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Electronic Nature of Ketone Directing Group as a Key To Control C-2 vs C-4 Alkenylation of Indoles

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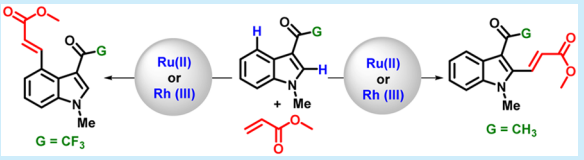
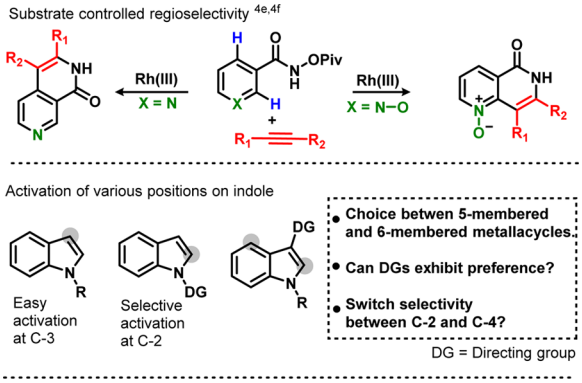
Supporting Information

ABSTRACT: A novel mode of achieving site selectivity between C-2 and C-4 positions in the indole framework by altering the property of the ketone directing group is disclosed. Methyl ketone, as directing group, furnishes exclusively C-2 alkenylated product, whereas trifluoromethyl ketone changes the selectivity to C-4, indicating that the electronic nature of the directing group controls the unusual choice between a 5-membered and a 6-membered metallacycle. The screening of other carbonyl-derived directing groups reveals that strong and weak directing groups exhibit opposite selectivity. Experimental controls and deuteration experiments lend support to the proposed mechanism.



C−H activation has emerged as a primary mode of functionalization for a wide variety of organic molecules.[1] Although a vast number of activation methods with a variety of metal catalysts, ligands, reaction conditions, reagents, etc., have been discovered, achieving selective functionalization still remains challenging.[2] Even with the use of directing groups, there are difficulties in selective activation especially when two or more C−H bonds are present, in the vicinity of the directing group, with a similar propensity to undergo C−H activation.[3] Further, the presence of multiple functional groups in a molecule leads to at least two different sites for C−H activation. The approaches for addressing this issue of selective activation include the use of special ligands, different catalytic systems, additives, and sometimes by substrate control (Scheme 1).[4] Only limited examples of such selectivity can be found in the literature, and the principles for the origin of such selectivity remain unclear. However, the works of Bedford[4a] and Houk[4h] have demonstrated some elegant methods for obtaining insight into the origin of selectivity.

Scheme 1. Concept of the Reaction



Functionalized indoles are an important class of heterocyclic compounds that are present in a variety of natural products and drugs.[5] Among them, 4-substituted indoles, known as *privileged frameworks*, are attractive synthetic targets, as they are the backbone of ergot alkaloids.[6] Functionalization of indole at C-3 is well addressed, while the functionalization at the C-2 and C-7 positions has received attention only in recent years.[7] Selective functionalization of C-4 by using a directing group at C-3, in the presence of a much more reactive C-2 position, is challenging because the C-4 activation has to proceed via an uncommon 6-membered metallacycle,[8a,b] whereas the activation at C-2 can proceed via an easier to obtain 5-membered metallacycle.[7] Developing such divergent and selective C−H functionalizations, between C-2 and C-4, on the indole framework can lead to easy and short synthetic routes for natural, unnatural, and biologically active compounds.[5] On the basis of our previous work on C-4 functionalization of indole,[8a] we focused our efforts to flip the selectivity toward C-2 using a directing group at C-3 itself. We hypothesized that the electronic factors of the directing group (strong or weak coordinating, electron rich or poor) may in some manner influence the selectivity of C−H activation. Accordingly, we carried out work to establish a switch in the site selectivity governed by the nature of the directing group. Our optimization studies began with the trifluoromethyl ketone derivative of indole, **1a**, and methyl acrylate, **3a**, as model substrates being subjected to previously established conditions for C−H activation with Ru(II) catalyst (entry 1, Table 1) to furnish the requisite C-4-functionalized product **4a** exclusively in 40% NMR yield. Concurrently, when methyl ketone **2a** was used instead of **1a**, under similar conditions, we found that it furnished C-2-functionalized product **5a** exclusively in 50% NMR yield (entry 2, Table 1). Thus, we obtained two different products **4a** and **5a** under the same reaction conditions, indicating that Ru(II)

