Sulfur-Directed C7-Selective Alkenylation of Indoles under Rhodium Catalysis

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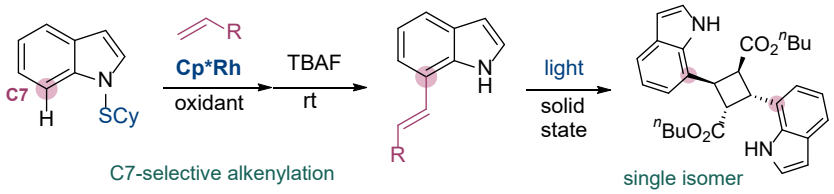
Supporting Information Placeholder

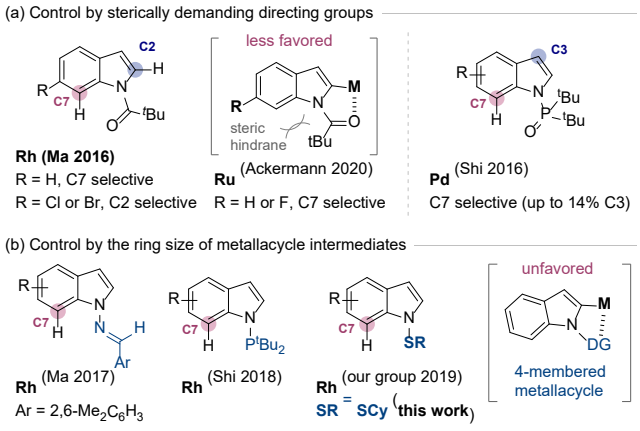


ABSTRACT: Regioselective direct functionalization of an indole benzenoid fragment has been a significant challenge because of its inherently lower reactivity. In this report, we introduce a Rh-catalyzed C7-selective alkenylation of indole derivatives utilizing a new sulfur directing group *N*-SCy. A notable feature of this system is that the directing group is readily installed to the indoles and easily removed after the catalysis under mild conditions.

Indoles and their functionalized analogues present in a wide range of natural products and have found various potent applications in medicinal chemistry as well as in material science.[1] Accordingly, significant efforts have been devoted to developing synthetic methods for the regioselective functionalization of indole scaffold. Over the past decade, transition-metal-catalyzed direct C–H functionalization has been a prominent topic in this area.[2] Considering the inherently higher reactivity of the pyrrol ring (C2 and C3), it would be sufficiently challenging to achieve the selective functionalization of the benzenoid core (C4–C7) of indoles which have no substituent at C2 and/or C3 positions.[3] In particular, the C7-selective C–H activation has been realized by installing suitable directing groups onto the indole nitrogen atom. The first regioselective C7-functionalization was accomplished by Hartwig using an *N*-silyl directing group for the Ir-catalyzed borylation.[4] Thereafter, a series of catalytic transformation has been developed with Ru,[5] Pd,[6] Rh,[7] and Ir[8] complexes.

In 2016, Tan and Ma reported a seminal work on the first C7-selective direct alkenylation of *N*-pivaloyl indoles under Rh catalysis (Scheme 1a). The bulkiness of the directing group was obviously beneficial to control the selectivity; however, the competing C2 functionalization could not be avoided for C6-substituted indoles.[7a] Recently, Ackermann utilized the same directing group for Ru-catalyzed amidation and alkenylation.[5a] As a similar approach, Shi adopted a sterically demanding *N*-P(O)^{t}Bu$_2$ (TBPO) directing group[9] for the C7-selective arylation and alkenylation using Pd catalyst.[6a] In this reaction system, small amounts (up to 14% yield) of C3 regioisomers were obtained as the byproducts. Despite the significant achievements in these elegant works, the steric control is sometimes insufficiently powerful to invalidate the reaction at the pyrrol moiety.

Scheme 1. Schematic Representation of the C7-Selective Direct Functionalization of Indoles



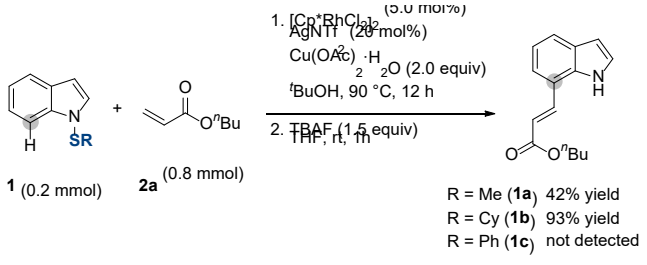
As an alternative approach, the ring size of possible metallacycle intermediates would be a handle to control the regioselectivity. In 2017, Tan and Ma demonstrated that

