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Weak Coordination Enabled Switchable C4-Alkenylation and Alkylation of Indoles with Allyl Alcohols

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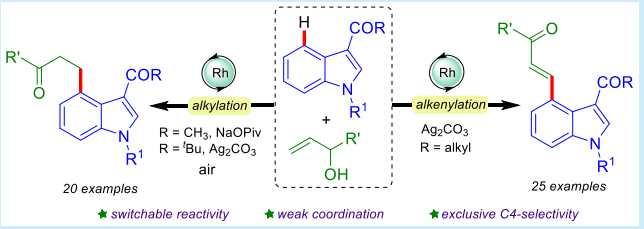
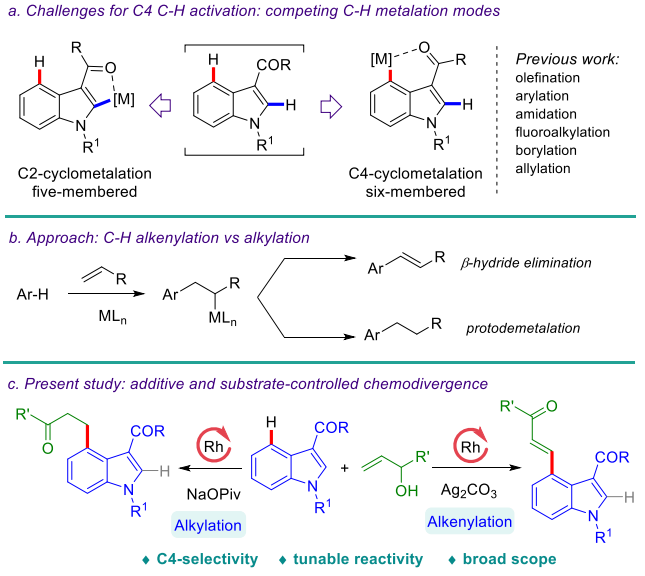
ABSTRACT: A weak carbonyl coordination facilitated tunable reactivity between alkenylation and alkylation of indoles at the C4 C−H site is presented using readily accessible allylic alcohols in the presence of Rh catalysis by switching the additives or directing group. Exclusive site selectivity, functional group tolerance, and late-stage modifications are the important practical features.



The indole framework is one of the most studied organic templates in the realm of organic synthesis,[1] as it features in plentiful natural products and pharmaceuticals.[2] The pursuit for expedited synthetic elaborations of the six available C−H functionalization sites on the indole backbone has thus emerged as a burgeoning research area. Owing to the inherent nucleophilic nature of the pyrrole type ring, C2 and C3 C−H functionalizations are replete with examples in the literature.[3] In contrast, the functionalization of the benzenoid segment (C4−C7) remains underdeveloped.[4] Along this line, selective editing at the C4-site of indole requires a directing group at the C3 position, which imposes an appreciable hurdle by prompting a competing C−H metalation pathway. The formation of five-membered cyclometalation at C2 is favored compared to the corresponding high energy six-membered cyclometalation at C4 (Scheme 1a). Hence, C4 functionalization of indole has garnered much attention and several groups devoted their efforts[5] to gain perspicuity of the above unsolved problem. Accordingly, olefination,[5a,b] arylation,[5c,d] amidation,[5e] fluoroalkylation,[5f] borylation,[5g] and allylation[5h] has been demonstrated at the C4 site of indoles. However, the development of an efficient and robust catalytic system which enables a switch in multiple reactive pathways by tuning the reactivity of substrates is desirable.[6] In this context, allylic alcohols are realized as a staple coupling partners in C−H functionalization as they are capable of selectively undergoing manifold reaction pathways by tuning the reactivity of the organometallic intermediate (Scheme 1b).[7] The use of allylic alcohols in C−H functionalization regulating either β-hydride or β-hydroxy elimination pathway has attracted considerable attention in recent years.[8] In addition, the implementation of a weakly coordinating directing group[9] to attain such tunable reactivity would be valuable. Here we report a carbonyl coordination guided controllable chemoselectivity between C4-alkenylation and alkylation of indoles with allyl alcohols by altering the additives and directing group in the presence of Rh catalysis (Scheme 1c).[10] In the case of Ag_2CO_3, selective β-hydride elimination provided alkenylation, whereas the presence of NaOPiv led to the alkylated product. When tertiary allyl alcohol was employed as a coupling partner selective allylation was achieved.