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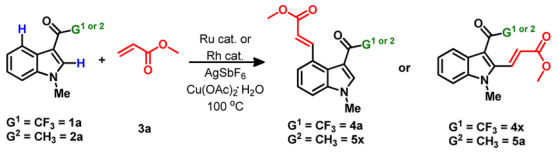
Table 1. Optimization Studies[a]



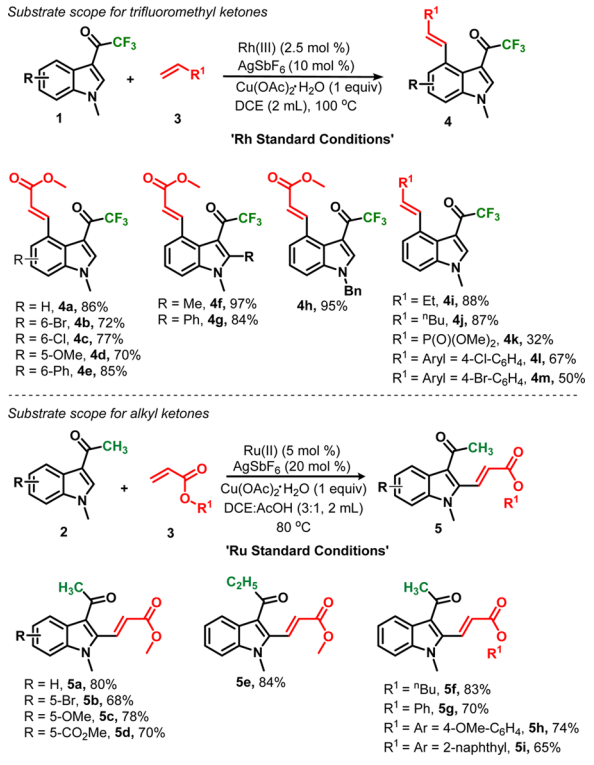
					yield[c] (%)				
entry	1a/2a	3a (equiv)	Ru/Rh[b] (mol %)	additive (equiv)	4a	4x	5a	5x	SM
1	**1a**–$COCF_3$	4	Ru (5)		40	0			38
2	**2a**–$COCH_3$	4	Ru (5)				50	0	0
3	**1a**–$COCF_3$	2	Ru (5)		35	0			30
4	**2a**–$COCH_3$	2	Ru (5)				52	0	0
5	**1a**–$COCF_3$	4	Ru (5)	AcOH (10)	31	0			36
6	**2a**–$COCH_3$	2	Ru (5)	AcOH (10)			72	0	0
7	**1a**–$COCF_3$	4	Rh (5)		87	0			0
8	**2a**–$COCH_3$	2	Rh (5)				15	0	0
9	**1a–$COCF_3$**	**4**	**Rh (2.5)**		**90 (85)**[d]				
10	**1a**–$COCF_3$	2	Rh (2.5)		85				
11	**2a–$COCH_3$**	**2**	**Ru (5)**	**AcOH (0.5 mL)**			**82 (80)**[d,e]		
12	**2a**–$COCH_3$	2	Ru (5)	AcOH (1 mL)			76[e]		

