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Cobalt-Catalyzed Regioselective Direct C-4 Alkenylation of 3-Acetylindole with Michael Acceptors Using a Weakly Coordinating Functional Group

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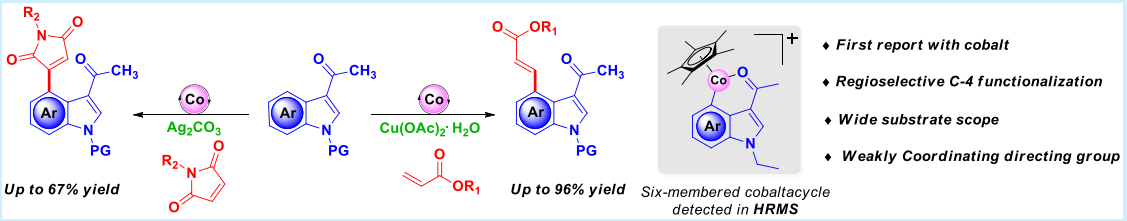
Supporting Information



ABSTRACT: Herein, we disclosed the first report on the selective C(4)−H functionalization of 3-acetylindole derivatives using first-row transition metal cobalt where an acetyl group is acting as a weakly coordinating directing group. Selective C(4)−H functionalization has been achieved using diverse Michael acceptors (acrylate and maleimide) simply by switching the additive from copper acetate to silver carbonate. Further the formation of a cobaltacycle intermediate was also detected through HRMS for mechanistic insight.

The heteroaromatic indole moiety is present in numerous marketed drugs such as Ondansetron (nausea), Sumatriptan (migraine), and Indomethacin (anti-inflammatory). It is considered as the fourth most commonly prevalent heteroaromatic skeleton among the currently marketed drugs.[1] Owing to its biological significance, synthetic modification of indole has been one of the frontline areas of research for a long time. The C-2 and C-3 functionalizations of indoles were well explored due to the inherent reactivity of N-heterocycle.[2] Traditionally functionalization at the benzenoid (C-4 to C-7) ring of indole was performed through metal-catalyzed coupling reaction using prefunctionalized substrates.[3] A recent advancement in metal-catalyzed C−H activation/functionalization reactions led to intense exploration of direct C−H activation methods at the relatively less explored C-4 and C-7 positions.[4] Functionalization at the C-4 position of indole is quite challenging due to the favorable five-membered cyclometalation step at C-2 as compared to the high energy six-membered cyclometalation step at C-4. During the past decade several research groups have made phenomenal progress on selective C-4 functionalization of indole via C−H activation using second- and third-row transition metals such as Rh, Ru, Ir, and Pd (Figure 1).[5] However, there is no report to date on the selective C-4 functionalization with first-row transition metals. In recent years there has been an impetus for mimicking the reactivity of noble metals (Rh, Ru, Ir, and Pd) through a first-row transition metal due to its low toxicity, easy availability, and low cost.[6]

In addition, C−H activation reaction through weakly coordinating directing groups is also gaining considerable attention recently. In continuation of our efforts to synthesize functionalized indole with a first-row transition metal using simple and weakly coordinating directing groups, we envisaged

