


Sulfur-directed site-selective functionalization of indole derivatives


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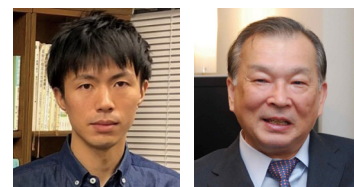
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Abstract

Indoles and their analogues have been one of the most ubiquitous heterocycles during the past century, and extensive studies have been conducted to establish practical synthetic methods for their derivatives. In particular, selective functionalization of the poorly reactive benzenoid core over the pyrrole ring has been a great challenge. We have developed transition-metal-catalyzed direct functionalization of the indole C4- and C7-positions with the assistance of sulfur directing groups. This transformation shows a wide range of functional-group tolerance with exceptional site selectivity. The directing group can be either easily removed or transformed after the catalysis.

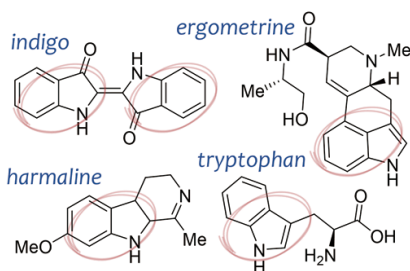
Background & Results

The indole heteroaromatic scaffold has been one of the most privileged heterocycles due to its wide prevalence in a variety of marketed drugs, biologically active compounds, and functional molecules. Accordingly, significant research interest has been focused on the development of site-selective decollation methods for indole derivatives, and the transition-metal-catalyzed direct C-H bond transformation has recently been recognized as an attractive synthetic tool for the late-stage functionalization. The indole core inherently offers the six distinctive reaction sites for the catalysis. Among these, selective functionalization of the benzenoid fragment over the highly reactive C2 and C3 positions (pyrrole ring) has remained as a big challenge for the synthetic community. To address this thorny issue, various catalytic protocols have been developed with the aid of appropriate directing groups during the past decade.

In this regard, we have interested in utilizing sulfur-based directing groups for the site-selective functionalization of indole skeleton. The sulfur functionality (thioether) could be readily installed at the indole N1 and C3 positions upon treatment indole derivatives with electrophilic sulfur reagent such as N-sulfanyl phthalimide. Additionally, these directing groups were easily removable under appropriate reaction conditions: treatment with TBAF (tetrabutylammonium fluoride) for the N1-SR groups, Raney Ni reduction or oxidation into Isatin (indole-2,3-dione) scaffold for the C3-SR groups. More importantly, the C3-S bond could be subjected to the Ni-catalyzed Kumada-type cross-coupling reaction with Grignard reagents to give C3-alkylated and C3-arylated indoles. With the aid of the sulfur directing group, we achieved C4- and C7-selective direct C-H functionalization of indole derivatives: Rh(III)-catalyzed alkenylation and acylmethylation, Ir(III)-catalyzed alkynylation.

Significance of the research and Future perspective

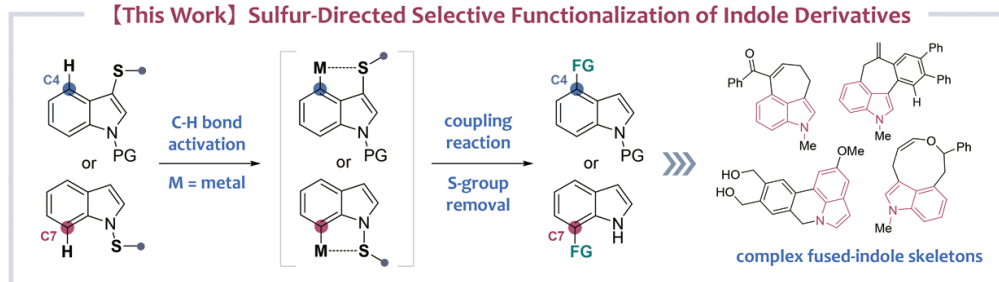
As described above, selective functionalization of the indole benzene ring has remained as a significant challenge, and limited achievement has been accomplished to date. In this work, we have successfully developed a series of catalytic direct functionalization methods. After the catalysis and removal of the sulfur directing group, the obtained substituted indole derivatives could be further transformed to synthetically valuable yet difficult to access ring-fused indoles, which highlighting the substantial importance in medicinal and materials chemistry.



Indoles: the privileged structure in various functional molecules (medicine, LED, etc.)

Controlled direct functionalization methods have attracted significant interest recently

[This Work] Sulfur-Directed Selective Functionalization of Indole Derivatives



Patent

Kona, Chandrababu Naidu; Nishii, Yuji; Miura, Masahiro. Iridium-Catalyzed Direct C4- and C7-Selective Alkynylation of Indoles Using Sulfur-Directing Groups *Angew. Chem. Int. Ed.* 2019, 58, 9856-9860. doi: 10.1002/anie.201904709

Treatise

Kona, Chandrababu Naidu; Nishii, Yuji; Miura, Masahiro. Thioether-Directed C4-Selective C-H Acylmethylation of Indoles Using α -Carbonyl Sulfoxonium Ylides *Org. Lett.* 2020, 22, 4806-4811. doi: 10.1021/acs.orglett.0c01617

Kona, Chandrababu Naidu; Nishii, Yuji; Miura, Masahiro. Sulfur-Directed C7-Selective Alkenylation of Indoles under Rhodium Catalysis *Org. Lett.* 2021, 23, 6252-6256. doi: 10.1021/acs.orglett.1c01990

URL

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Keyword

catalysis, coupling reaction, indole, transition metal