[a]Conditions: **1a** (0.3 mmol), DCE (2 mL), $AgSbF_6$ (4 times the mol % of Ru/Rh cat. used), $Cu(OAc)_2{\cdot}H_2O$ (1 equiv). [b]Ru = $[Ru(p\text{-cymene})Cl_2]_2$; Rh = $[RhCp^*Cl_2]_2$. [c]^1H NMR yield, using terephthaldehyde as internal standard. [d]Isolated yield in parentheses. [e]Reaction at 80 °C

switches between two different sites via the formation of either a 6-membered or a 5-membered ruthenacycle by merely changing the electronic factors of the directing group. In order to optimize this selectivity, the amount of acrylate was reduced, and we found that it did not lead to any significant changes in the yields (entries 3 and 4). Further, acetic acid was used as an additive, and it was found that it still furnished exclusive products but increased the formation of product from **2a** (72%, entry 6); it was also found that it disfavored the yield of the product from **1a** (31%, entry 5). Switching from Ru(II) to Rh(III) led to a noticeable change in the reaction yield. Rh(III) was found to prefer the electron-deficient $COCF_3$ and increased the yield up to 87% (entry 7); however, it drastically reduced the yield with methyl ketone substrate, probably due to the promotion of enolization of α-protons (entry 8). However, unable to realize good yields with identical conditions for both **1a** and **2a**, we were compelled to optimize the two reactions separately and establish two independent conditions for the alkenylation reaction (see the SI for full details of optimization studies). The C-4 alkenylation with **1a** was eventually optimized with 2.5 mol % of Rh(III) catalyst leading to an isolated yield of 85% (entry 9), while the C-2 alkenylation was optimized with **2a** as the substrate using Ru(II) catalyst and AcOH as cosolvent (80%, entry 11). Through the optimization, the other position-coupled products (**4x** and **5x**) were never detected. In addition, the starting materials underwent extensive decomposition in the process of the reaction and were rarely observed after workup.

The substrate scope of the reaction was explored with various indole derivatives and olefins to furnish the corresponding C-4- and C-2-alkenylated products in good to excellent yields (Scheme 2). Electron-rich indoles were tolerated in the reaction for both C-4 as well as C-2 activation reactions. Aliphatic acrylate derivatives, namely, methyl, ethyl, and *n*-butyl, and aromatic derivatives, such as phenyl, anisyl, and naphthyl, were found to furnish good to excellent yields (Scheme 2). Useful olefin partners such as styrene derivatives and vinyl phosphonates were also found to react smoothly to afford the corresponding styrene and phosphonate products.

Scheme 2. Substrate Scope



Further, we explored various carbonyl-derived directing groups and examined its effect on the selectivity of the reaction (Scheme 3). First, we explored simple derivatives of ketone itself and found that pivaloyl as directing group at C-3, under the standard conditions (Rh and Ru), yielded double-alkenylated (C-2 and C-4) product in 54% and 50% yield, respectively (**6a**, Scheme 3). The C-3 benzoyl as directing group resulted in C-2 selectivity, but the product was double alkenylated on both the indole as well as the phenyl ring (13% and 39%, **7a**, Scheme 3). We found that amide as a directing group furnished exclusively

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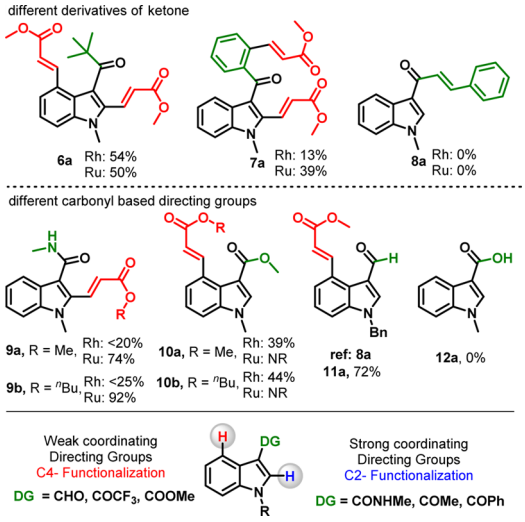
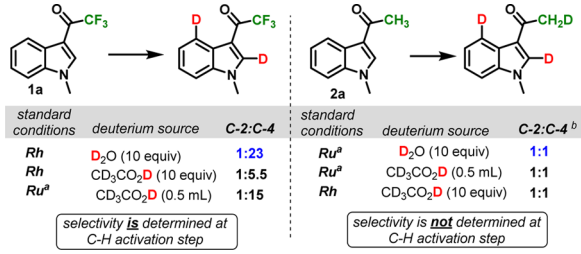
Scheme 3. Selectivity with Other Carbonyl Directing Groups



C-2 alkenylation in excellent yields (**9a**, **9b**, Scheme 3), while ester as a directing group furnished exclusively C-4 alkenylation, albeit in moderate yields (**10a**, **10b**). In our previous report,[8a] we demonstrated that the use of aldehyde as a directing group leads to C-4 alkenylation (**11a**). When carboxylic acid was used as the directing group, a complex mixture was obtained.