N-imino indoles can be coupled with acrylates with exclusive C7 selectivity (Scheme 1b).[7b] The C2-functionalization is not possible because that only occurs through disfavoured four-membered metallacycle species. The *N*-imino indoles are prepared from less common *N*-aminoindoles, and relatively strong reductive conditions (Zn/NH_4Cl or Raney Ni/H_2) are required to remove the directing group. In 2018, Shi also established C7-selective coupling reactions of *N*-P^{t}Bu$_2$ indoles with carboxylic acid derivatives. Meanwhile, we have recently developed the first C7-selective alkynylation with the aid of a novel SMe directing group placed on the indole nitrogen atom.[10] A notable feature of our design is that the sulfur directing group[11] can be installed in one step to the parent indole and be easily removed under mild conditions. Within our program of regioselective functionalization of indole derivatives,[12] we herein report a Rh-catalyzed C7-selective direct alkenylation. A key to success is the development of a more robust *N*-SCy directing group.

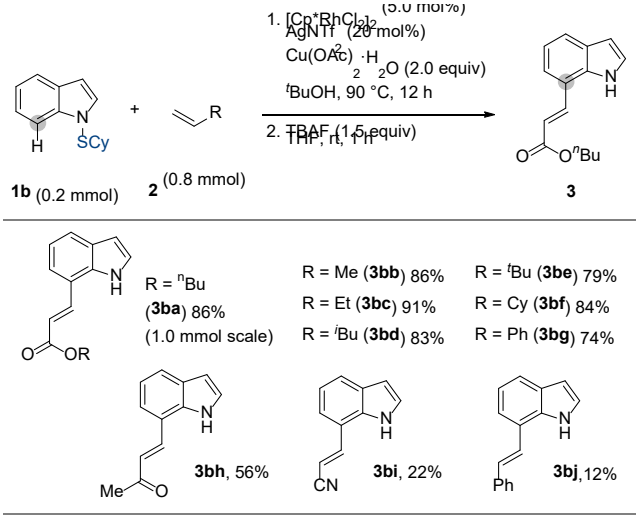
As an initial attempt, we carried out an optimization study for the reaction of *N*-SMe-indole (**1a**) with butyl acrylate (**2a**). Under the standard conditions adopting $[Cp^*RhCl_2]_2$/$AgNTf_2$ catalyst and $Cu(OAc)_2{\cdot}H_2O$ oxidant, the target C7-alkenylated product was isolated in 42% yield (Scheme 2). Here the crude material was treated with tetrabutylammonium fluoride (TBAF) in THF at room temperature to remove the directing group. After further optimization of the reaction conditions, however, the yield was not improved (for details, see the Supporting Information). This is probably due to the insufficient stability of the N–SMe bond under the conditions. Actually, we often found that the SMe group migrated to the indole C3 position as a side reaction.

In order to address this problem, we modified the directing group with cyclohexyl and phenyl substituents. To our delight, *N*-SCy-indole (**1b**) was quantitatively converted to the desired product as a single isomer, and the subsequent directing group removal upon treatment with TBAF furnished the corresponding *N*-H-indole in 93% yield. On the other hand, *N*-SPh-indole (**1c**) remained unchanged throughout the reaction. We thereby selected a new SCy directing group as optimal for the C7-selective C–H functionalization.

