Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Thioether-Directed Selective C4 C−H Alkenylation of Indoles under Rhodium Catalysis

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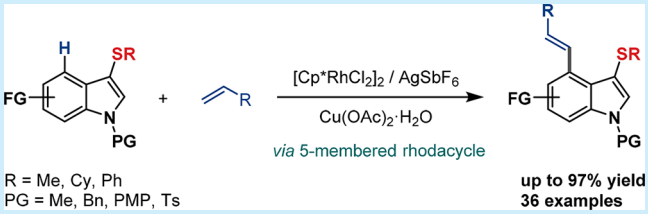
Supporting Information

ABSTRACT: A thioether-directed Rh(III)-catalyzed C4 selective C−H alkenylation of indoles via the formation of 5-membered metallacycle intermediates is reported. This protocol allows a wide functional group compatibility and broad substrate scope. The directing group can be readily removed or transformed into other functional groups after the C−H functionalization event. The catalytic method is also applicable to related heterocyclic systems involving benzo[*b*]thiophene and benzo[*b*]furan scaffolds.



The indole motif is one of the most widely studied heterocycles to date because of its unique biological activities as well as substantial importance in material science. The past decades have witnessed a rapid advancement in novel synthetic methods for the elaboration of an indole scaffold to meet the increasing demand in the medicinal chemistry field.[1]

Meanwhile, transition-metal-catalyzed regioselective aromatic C−H bond functionalization has attracted much interest due to its atom- and step-economic benefits.[2] For the functionalization of the indole nucleus,[3,4] the C4−C7-selective reactions over the C2−C3 positions have been a challenging task since the benzo ring has inherently poor reactivity relative to the pyrrole skeleton. The direct C−H activation at the C4 position among others has been achieved with the aid of directing groups placed at the C3 position. As an early example, Jia and co-workers reported a Pd-catalyzed direct C4 alkenylation of tryptophan derivatives where the amine moiety could act as the directing function.[5] Besides this seminal achievement, a series of direct C4 functionalization methods were developed with Pd, Ru, Ir, and Rh catalysts mainly employing carbonyl-based directing groups.[4] In these reactions, formation of 6-membered metallacycles rather than 5-membered ones is the key to attaining significant regioselectivity (Figure 1a).

In recent years, considerable attention has been paid to thioether directing groups owing to their labile nature. They can be easily removed under reductive conditions[6] or catalytically converted into other synthetically useful functions.[7] Our group has been developing Rh-catalyzed direct C−H functionalization reactions using sulfur-containing directing groups[8] and recently reported a thioether-directed *peri*-selective C−H alkenylation of acenes though a 5-membered metallacycle.[9] Consequently, we have taken steps to develop a C4-selective functionalization of indole derivatives employing thioether directing groups. We herein describe an effective Rh-catalyzed direct C4 alkenylation protocol. This catalytic system

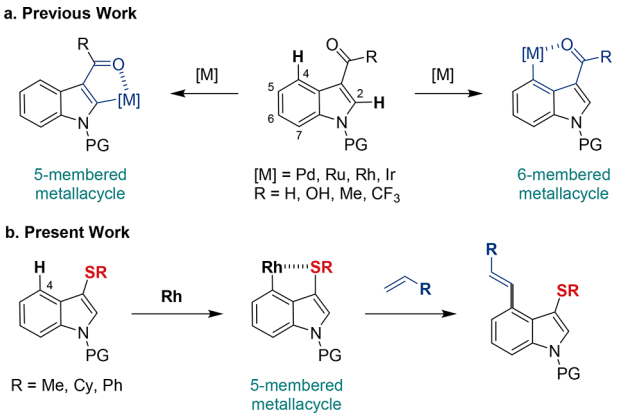


Figure 1. Schematic representation of regioselective C−H activation of indole derivatives.

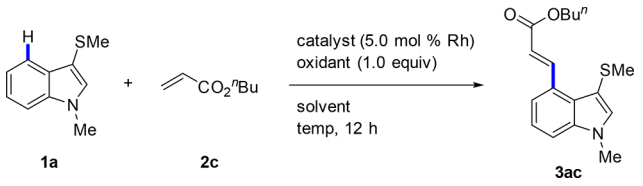
exhibits tolerance of a wide range of coupling substrates, and thereafter, the sulfur directing group is readily converted into other functional groups (Figure 1b). Furthermore, related heterocyclic motifs such as benzo[*b*]thiophene and benzo[*b*]furan can be accommodated.