Deuterium incorporation studies were carried out to shed light on the site of metallacycle formation. Compounds **1a** and **2a** were independently subjected to standard conditions with both Rh and Ru, along with either D_2O or AcOD as the deuterium source (Scheme 4). We found that with **1a** as the substrate C-4

Scheme 4. Deuterium Incorporation Studies



standard conditions	deuterium source	C-2:C-4
Rh	D_2O (10 equiv)	1:23
Rh	CD_3CO_2D (10 equiv)	1:5.5
Ru[a]	CD_3CO_2D (0.5 mL)	1:15

selectivity **is** determined at C-H activation step

standard conditions	deuterium source	C-2:C-4 [b]
Ru[a]	D_2O (10 equiv)	1:1
Ru[a]	CD_3CO_2D (0.5 mL)	1:1
Rh	CD_3CO_2D (10 equiv)	1:1

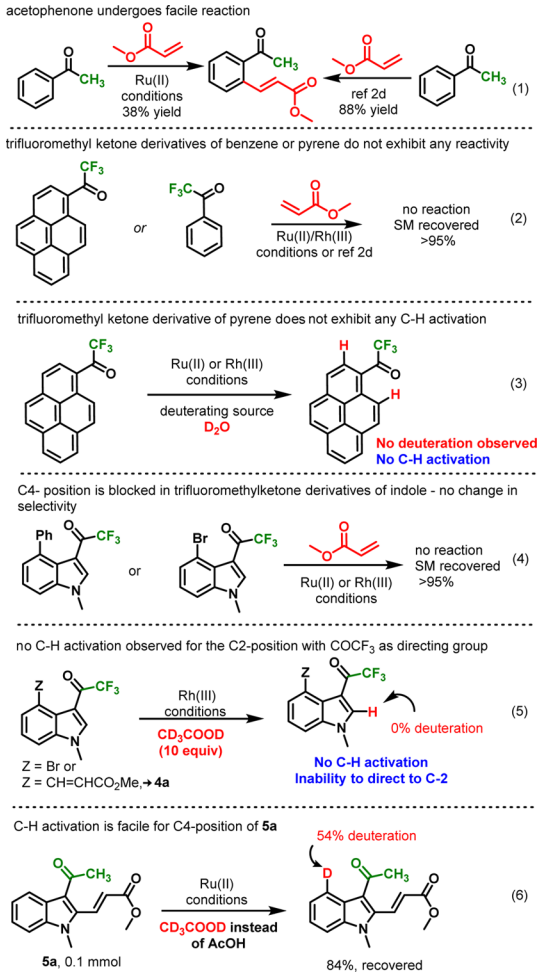
selectivity is **not** determined at C-H activation step

[a]Deuterium source was used in place of AcOH. [b]Deuteration of acetyl was observed.

deuteration was 23 times more successful than C-2 deuteration when D_2O was used as deuterium source, while **2a** resulted in equal amounts of C-2 and C-4 deuteration. This indicates that $COCF_3$ favors the C-4 metallacycle, whereas $COCH_3$ has no such preferences. Moreover, exchanging the metal catalysts (Scheme 4) did not lead to any change in the site of C−H activation, indicating that the observed selectivity is independent of the metal used.