Scheme 2. Evaluation of the Sulfur Directing Group

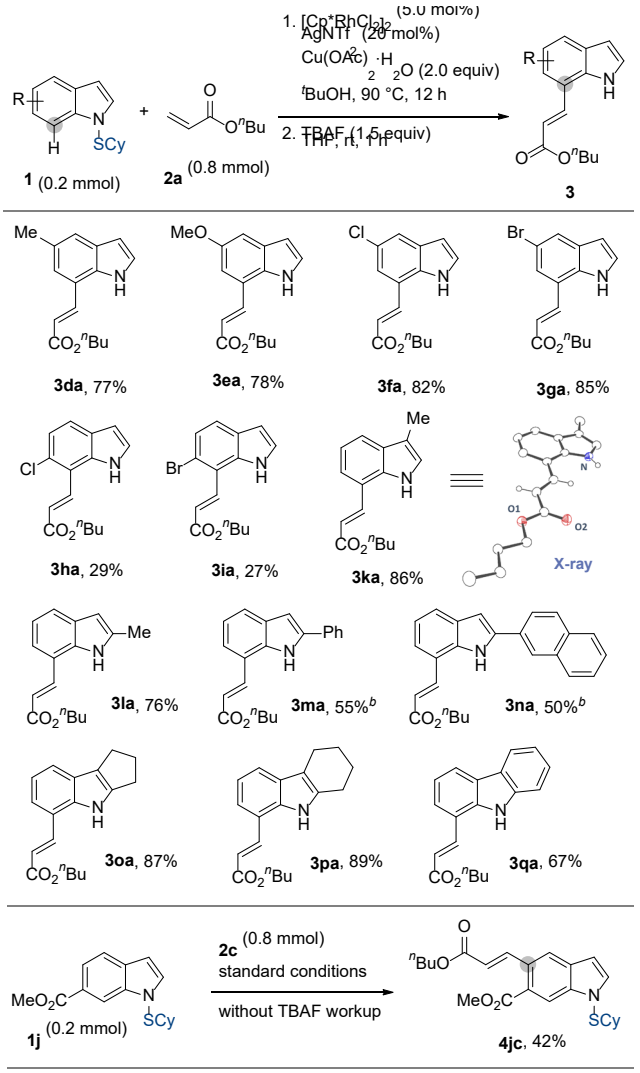


Scheme 3. Scope of Alkenes [a]



[a] Reaction conditions: **1b** (0.2 mmol), **2** (0.8 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol %), $AgNTf_2$ (20 mol%), and $Cu(OAc)_2{\cdot}H_2O$ (0.4 mmol) in ^{t}BuOH (2.0 mL) at 90 °C for 12 h.

Scheme 4. Scope of Indoles [a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.8 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol %), $AgNTf_2$ (20 mol%), and $Cu(OAc)_2{\cdot}H_2O$ (0.4 mmol) in ^{t}BuOH (2.0 mL) at 90 °C for 12 h. [b] At 80 °C.

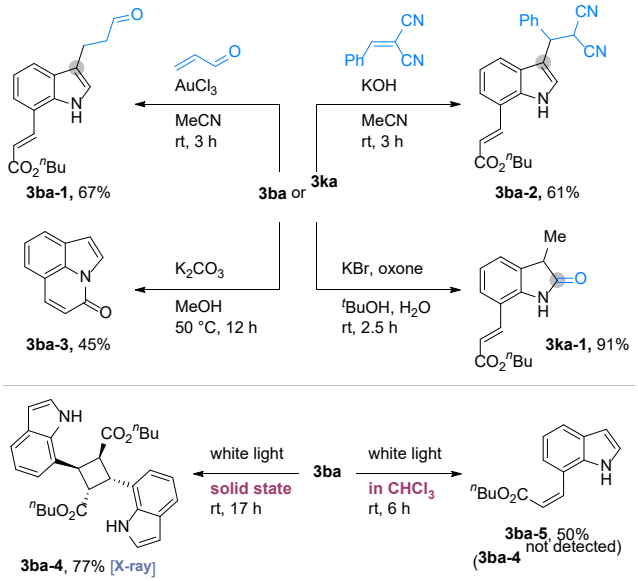
Next, we investigated the scope of alkenes for the present protocol (Scheme 3). The reaction of **1b** with butyl acrylate (**2a**) could be conducted in 1.0 mmol scale to give **3ba** in 86% yield. A series of acrylates **2b-2g** were successfully coupled with **1b**, affording the corresponding products **3bb-3bg** in good to excellent yields. Methyl vinyl ketone (**2h**) and acrylonitrile (**2i**) were also applicable to the reaction to give **3bh** and **3bj** in 56% and 22% yields, respectively. Additionally, a less activated styrene (**2j**) was usable for the present transformation though it requires further optimization.

Subsequently, we evaluated the scope of indole derivatives (Scheme 4). It can be emphasized that all these substrates were readily prepared in one step from the parent indoles. A series of C5-substituted indoles **1d-1g** smoothly underwent the alkenylation and delivered the corresponding products **3da-3ga** in good to excellent yields. As mentioned above, the direct C7 functionalization of C6-substituted indoles has been a significant challenge due to the considerable steric congestion. Intriguingly, the developed reaction system was applicable to substrates bearing 6-Cl (**1h**) and 6-Br (**1i**) functionalities albeit with somewhat lower yields. On the other hand, for 6-CO_2Me indole (**1j**), the ester group acted as a more potent director to preferentially form C5-alkenylated product **4jc**. Indoles with 3-Me (**1k**) and 2-Me (**1l**) were also well tolerated, and no SCy group migration was observed. The structure of **3ka** was confirmed by an X-ray crystallographic analysis (CCDC 2089543). The sulfur directing group exclusively mediated the C7-alkenylation with either phenyl (**1m**) or napthyl (**1n**) substituent at the C2 position. Additionally, 2,3-dialkylindoles **1o** and **1p** were successfully converted to the desired products **3oa** and **3pa** in 87% and 89% yields, respectively. For the reaction of *N*-SCy-carbazole **1q**, the monofunctionalized product **3qa** was selectively obtained under the standard conditions.