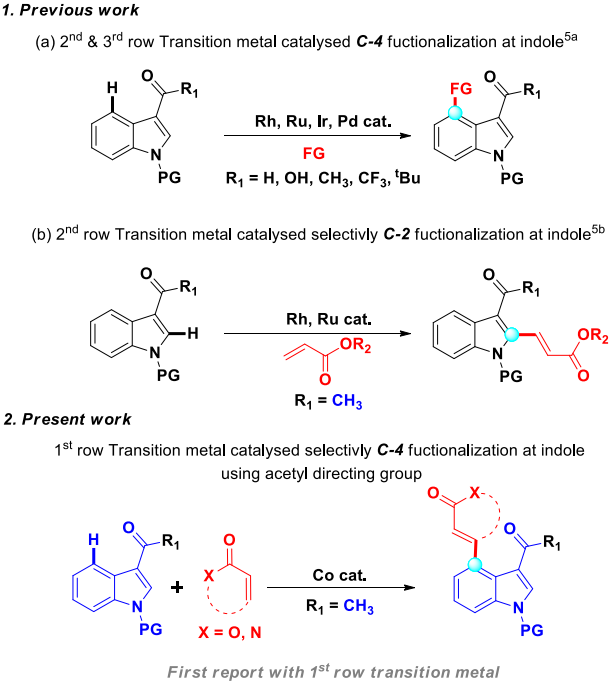


Figure 1. C−H functionalization of 3-acylindole.

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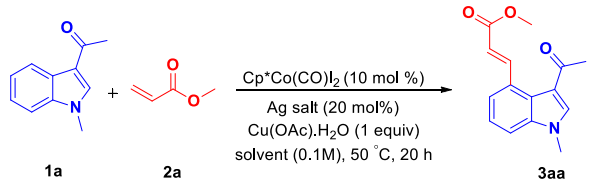
synthesizing C-4 functionalized indole[7] with commonly used Michael acceptors such as acrylates[8] and maleimides.[9] We have successfully achieved our desired cobalt-catalyzed C-4 functionalization of indoles with those Michael acceptors.

To test our hypothesis, we chose indole **1a** and methyl acrylate **2a** as the model substrates, in the presence of Cp*Co catalyst, silver hexafluoroantimonate ($AgSbF_6$) additive, and copper acetate as an oxidant.

For the optimization of C-4 alkenylation initially, we started with a hydrocarbon and an oxygenated solvent such as toluene, tetrahydrofuran, and 1,4-dioxane, but the reaction failed in those solvents. However, when we used a chlorinated solvent such as dichloromethane, 1,2-dichloroethane, and 1,2-dichlorobenzene for the reaction, it worked well producing a moderate to good yield of the desired product **3aa** (Table 1, entries 4–6). In order to further improve the product yield, we next focused on fluorinated solvents. When we performed the reaction in trifluoroethanol (TFE), a slight enhancement of the yield was observed (Table 1, entry 7). This result encouraged us to check this transformation in other fluorinated solvents such as hexafluoroisopropanol (HFIP) and trifluorotoluene (TFT). Interestingly HFIP turned out to be the best solvent for the titled transformation resulting in an 88% yield of **3aa** (Table 1, entry 9). To investigate the role of the silver additive, we performed this reaction in the absence of $AgSbF_6$ but the reaction failed to give significant yield and we recovered the starting material (Table 1, entry 11). This implies that $AgSbF_6$ is playing crucial role in the alkenylation reaction. Motivated by this outcome we envisioned that screening of the other silver salts might improve the yield. Hence, different silver salts such as $AgBF_4$, Ag_2O, and $AgNTf_2$ were used, still no improvement in the yield of **3aa** was observed (Table 1, entries 12–14). Thus, the combination of $AgSbF_6$ as the silver salt and HFIP as solvent proved to be the right conditions for the C-4 alkenylation reaction (Table 1, entry 9). To understand the influence of the Cp*Co catalyst on the titled reaction, we carried out the reaction in the absence of the catalyst which failed to give the adduct (Table 1, entry 16).

Table 1. Optimization of the C-4 Alkenylation Reaction[a]