First, we found a previous report for the alkenylation of acetophenone under almost similar conditions (eq 1, Scheme 5). However, no report for the trifluoromethyl derivative was found. When the trifluoromethyl derivatives of pyrene or benzene were used under the established conditions, Rh or Ru did not provide any trace of the requisite product (eq 2, Scheme 5). Since no product formed does not necessarily mean absence of C−H activation, we subjected the pyrene[9] derivative to deuteration under both conditions (Rh and Ru) using D_2O as deuterating

Scheme 5. Control Experiments



source and found no trace of deuteration (eq 3, Scheme 5). These controls indicate that $COCF_3$ cannot function as a directing group to activate the vicinal C−H bonds. However, it appears that it can only assist those C−H bonds that have proclivity toward electrophilic metalation. This hypothesis was further confirmed by the inability of $COCF_3$ to even functionalize C-2 in indole. Accordingly, we blocked C-4 in **1a** with either Br or phenyl substituents. Certainly, due to the low electron density of C-2, no expected product was formed (eq 4, Scheme 5). In addition, 4-bromoindole was subjected to deuteration, and as expected, no deuteration incorporation was observed on the C-2 position (eq 5, Scheme 5). Further, when **4a** (the alkenylated product) was subjected to deuteration, it did not furnish even trace amounts of deuteration at C-2 (eq 5). Once again, this can be rationalized by the further deactivation (i.e., lessening of electron density) of the indole moiety by the conjugated ester at C-4. However, when **5a** (with $COCH_3$) was subjected to deuteration, it was able to activate the C-4 position (eq 6), as evidenced by 54% deuteration. Since $COCH_3$ was able to activate the C-4 position, we thought if the C-2 is blocked then surely alkenylation should take place at C-4. To our surprise, the product **5a**, when subjected to alkenylation again with the Ru catalyst, was unable to furnish the alkenylation at C-4 (Scheme 6), in spite of the activation that it can accomplish. This clearly indicates that although C−H activation at C-4 is very feasible with $COCH_3$ as directing group, the insertion process appears to be nonfeasible with Ru catalyst. However, with Rh catalyst, we

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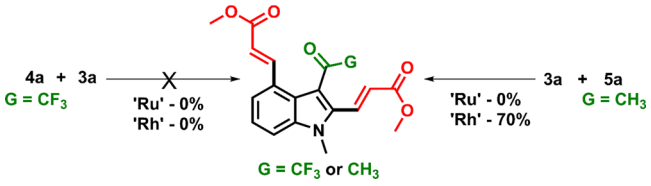
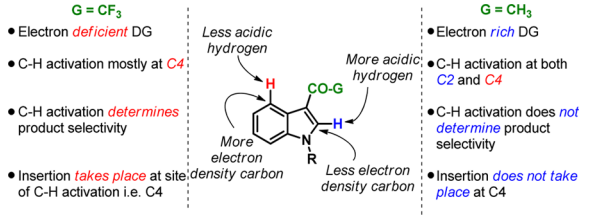
Scheme 6. Consecutive Alkenylation



observed the formation of C-4 alkenylation. As expected, when **4a** was subjected to further alkenylation, with Ru or Rh, no reaction was observed. The control experiments indicate that $COCF_3$ is effective for direct activation only at C-4 in indole and not C-2. One possible explanation for these observations is that $COCF_3$ does not direct C−H activation by precoordination to the metal but instead only stabilizes a metal−arene σ complex that forms due to electrophilic metalation. Hence, the reason for C-4 activation in indole must surely have to do with the electron density at C4.[10]

In summary (Scheme 7), we have presented a directing group dependent site-selective C−H activation and functionalization of

Scheme 7. Summary of Observations



indole using Ru(II) or Rh(III) catalysts. The use of trifluoroacetyl as directing group has been disclosed for the first time. The reaction is found to be tolerant to a wide variety of indole derivatives and olefin partners like acrylates, styrenes, and vinyl phosphonates. Examining different carbonyl-based directing groups, we found that weak coordinating directing groups provide exclusive C-4 alkenylated products, while strong coordinating groups provide C-2 products. Further work regarding the origin of selectivity is being carried out in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02698.

Experimental procedure and characterization data for all compounds (PDF)

X-ray crystallographic data for compounds **4a** and **5a** (CIF)

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Notes

The authors declare no competing financial interest.

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(9) Trifluoromethylacetophenone is lost when subjected to high vacuum. Hence, deuterium labeling has been done with pyrene only.

(10) For electron density calculations and prediction of pK_a values, see the Supporting Information.

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