Scheme 1. C4 Functionalization of Indoles with Allyl Alcohols



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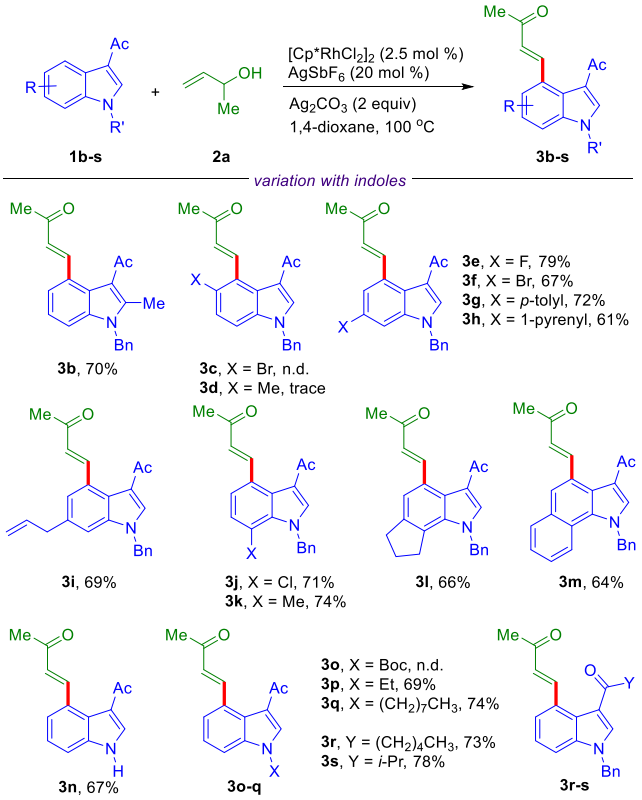
First, our optimization studies commenced reacting 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one **1a** with but-3-en-2-ol **2a** as the test substrates (see Table S1 for details). To our delight, the reaction occurred to give C4-alkenylated **3a** in 17% yield along with a trace of alkylated **4a** when the substrates were stirred with 2.5 mol % of $[Cp^*RhCl_2]_2$, 20 mol % of $AgSbF_6$, and 2 equiv of $Cu(OAc)_2$ in $(CH_2Cl)_2$ at 100 °C. Screening of the ethereal solvents, such as THF and 1,4-dioxane, revealed that the formation of **3a** was facilitated. Addition of Ag_2CO_3 in place of $Cu(OAc)_2$ led to improve the yield of **3a** to 74%, whereas AgOAc produced inferior result. Thus, Ag_2CO_3 was found to be the optimal additive[11] to furnish the alkenylation product selectively. Further screening of the alcoholic solvents such as, HFIP, TFE, and ^{t}BuOH favored the formation of **4a** compared to **3a**. Switching the additive from Ag_2CO_3 to $NaOPiv{\cdot}H_2O$ and a combination with AgOTf selectively produced the alkylated **4a** as the sole product. PivOH was also found to be effective, delivering **4a** in 61% yield, whereas AcOH was ineffective. Thus, $NaOPiv{\cdot}H_2O$ was beneficial to achieve alkylation selectively. Control experiments confirmed that the combination of $AgSbF_6$ or AgOTf and Rh(III) catalyst is decisive and no product formation was observed in its absence. Notably, C4 functionalization of indole was occurred selectively and no C2-functionalized product was detected. From the density functional theory (DFT) calculation, it was proposed that introducing a carbonyl group at the C3 C−H site can significantly increase the electron density at C4 site compared to the C2 site.[5i] This may drive the selective C4 functionalization by an electrophilic metalation-type process.