We commenced our investigation with the optimization study for a model reaction of 1-methyl-3-(methylthio)indole (**1a**)[10] with butyl acrylate (**2c**) in the presence of a Rh(III) catalyst (Table 1). Initially, the C4-alkenylated product **3ac** was obtained in 35% yield by using a cationic complex $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ (5 mol %) together with AgOAc (10 mol %) and $Cu(OAc)_2·H_2O$ (1.0 equiv) in MeOH at 100 °C (entry 1). Solvent screening was then conducted and the yield was improved to 55% with DCE (entry 3), whereas increase in the reaction temperature to 120 °C had a minimal

Received: June 29, 2018

DOI: 10.1021/acs.orglett.8b02038
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization Studies



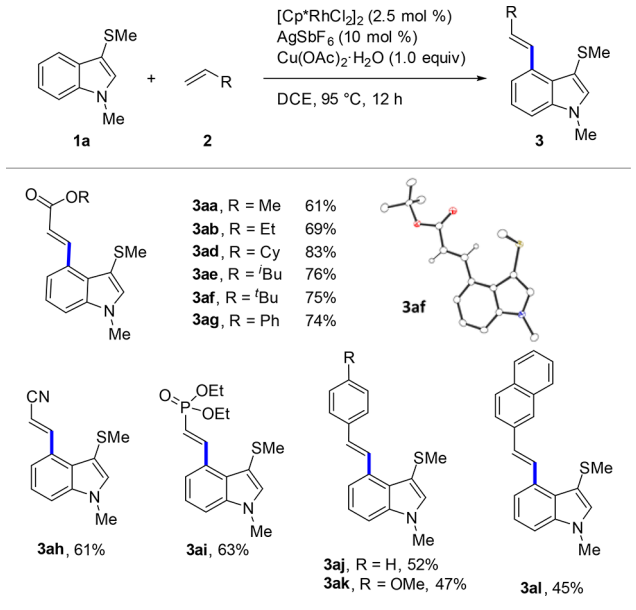
entry	catalyst	solvent	temp (°C)	3ac[d] (%)
1[a]	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	MeOH	100	35
2[a]	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	$PhCF_3$	100	25
3[a]	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	DCE	100	55
4[a]	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	DCE	120	54
5[b]	$[Cp^*RhCl_2]_2$	DCE	95	76
6[b]	$[Cp^*RhCl_2]_2$	DCE	95	78
7[b,c]	$[Cp^*RhCl_2]_2$	MeOH	95	n.d.
8[b]	$[Cp^*RhCl_2]_2$	^{t}AmOH	95	n.d.
9[b]	$[Cp^*RhCl_2]_2$	dioxane	95	n.d.
10[b]	$[Cp^*RhCl_2]_2$	$PhCF_3$	95	31

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ (5.0 mol %), AgOAc (10 mol %), and $Cu(OAc)_2\cdot H_2O$ (0.2 mmol) in solvent (2 mL). [b]Reaction conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), and $Cu(OAc)_2\cdot H_2O$ (0.2 mmol) in solvent (2 mL). [c]2.0 equiv (0.4 mmol) of $Cu(OAc)_2\cdot H_2O$ was used; [d]Isolated yield; nd = not detected.

impact on the reaction efficiency (entry 4). After further modifications, the highest 76% yield was achieved by employing a $[Cp^*RhCl_2]_2/AgSbF_6$ catalyst at 95 °C (entry 5). A small increase in the yield of **3ac** was found by use of 2.0 equiv of the Cu(II) oxidant (entry 6). Decreasing the amount of DCE to 1.0 mL did not affect the product yield, while it considerably dropped to 54% by using 4.0 mL of the solvent (not shown).

With the optimized conditions in hand, we examined the scope of alkenes using **1a** as the representative substrate (Scheme 1). With acrylates **2a**–**g**, the corresponding C4-alkenylated products **3aa**–**ag** were selectively obtained in good to high yields. The regioselectivity and *trans*-configuration of the alkene moiety was further evidenced by the single-crystal X-ray analysis of **3af**. Additionally, the present reaction system was applicable to acrylonitrile (**2h**), vinyl phosphonate (**2i**), and styrene derivatives **2j**–**l** and allowed us to deliver the corresponding C4-alkenylated products in moderate to high yields. The reaction with ethyl crotonate did not occur.

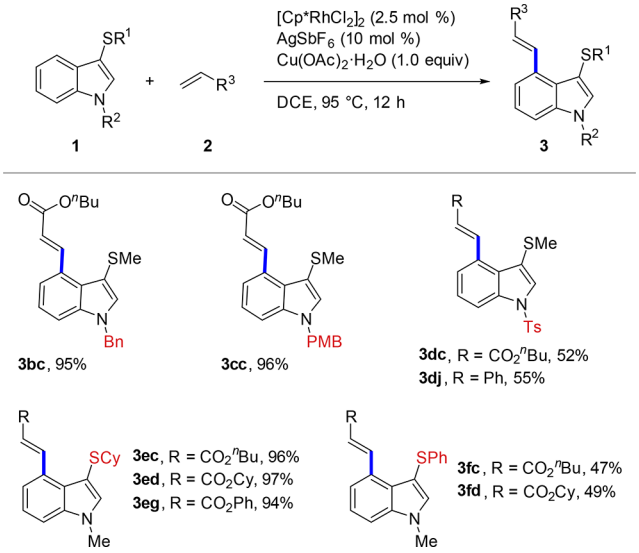
Scheme 1. Substrate Scope for Alkenes[a]



[a]All reactions were carried out on a 0.2 mmol scale.

