Rh(III)-Catalyzed Regioselective C8-alkenylation of isoquinolones with methoxyallene: A Facile Access to aldehyde bearing isoquinolones

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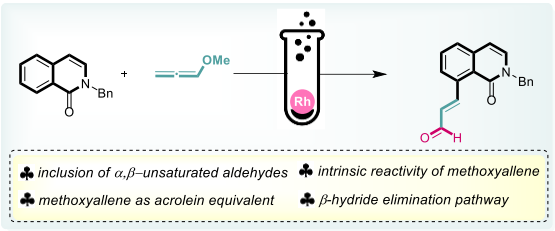
Supporting Information

ABSTRACT: A simple and facile access to isoquinolone aldehyde scaffolds has been achieved through a rhodium-catalyzed reaction between isoquinolone and methoxyallene. Herein, methoxyallene serves as an acrolein equivalent, resulting in this unique functionalization. Furthermore, the compatibility with natural complex and drug molecules underscores the significance of this developed protocol. Based on kinetic studies and several control reactions, a plausible reaction mechanism has also been proposed for this regioselective transformation.



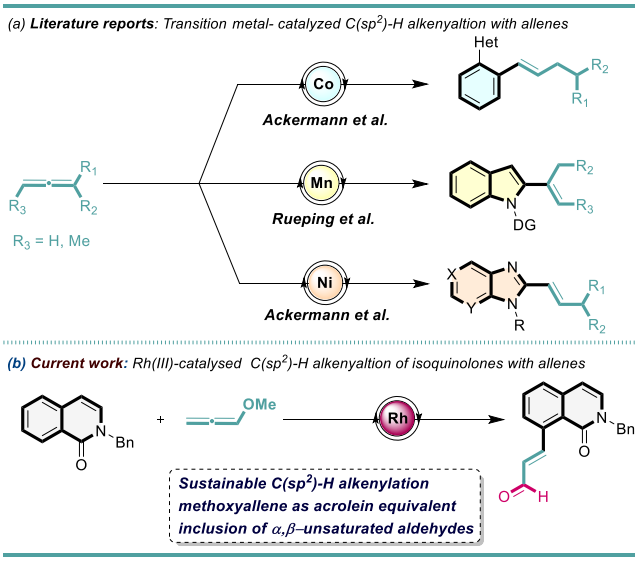
Allenes are one of the most versatile substrate classes, serving many valuable synthetic precursors for diverse transformations in organic synthesis.[1] Owing to their vibrant chemistry and high reactivity associated with the centered carbon of the cumulated diene render their diversity in natural products,[2] organic materials,[3] and pharmaceuticals.[4] Based on the stereoelctronically biased nature of allene, two highly reactive intermediates are formed *viz* metal-alkenyl intermediate through 1,2-migratory insertion of substrate-metal intermediate (formed after C-H activation) on allene and metal-allyl intermediate through 2,3-migratory insertion.[5]

The direct functionalization of simple C-H bonds with allenes *via* transition metal catalysis has been extensively studied.[6] However, these protocols are exploited mainly for allytion,[7] allenylation,[8] dienylation,[5b,9] and annulation.[10] Meanwhile, analogously, transition metal-catalyzed alkenylation transformations with allenes continue to be scarce. C-H alkenylation with disubstituted allene was pioneered by Ackermann and co-workers in 2016 *via* a cobalt-alkenyl intermediate pathway.[11] Later, Rueping's group reported C-H alkenylation of indole with electronically biased allenoates under manganese catalysis.[12] In 2017, Ackermann's group disclosed a nickel-catalyzed directing group-free approach for C-H alkenylation of purines with disubstituted allene.[13]

Furthermore, electronically biased allenes, especially alkoxyallenes, are highly versatile C3 building blocks.[14] Moreover, it is well known that methoxyallene can be utilized as safer acrolein equivalents,[14-15] because acrolein has a toxic profile.[16] Within a modular approach for sustainable C–H functionalization, one can design a system that efficiently captures *in situ* formed acrolein. Therefore, in this respect, introducing an alkenyl moiety with such a valuable functional group into molecules is of longstanding interest in organic synthesis.

At the same time, the functionalization of *N*-heterocycles is of prime interest in terms of synthetic and medicinal aspects.[17] Isoquinolone is an important scaffold and plays an essential role in organic synthesis, owing to its abundance in natural alkaloids and biologically active molecules.[18] In continuation of our ongoing efforts to expand the scope of isoquinolones C-H functionalization,[19] herein, methoxyallene has been used as a safe and operationally simple acrolein surrogate in the rhodium catalyzed C-H alkenylation of *N*-benzylisoquinolone to produce the corresponding alkenylated product **3a** (Scheme 1b).