With the optimal reaction conditions established, the scope of C4 alkenylation was assessed for substituted indoles **1b−s** with allyl alcohol **2a** as a standard substrate (Scheme 2). The reaction of 2-methylindole **1b** afforded **3b** in 70% yield. 5-Substituted indoles bearing bromo (**1c**) and methyl (**1d**) functionalities were unsuccessful, which was presumably due to the steric congestion near the C4 site. However, the substrates containing substitution at the 6 position of indole, with fluoro (**1e**), bromo (**1f**), *p*-tolyl (**1g**), and 1-pyrenyl (**1h**) groups afforded the target alkenylated products **3e−h** in 61−79% yields. Delightfully, sensitive 6-allylated indole **1i** afforded **3i** in 69% yield. Similar results were obtained with 7-chloro (**1j**) and 7-methyl (**1k**) substituted indoles furnishing **3j** and **3k** in 71 and 74% yields, respectively. Fused indole congeners **1l** and **1m** produced **3l** and **3m** in 66 and 64% yields, respectively. Interestingly, NH-free indole was successfully coupled to give **3n** in 67% yield. Variation in *N*-protecting groups such as Boc (**1o**), ethyl (**1p**), and octyl (**1q**), the former was ineffective, while as others was amenable, delivering **3p** and **3q** in 69 and 74% yields, respectively. Likewise, 3-hexanoyl derivative **1r** and isobutyryl derivative **1s** conveyed **3r** and **3s** in 73 and 78% yields, respectively. These results suggest that C4 alkenylation of indoles can be accomplished with functional group tolerance.

With these intriguing results, the alkenylation scope was further explored using substituted allyl alcohols **2b−i** with indole **1a** as a standard substrate (Scheme 3). 1-Phenylprop-2-en-1-ol **2b** underwent reaction to afford **3t** in 64% yield. The reaction of 3-trifluoromethyl analogue **2c** produced **3u** in 58% yield, whereas 4-chloro (**2d**) and 4-fluoro (**2e**) derivatives delivered the corresponding alkenylated product **3v** and **3w** in 63 and 51% yields, respectively. Similar results were perceived with alkyl substitutions at the carbinol carbon of the allyl alcohols **2f−h**, delivering **3x−z** in 53−68% yields. Naturally

Scheme 2. Scope of C4 Alkenylation with Indoles[a,b]



[a]Reaction conditions: **1b−s** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.2 mmol), 1,4-dioxane (1.5 mL), 100 °C, 6 h, air. [b]Isolated yields.

occurring terpene alcohol isophytol **2i** participated in the reaction to give the C4 allylated product **3aa** in 41% yield. The reaction of tertiary allyl alcohol precludes the *β*-hydride elimination pathway, and the reaction proceeds *via β*-hydroxy elimination pathway to deliver allylated product.[8d] This result confides that C4-selective allylation of indoles can be achieved employing *tert*-allyl alcohols as a coupling partner.

Next, the C4 alkylation scope was investigated utilizing diversely substituted indoles with allyl alcohol **2a** as a standard coupling partner (Scheme 4). The reaction of 2-methylindole **1b** furnished the C4 alkylated product **4b** in 53% yield. Likewise, 5-methoxy (**1t**), 7-methyl (**1k**), *N*-phenyl (**1u**), and 3-isovaleryl (**1v**) containing indoles converted to the alkylated scaffolds **4d−g** in 63−69% yields, whereas 5-bromoindole **1c** was an unsuccessful substrate, which may be due to steric hindrance.