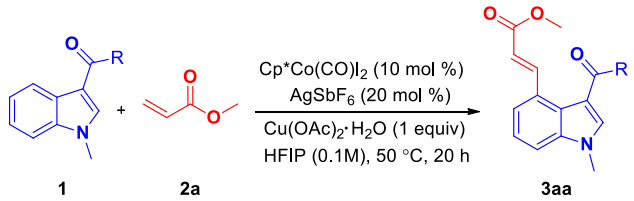
1a 2a 3aa

entry	solvent	Ag salt	yield (%)[b]
1	toluene	$AgSbF_6$	0
2	THF	$AgSbF_6$	0
3	1,4-dioxane	$AgSbF_6$	0
4	DCM	$AgSbF_6$	55
5	DCE	$AgSbF_6$	62
6	1,2-DCB	$AgSbF_6$	41
7	TFE	$AgSbF_6$	69
8	TFT	$AgSbF_6$	22
9	**HFIP**	**$AgSbF_6$**	**88**
10	HFIP	$AgSbF_6$, rt	56
11	HFIP	–	24
12	HFIP	$AgBF_4$	44
13	HFIP	$AgNTF_2$	80
14	HFIP	Ag_2O	38
15	HFIP	$AgSbF_6$, without $Cu(OAc)\cdot H_2O$	16
16	HFIP	$AgSbF_6$, without $Cp^*Co(CO)I_2$	0

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (4 equiv), $CoCp^*(CO)I_2$ (10 mol %), Ag salt (20 mol %), additive (1 equiv), hexafluoroisopropanol (0.1 M) as a solvent, 50 °C, 20 h. [b]Isolated yields.

To further optimize the reaction in terms of directing groups, we planned to examine the reaction with different electron-rich and electron-poor directing groups, while maintaining the same coupling partner **2a**. We checked our optimized reaction conditions with acetyl, trifluoroacetyl, pivaloyl, carboxaldehyde, carboxylic acid, and acid derivative substituted indoles (Table 2, entries 1–7). Among these substrates, acetyl- and pivaloyl-substituted indoles gave excellent yields of **3aa** and **3aa3** (Table 2, entries 1 and 4). However, in the case of indole bearing carboxaldehyde and a trifluoroacetyl directing group moderate yields were obtained (Table 2, entries 2 and 3). Also, we screened acid and ester as a directing group and the result was insignificant (Table 2, entries 5 and 6). In the case of an amide directing group, both C-4 and C-2 alkenylated adducts **3aa6** and **3aa7** were obtained in a moderate yield (Table 2, entry 7). In contrast to the earlier reports,[5a,b] an electron-rich directing group such as acetyl- and pivaloyl-substituted indoles gave a C-4 regioselective adduct with a cobalt catalyst. This complementary nature of cobalt catalyst could be useful for selective synthesis of C-4 functionalized indoles containing electron-rich directing groups.

Table 2. Screening of Directing Groups for C-4 Alkenylation of Indole with Methyl Acrylates



1 2a 3aa

entry	R	yield (%)
1	**CH_3**	**88** (3aa)
2	H	33 (3aa1)
3	CF_3	52 (3aa2)
4	^{t}Bu	81 (3aa3)
5	OH	0 (3aa4)
6	OMe	23 (3aa5)
7	NH_2CH_3	38 (3aa6)

With the optimized conditions in hand, we proceeded to screen the generality of this catalytic reaction with various indoles and acrylates to obtain an array of diversely functionalized C-4 alkenylated indoles. The steric and electronic influence of the alkyl substituent of acrylate for the designed catalytic transformation was first tested with **1a**. It was observed that with increasing chain length of the alkyl group, the yield of the corresponding alkenylated product decreased (Scheme 1, **3aa**–**3ac**). This indicates that the presence of an electron-rich alkyl substituent on the ester group of acrylates retards the catalytic reaction. In the case of the bulkier *tert*-butyl (Scheme 1, **3ad**) substituent, the reaction failed under the optimized reaction conditions. Overall, it implies that the reaction seems highly sensitive to the steric and electronic nature of the alkyl substituents in acrylates. However, it is encouraging to note that C-5 substituted indole

