iridium(III)-catalyzed electrooxidative intramolecular dehydrogenative C–H/N–H coupling of unprotected 2-alkenyl anilines. This method enables the synthesis of various 3-substituted N–H indole scaffolds under undivided electrolytic conditions. Mechanistic studies suggest that the reaction proceeds through an electro-oxidation-induced reductive elimination pathway.

References

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