The reaction conditions were extended to the coupling of substituted allyl alcohols **2j−p** with indole **1a** as a standard substrate (Scheme 4). The reaction of pent-1-en-3-ol **2j** gave **4h** in 69% yield. Similarly, substitution of the phenyl ring at the carbinol carbon with 4-methoxy (**2k**) and 4-phenyl (**2l**) groups underwent reaction to afford **4i** and **4j** in 68 and 66% yields, respectively. Remarkably, conjugated *π*-system based allyl alcohols **2m−p** efficiently conveyed the alkylation products **4k−n** in 63−72% yields. These results displayed the captivating potential of the method for C4 alkylation of indoles to synthesize *β*-arylated ketones.

To divulge the importance of carbonyl based coordinating groups, the reaction of **2a** was conducted with a series of C3-carbonyl attached indole derivatives. Pivaloyl indole **1A**

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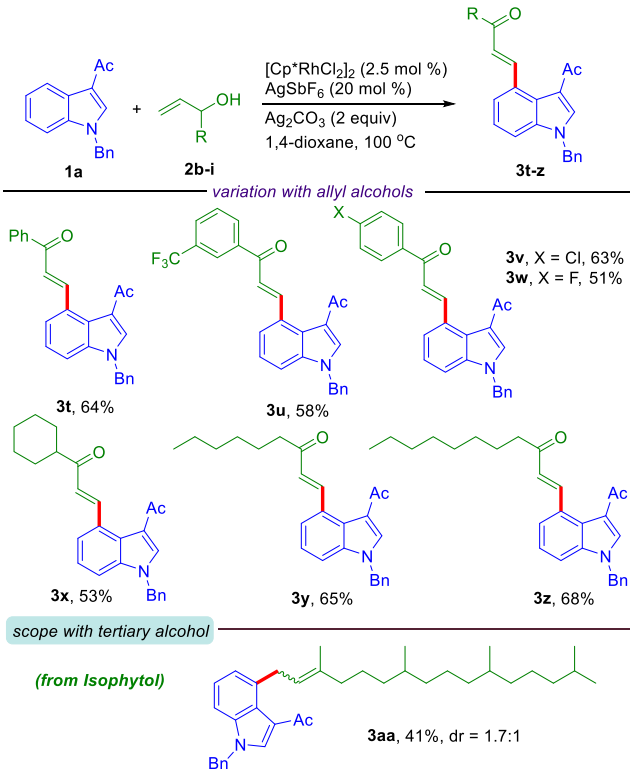
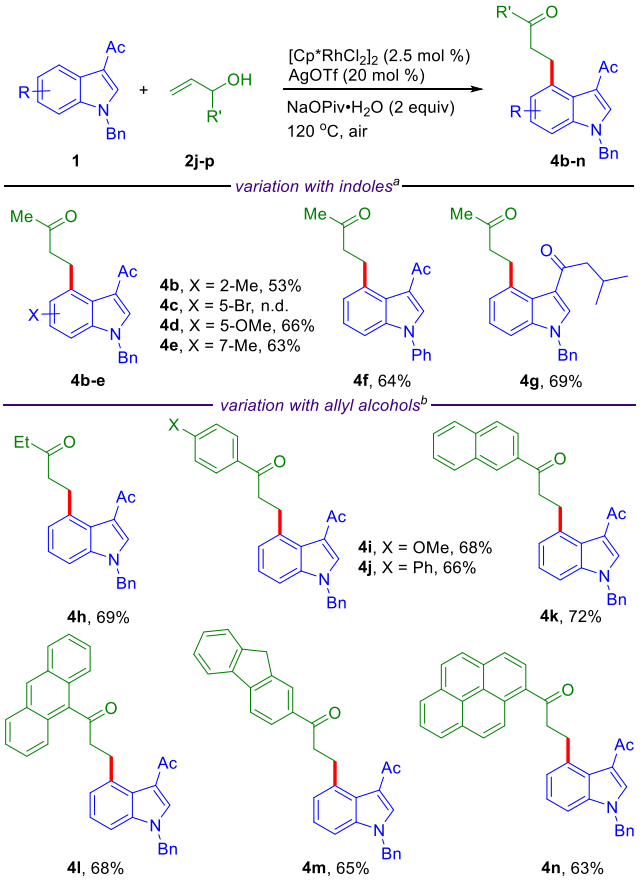
Scheme 3. Scope of C4 Alkenylation with Allyl Alcohols[a,b]



[a]Reaction conditions: **1a** (0.1 mmol), **2b−i** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.2 mmol), 1,4-dioxane (1.5 mL), 100 °C, 6 h, air. [b]Isolated yields.