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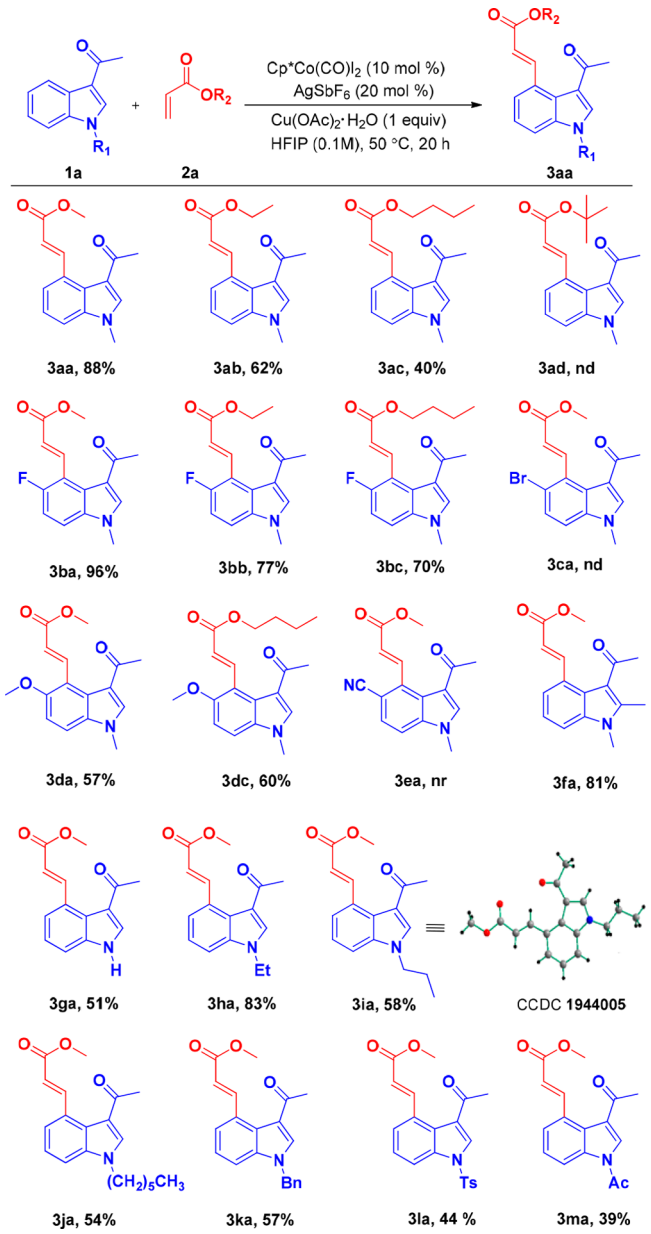
Scheme 1. Scope of C-4 Alkenylation of Indole with Acrylates[a,b]



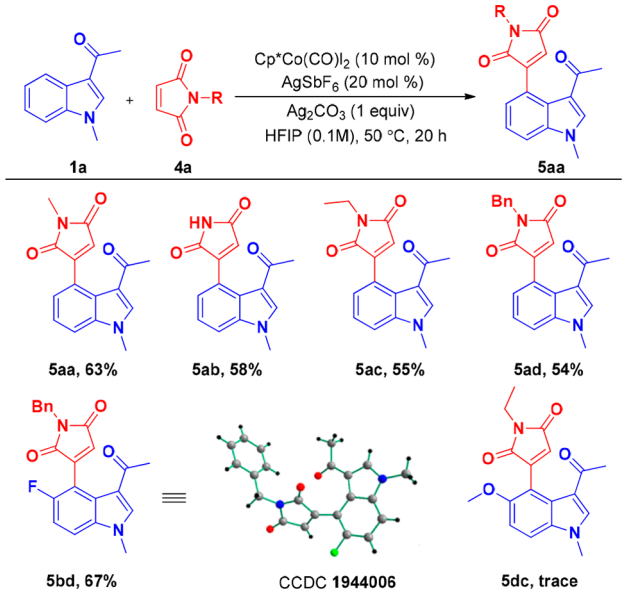
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (4 equiv), $CoCp^*(CO)I_2$ (10 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2.H_2O$ (1 equiv), hexafluoroisopropanol (0.1 M) as a solvent, 50 °C, 20 h. [b]Isolated yields.

such as 5-fluoro indole reacted with different acrylates resulting in excellent yields of desired products **3ba** (96%), **3bb** (77%), and **3bc** (70%). In contrast, bromo-substituted indole (1, **3ca**) did not react. It is possibly due to steric hindrance near the reaction site. Indole bearing a methoxy group at the C-5 position also provided the desired products **3da** and **3dc** in good yields.