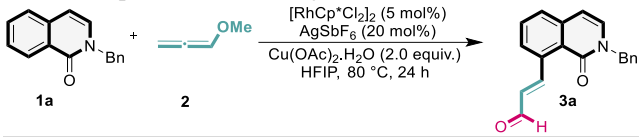
Scheme 1: Transition metal-catalyzed C(sp²)-H alkenylation with allenes



Initially, *N*-benzylisoquinolone (**1a**) and methoxyallene (**2**, 1.5 equiv.) were reacted in the presence of [Ru(*p*-cymene)Cl_2]$_2$/$AgSbF_6$ combination, Cu(OAc)$_2$.H_2O (1.0 equiv.) and chlorobenzene (PhCl) as solvent at 80 °C for 12 h to get a unique alkenylated product (**3a**), albeit in poor yield (19% GC yield) (Table 1, entry 2). Subsequent testing of various combinations of catalytic systems and solvents revealed [RhCp*Cl_2]$_2$/ $AgSbF_6$ with HFIP as the best combination (Table 1, entry 3-5). Control experiment without Cu(OAc)$_2$.H_2O entails its significance in the current reaction (Table 1, entry 6). Use of molecular oxygen as an oxidant did not prove fruitful, whereas anhydrous Cu(OAc)$_2$ provided an inferior

yield of **3a** (Table 1, entry 7-8). Gratifyingly, the yield of **3a** was dramatically improved when 5.0 equivalents of **2** was used (see SI). The final optimized reaction condition yielded 92% yield of alkenylated product (Table 1, entry 1). Increasing the time and temperature leads to decreased product yield (Table 1, entries 9-12). For a detailed optimization study, please see supporting information (SI).

Table 1. Optimization Study[a]

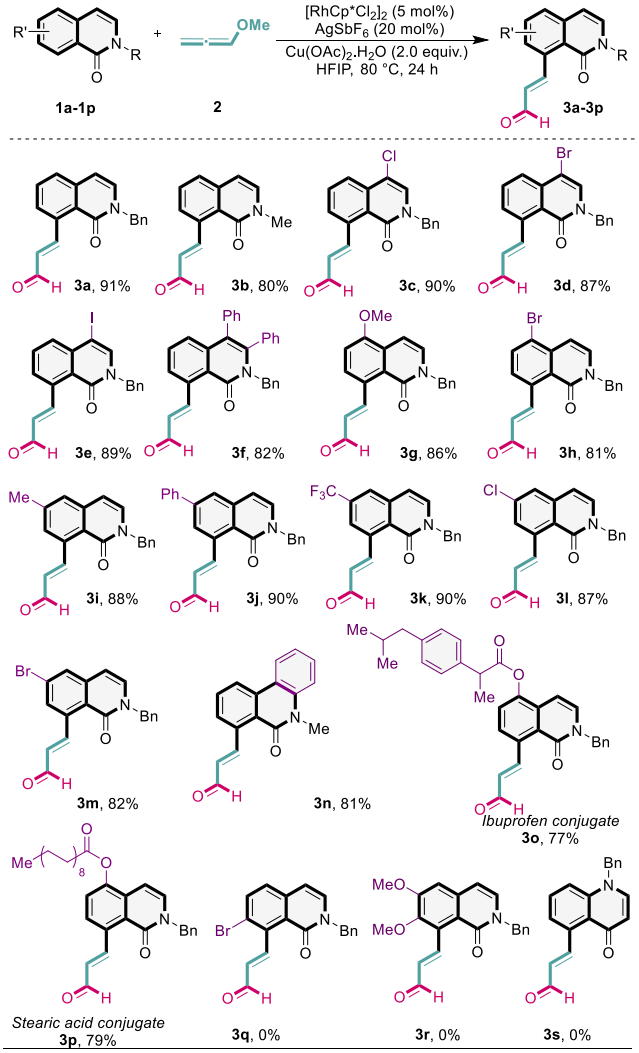


Sr. no.	Variation from standard condition	yield (%)[c]
1	None	92 (91)[d]
2[b]	[Ru(*p*-cymene)Cl_2]$_2$ complex	19
3[b]	[IrCp*Cl_2]$_2$ & CoCp*(CO)I_2 in place of Rh complex	n.d.
4[b]	[RhCp*Cl_2]$_2$/ $AgSbF_6$, PhCl solvent	34
5[b]	HFIP as solvent	54
6[b]	without Cu(OAc)$_2$.H_2O	n.d.
7[b]	Anhydrous Cu(OAc)$_2$ in place of Cu(OAc)$_2$.H_2O	44
8	O_2 as an oxidant in place of Cu(OAc)$_2$.H_2O	n.d.
9	12 h	62
10	36 h	66
11	60 °C	37
12	120 °C	52

[a]reaction conditions: **1a** (0.05 mmol), **2** (5.0 equiv.), [RhCp*Cl_2]$_2$ (5.0 mol%), $AgSbF_6$ (20 mol%), Cu(OAc)$_2$.H_2O (2.0 equiv.), HFIP (0.2 M), 24 h. [b]**2** (1.5 equiv.), Cu(OAc)$_2$.H_2O (1.0 equiv.). [c]GC yield (*n*-decane as an internal standard). [d]Isolated yield in parenthesis. n.d.: not detected.