Scheme 4. Scope of C4 Alkylation with Indoles and Allyl Alcohols[a,b]



[a]Reaction conditions: **1** (0.1 mmol), **2j−p** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), AgOTf (20 mol %), NaOPiv·H_2O (0.2 mmol), solvent (1.5 mL), 120 °C, 12 h, air. [b]Isolated yields. [a]*t*-BuOH used. [b]TFE used.

conveyed the C4 alkylated product **5a** in 67% yield, whereas formyl, **1a′**, benzoyl **1b′**, and trifluoromethylacetyl **1c′** were unsuccessful substrates (Scheme S1). These results indicate that, depending on the directing group a switch in product distribution between C4-selective alkenylation and alkylation can be achieved under identical reaction conditions.[6b]

We then turned our attention to assess the generality of C4 alkylation with respect to pivaloyl indoles **1B−G** with **2a** as a standard substrate (Scheme 5). 5-Bromo derivative **1B** was an unsuccessful substrate, which may be due to the steric hindrance near coupling site. However, 5-methoxy (**1C**), 6-bromo (**1D**), and 7-chloro (**1E**) indoles underwent reaction to deliver the alkylated products **5c−e** in 63−71% yields. The structure of **5d** was determined using single-crystal X-ray analysis (see the SI). The reaction of a fused indole derivative **1F** gave **5f** in 65% yield. Interestingly, prop-2-en-1-ol **2q** was smoothly coupled with **1A** to give the *β*-aryl aldehyde **5g** in 67% yield. In addition, fibrate drug gemfibrozil derived indole **1G** was alkylated to furnish **5h** in 70% yield. This showcase the remarkable potential of the method for the late-stage drug modification and the chemoselectivity can be altered depending on the directing group.[6b]

To gain insight into the reaction pathway, control, H/D exchange, and kinetic isotope experiments were conducted (Scheme S2). The reaction of **1a** and **2a** was performed under argon atmosphere. Alkenylation product **3a** was obtained in 71% yield, whereas alkylation **4a** was obtained albeit in lower yield (Scheme S2a). These results suggest that air might be playing as an oxidant in case of alkylation. Under standard conditions, allyl alcohol **2b** afforded isomerization products 1-phenylprop-2-en-1-one **2b′** and propiophenone **2b′′** as detected in NMR (Scheme S2b), which suggests that the reaction may proceed through the isomerized enone intermediate.[12a,e] In the absence of $[Cp^*RhCl_2]_2$, no H/D exchange was detected at both C4−H and C2−H bonds, implying the essential role of the Rh-catalyst in C−H activation. Whereas, H/D exchange experiments of **1a** and **1A** independently in the presence or absence of **2a** using D_2O as a cosolvent revealed significant deuterium incorporation at C4 site (Scheme S2c), signifying the reversibility of the C−H activation step. The H/D exchange of **1A** with **2a** revealed significant deuterium incorporation at the *α*-carbon of the carbonyl group of $[D_n]$-**5a**, thereby indicating the formation of a rhodium-oxa-*π* alllyl species.[12f] Further, kinetic isotope experiment using **1a** and $[D_2]$-**1a** with **2a**, yielded a k_H/k_D = 1.48 (Scheme S2d). This result indicates that the C4−H bond cleavage might not be involved in the rate-determining step.[12b]