However, electron-deficient indole (5-cyanoindole, **1e**) showed insignificant result (**3ea**). Besides C-5 substituted indole, the C-2 substituted indole was also compatible with the reaction conditions leading to the formation of respective adduct **3fa** in 81% yield. Moreover, many *N*-protected indoles were found to be effective, including alkyl, benzyl, tosyl, and acetyl groups giving the product (Scheme 1, **3ha**−**3ma**) in moderate to excellent yields. It is worth mentioning that even though, **3la** and **3ma** were obtained in diminished yields, 2-alkylated indole derivatives were not obtained as side products. Notably, the unprotected 3-acetyl indole showed good reactivity for the present catalytic system (Scheme 1, **3ga**).

Further, to show the diversity of the reaction, we utilized *N*-methyl maleimide as a coupling partner and subjected it to the same reaction conditions. Unfortunately, we observed only a 38% yield of desired product **5aa**. Hence, to enhance the product yield, we explored different additives and oxidants. A better yield was obtained with Ag_2CO_3 (please see the optimization table included in the Supporting Information). It is noteworthy to mention here that with *N*-substituted maleimides the reaction worked well (Scheme 2, **5aa**, **5ac**, and **5ad**).

Scheme 2. Scope of C-4 Alkenylation of Indole with Maleimides[a,b]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (4 equiv), $CoCp^*(CO)I_2$ (10 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (1 equiv), hexafluoroisopropanol (0.1 M) as a solvent, 50 °C, 20 h. [b]Isolated yields.

In the case of C-5 substituted indoles, a significant difference of reactivity was observed. Fluoro-substituted indole **2b** reacted efficiently to give the desired adduct **5bd** in 67% yield while methoxy-substituted indoles **2d** was less prone to react under the same reaction conditions. To check the feasibility of the transformation on large scale, we also performed the reaction in 1 mmol scale and obtained an excellent yield of **3aa**.[10] In the absence of the Michael acceptor, both C(2)−H and C(4)−H of 3-acetyl indole under the same reaction conditions became deuterated by 16% and 31% respectively, with 10 equiv of D_2O (Figure 2a).

The ratio of C(2)−H and C(4)−H deuteration did not change notably after continuing the reaction for a longer time which reveals that the first step might be a reversible step. In addition, we also performed a competition study between an electron-rich (1-(1-methyl-1*H*-indol-3-yl)ethanone) and an electron-poor (2,2,2-trifluoro-1-(1-methyl-1*H*-indol-3-yl)-ethanone) substrate. We found that the catalytic C-4 alkenylation is selective to electron-rich indole leading to the

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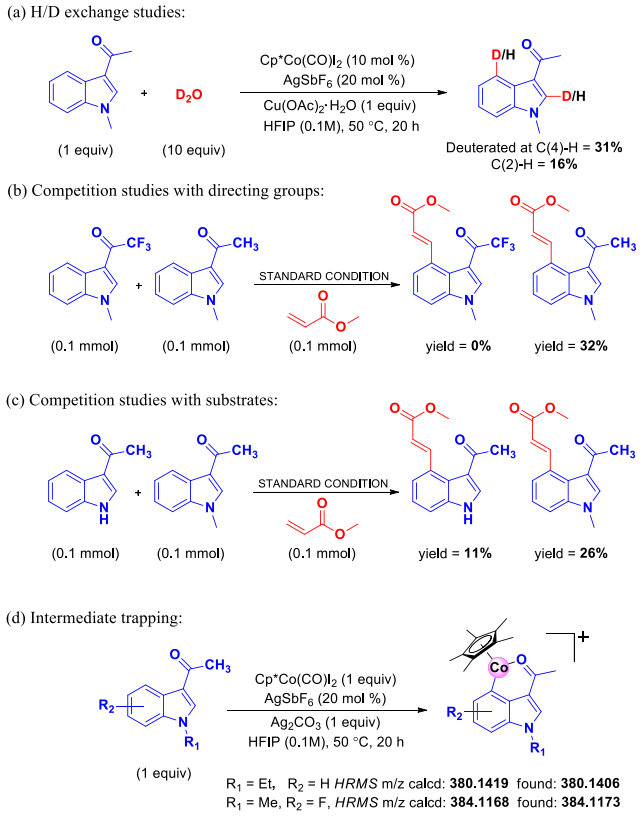