The developed catalytic protocol would be synthetically valuable because the pyrrol fragment of the coupling product is fully available for the postfunctionalization. Some particular examples are shown in Scheme 5. Michael addition of **3ba** to acrolein adopting $AuCl_3$ as a catalyst produced an aldehyde **3ba-1** in 67% yield. Similarly, base-mediated addition to 2-benzylidenemalononitrile furnished the C3 adduct **3ba-2** in 61% yield. In the case a suitable acceptor molecule was not provided, intramolecular cyclization proceeded to give a tricyclic compound **3ba-3**.[13] The pyrrol ring within **3ka** was oxidized to the corresponding lactam upon treatment with KBr and Oxone to afford **3ka-1** in 91% yield.[14]

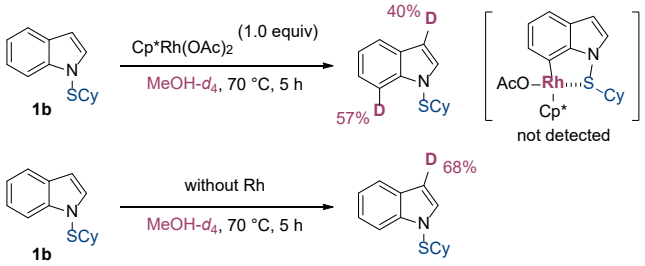
Unexpectedly, the solid **3ba** underwent [2+2] cyclodimerization to give the corresponding cyclobutane **3ba-4** under light irradiation. This reaction proceeded slowly even under the ambient conditions (20% conversion after 7 days). The cycloadduct was obtained as single isomer and its structure was determined by an X-ray crystallographic analysis (CCDC 2089544). This outcome can be attributed to the packing structure of **3ba** (for details, see the Supporting Information). Two molecules are aligned as locating their alkene fragments close to each other, and the packing mode is consistent with the molecular structure of **3ba-4**.[15] In accordance with this idea, light irradiation of **3ba** in chloroform solution did not produce the cyclobutane and ended up with *E*/*Z*-isomerization.

Scheme 5. Derivatization of the Coupling Products



In order to gain mechanistic insights, we attempted to synthesize a sulfur-coordinated rhodacycle species (Scheme 6). The standard substrate **1b** was treated with an equimolar amount of $Cp^*Rh(OAc)_2$ in MeOH-d_4 solvent for 5 h at 70 °C, but the expected metallacycle species was not detected by NMR analyses. Alternatively, considerable deuterium exchange was observed at C7 (57%) as well as at C3 (40%) positions. A control experiment confirmed that the C3 deuteration occurs in the absence of the Rh complex. These results indicated that the C–H activation at C7 position was reversible, and the resulted rhodacycle was a transient thermodynamically unstable species. The reversibility was also confirmed under the catalytic conditions (for details, see the Supporting Information). In addition, the Hirshfeld population analysis revealed that the *N*-SCy-indole (**1b**) carried a smaller negative charge of -0.829 at the C3 atom, whereas an indole molecule exhibited -0.873 (for details, see the Supporting Information). This result suggests that the SCy group act rather as an electron withdrawing group to decrease the nucleophilicity of the C3 position.[16]

Scheme 6. Deuterium Incorporation



In summary, we have introduced a new *N*-SCy directing group for the C7-selective alkenylation of indole derivatives under the Cp*Rh(III) catalysis. The cyclohexyl substituent considerably improves the stability of sulfur directing group under the catalytic conditions, whereas its removal is easily achieved using TBAF at room temperature. This reaction is effectively applicable to C2/C3-unmodified indoles bearing a C5- or C6-substituent. The standard coupling product undergoes a unique light-induced [2+2] stereospecific cyclodimerization in the solid state.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.xxxx. Additional experimental data, details of experimental procedures, product identification data, X-ray crystallography data, computation data, and copy of NMR spectra (PDF)

Accession Codes

CCDC 2089543 and 2089544 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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