We next turned our attention to the effect of protecting groups and examined the reaction of indoles bearing benzyl (Bn, **1b**), *p*-methoxybenzyl (PMB, **1c**), and *p*-tolylsulfonyl (Ts, **1d**) groups on the nitrogen atom (Scheme 2). The relatively electron-rich indoles **1b** and **1c** reacted smoothly to furnish the alkenylated products **3bc** and **3cc** in 95% and 96% yields, respectively. While the electron-withdrawing Ts on **1d** retarded the reaction with acrylate **2c** as well as with styrene **2j**, the desired compounds **3dc** and **3dj** were produced in synthetically usable yields. It is worth noting that these protecting groups are of genuine synthetic utility, as they can be readily removed under mild conditions.

Scheme 2. Substrate Scope with Respect to the Directing Group and the Protecting Group[a]



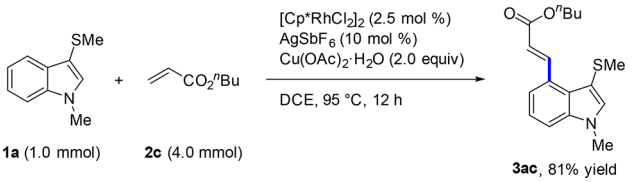
[a]All reactions were carried out on a 0.2 mmol scale.

Subsequently, we conducted a quick survey on the scope of thioether directing groups. Under the standard reaction conditions, the directing ability of the SCy (Cy = cyclohexyl) and SPh groups was tested with acrylates. Interestingly, we found that the SCy group also acted as an efficient directing group with exclusive C4 selectivity to give the desired products **3ec**, **3ed**, and **3eg** in excellent yields. In contrast, the use of an SPh directing group in **1f** resulted in the considerable drop of yields in the reaction with **2c** (47%) and **2d** (49%). The present catalytic protocol was successfully scaled up; when the reaction of indole **1a** with acrylate **2c** was carried out on a 1.0 mmol scale, the coupling product **3ac** was isolated in 81% yield as the sole product (Scheme 3).

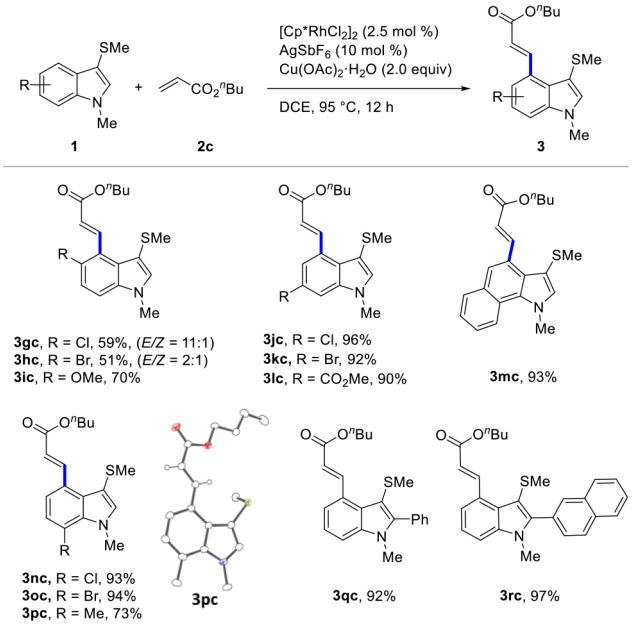
We next investigated the scope of various functionalized indoles with butyl acrylate (**2c**) (Scheme 4). Indoles bearing 5-Cl **1e** and 5-Br **1f** were well tolerated under the conditions and converted into the C4-alkenylated products **3gc** and **3hc** as the

DOI: 10.1021/acs.orglett.8b02038
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 3. Scale-up Experiment



Scheme 4. Substrate Scope for Indoles[a]



[a]All reactions were carried out on a 50 mg scale.

mixture of *E*/*Z* isomers. In contrast, 5-OMe indole **3i** was obtained exclusively in the *E* form with a good yield.