On the basis of mechanistic considerations and literature,[8,12] a plausible mechanism is depicted in scheme S3. The catalytic cycle commenced with the generation of a cationic rhodium species ***a*** or ***a′*** by the reaction of dimeric Rh(III)-catalyst in the presence of Ag(I) salts (AgOTf or $AgSbF_6$) and additives, Ag_2CO_3 or NaOPiv. Allyl alcohols under basic condition may give the isomerized enone ***f***.[12a,e] The weak precoordination of carbonyl oxygen of **1** with ***a*** may deliver rhodacycle ***b***, whereas coordination of **1** with ***a′*** furnishes ***b*** along with the generation

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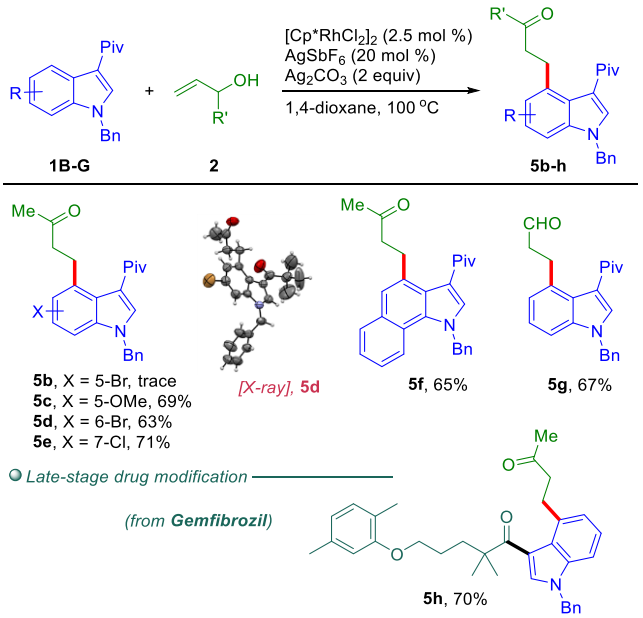
Scheme 5. Scope of C4 Alkylation with Pivaloyl Indoles[a,b]



[a]Reaction conditions: **1B−G** (0.1 mmol), **2** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.2 mmol), 1,4-dioxane (1.5 mL), 100 °C, 6 h, air. [b]Isolated yield.

of PivOH. Subsequent reaction of ***b*** with ***f*** may lead to the formation of ***c***. The latter may undergo reaction in two distinct pathways to provide the target products. When Ag_2CO_3 is present as a base additive in the medium, the intermediate ***c*** may undergo β-hydride elimination (path a) to deliver the alkenylated indoles **3**. On the other hand, the intermediate ***c*** may undergo preferential protodemetalation in the presence of PivOH (path b) to give the alkylated products **4**.[10a] In case of pivaloyl indoles **1A−G**, the electron-rich and bulkier carbonyl group may yield a rigid metalacycle ***c′*** which can prevent the β-H elimination and undergo isomerization to give the oxa-π allyl species ***g***.[6b,12d,f] Tautomerization can afford the alkylated product **5**. The active Rh-catalyst may regenerate with the help of Ag(I) and air to complete the catalytic cycle.

To display the practicality of the protocol, scale-up synthesis was carried out (Scheme S4). The scale-up (1 mmol) with **1a** and **2a** as the representative example gave the target alkenylated product **3a** in 66% yield. The acetyl directing group can be removed by a reverse Friedel−Crafts reaction.[5b] It is notable to mention that, the α,β-unsaturated carbonyl residue at the C4-site of indole can function as a versatile functional handle for further synthetic modifications.

In summary, we have demonstrated a robust Rh-catalyzed tunable C4 alkenylation and alkylation of indoles engaging allylic alcohols with high selectivity and functional group diversity. The dichotomy in product distribution can be achieved by switching the additives or directing group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04612.

General procedures, characterization data, NMR spectra (PDF)

Accession Codes

CCDC 1959139 contains 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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