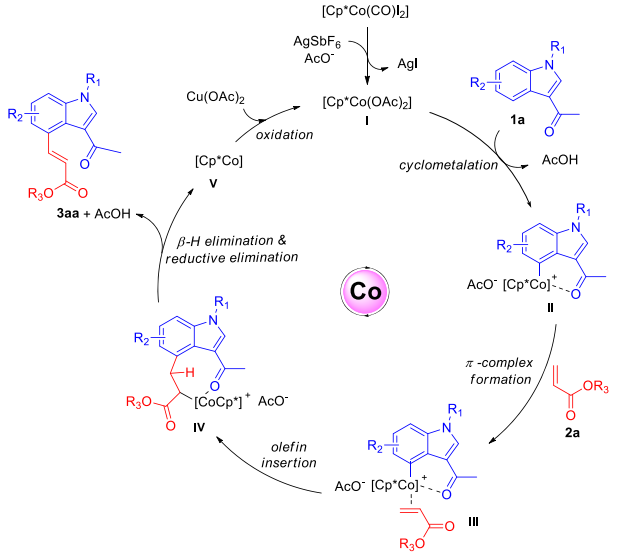
Figure 2. Mechanistic studies.

formation of the respective C-4 alkenylated adduct as the exclusive product (Figure 2b). Likewise to examine the effect of the *N*-protecting group in the catalytic reaction, another competition study was accomplished between 1-(1*H*-indol-3-yl)ethanone and 1-(1-methyl-1*H*-indol-3-yl)ethanone. The catalytic C-4 alkenylation was found to be more facile with the *N*-protected indole producing a higher yield of the alkenylated compound (Figure 2c). Further we have performed the stoichiometric reaction with a cobalt catalyst to trap the cobaltacycle intermediate whereby the six-membered intermediate has been detected through HRMS for different derivatives of indole (Figure 2d).

Based on kinetic studies and literature precedents,[11] we proposed a plausible catalytic cycle (Scheme 3) where $Cp^*Co(CO)I_2$ reacts with $AgSbF_6$ to generate an active catalyst **I** that forms a six-membered cyclometalated species **II** in the presence of **1a** which was detected in HRMS (Figure 2d). Then, the cationic cobalt(III) species undergoes π-complexation with the Michael acceptor **2a** followed by olefin insertion to give intermediate **IV**. Then β-hydride elimination followed by reductive elimination gives the desired product **3aa** and cobalt(I) complex **V**, which is further oxidized by copper acetate to regenerate the active cobalt(III) catalyst **I** for the next catalytic cycle.

In summary, we developed cobalt-catalyzed regioselective C-4 alkenylation of indole with activated olefins using a weakly coordinating directing group. We also detected the six-membered cobaltacycle through HRMS which supports our proposed mechanism. The developed protocol works well with various Michael acceptors and indoles. Further work regarding the origin of C-4 selectivity is being carried out in our laboratory.

Scheme 3. Proposed Catalytic Cycle



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03243.

General procedure and characterization data of all the compounds (PDF)

Accession Codes

CCDC 1944005−1944006 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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DEDICATION

Dedicated to Professor Fraser F. Fleming, Drexel University on the occasion of his 55th birthday.

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