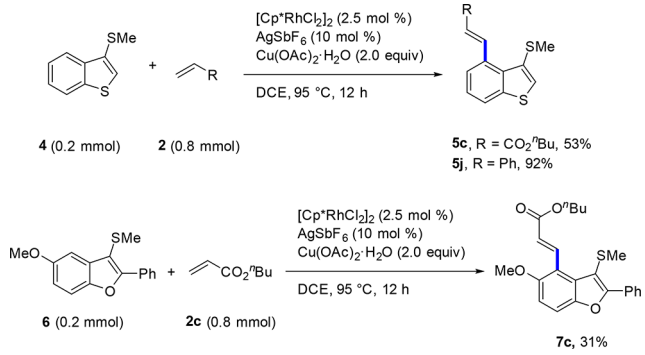
In the case of the indoles with a functionality on the C6 position, the reaction proceeded smoothly to afford products **3jc**−**lc** in 90−96% yields. A benzo-fused indole **2m** as well as C7-substituted indoles **2n**−**p** were also suitable substrates for the present reaction and were effectively transformed to the corresponding products **3mc**−**pc** in excellent yields. The structure of **3pc** was unambiguously determined by X-ray crystallography. It should be noted that phenyl and 2-naphthyl substituents on the C2 position did not affect the regioselectivity, giving **3qc** and **3rc** as the single products, and no reaction on the C2 aryl rings was observed.

It is worth noting that some of the present products were found to be highly luminescent. Compounds **3af** and **3pc** are representative and showed their emission maxima at 529 nm in $CHCl_3$ solutions with quantum yields of 0.59 and 0.45, respectively (see the Supporting Information).

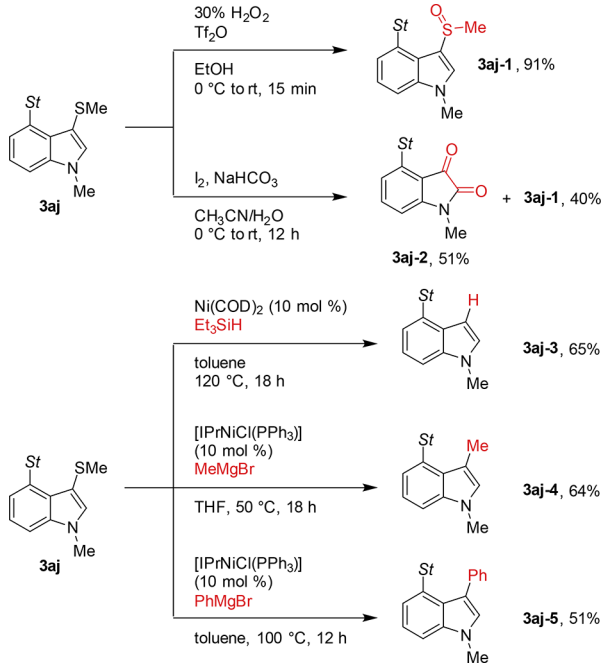
The significance of the current method was not limited to indoles, but it could be adapted to benzo[*b*]thiophene and benzo[*b*]furan derivatives (Scheme 5). The reactions of **4** with **2c** and **2j** and of **6** with **2c** afforded the corresponding products **5c**, **5j**, and **7c** in moderate to high yields, demonstrating the generality of the present catalytic protocol.

In order to demonstrate the potential advantage of the methylthio directing group, we have performed some derivatization reactions of **3aj** as the representative compound (Scheme 6). It can be easily oxidized by using H_2O_2/Tf_2O to the corresponding sulfoxide **3aj-1**.[11] Interestingly, when the

Scheme 5. C4 Alkenylation of Benzo[*b*]thiophene and Benzo[*b*]furan Derivatives



Scheme 6. Transformation of the SMe-Directing Group of 3aj[a]



[a]*St* = *E*-styryl.

indole was oxidized with $I_2/NaHCO_3$ in the presence of water, an isatin (indole-2,3-dione) derivative **3aj-2** was obtained as the major product along with **3aj-1**.[12] The methylthio group can be removed by selective reduction using $Ni(COD)_2$ and triethylsilane, giving **3aj-3**.[6a] Additionally, the methylthio group was successfully converted to methyl (**3aj-4**) and phenyl (**3aj-5**) groups by a Ni-catalyzed coupling reaction with the corresponding Grignard reagents.[13]

In summary, we have developed a thioether directed C4-selective C−H alkenylation of indoles under rhodium catalysis. The protocol allows a broad substrate scope and can be extended to the other heterocycle systems such as benzo[*b*]-furan and benzo[*b*]thiophene derivatives. Some of the products exhibit relatively strong fluorescence. Additionally, the thioether directing group can be readily removed or transformed into other functional groups, acting as a traceless directing group.

DOI: 10.1021/acs.orglett.8b02038
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02038.

Detailed experimental procedures, spectroscopic data, NMR spectra (PDF)

Accession Codes

CCDC 1852275 and 1852277−1852278 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.

■ ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grant No. JP 17H06092 (Grant-in-Aid for Specially Promoted Research) to M.M.

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DOI: 10.1021/acs.orglett.8b02038
Org. Lett. XXXX, XXX, XXX−XXX