The optimal conditions were then implemented to explore the scope of isoquinolones for C(sp^2)-H alkenylation. An array of diversely substituted isoquinolones were utilized for this transformation, affording excellent yields of the desired alkenylated products up to 91% yield. The reaction was amenable with methyl-protected isoquinolone, selectively furnishing the alkenylated product in 80% yield (**3b**). C4-halogen-bearing isoquinolones also participated well in this transformation, delivering the corresponding products in excellent yields (**3c**-**3e**). Gratifyingly, the treatment of di-substituted isoquinolone under standard conditions resulted in the formation of alkenylated product **3f** in high yield. Furthermore, C5-methoxy and halogen derivatives underwent regioselective alkenylation to afford **3g** and **3h** in good yields. Moreover, this protocol could also be extended to various C6-substituted isoquinolones, delivering the corresponding products in 82-90% yields (**3i**-**3m**). Simple phenanthrodinone substrate was also transformed into the corresponding product **3n** in 81% yield. In addition, complex molecules, such as ibuprofen-conjugate (**1o**) and stearic acid-conjugate (**1p**) were also tested to get the corresponding alkenylated products in 77–79% yields, underscoring facile access to the valuable natural scaffolds.

Table 2. Substrate scope for C(sp^2)-H alkenylation of diversely substituted isoquinolones



Reaction conditions: **1a**-**1p** (0.2 mmol), **2** (5.0 equiv.), [RhCp*Cl_2]$_2$ (5 mol%), $AgSbF_6$ (20 mol%), Cu(OAc)$_2$.H_2O (2.0 equiv.), HFIP (0.2 M), 80 °C, 24 h.

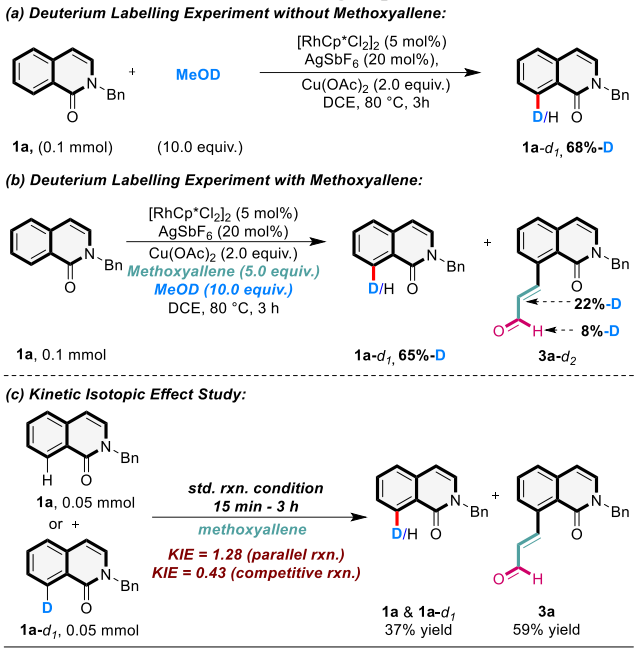
However, C7-substituted isoquinolones were found unsuitable for this reaction (**1q**-**1r**), which might be due to steric factors. Unfortunately, *N*-benzylquinolone (**1s**) was also incompatible with this reaction protocol.

Preliminary mechanistic investigations have been conducted to gain mechanistic insight into the developed C(sp2)–H alkenylation (Scheme 2). As shown in Scheme 2a, 68% deuteration was observed at the C8 position of **1a** when the deuterium labeling experiment was conducted without a coupling partner for 3 h in the presence of MeOD. This result suggested the reversible nature of C-H activation step. Moreover, when the methoxyallene was included in H/D experiment, 8% deuteration was observed on the aldehydic proton, and 22% deuteration was incorporated on *β*-proton of **3a**, concluding the involvement of 1,2-migratory insertion pathway.

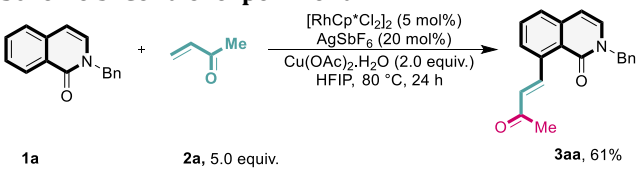
On the other hand, parallel and competitive experiments with **1a** and **1a**-d_1 gave kinetic isotope values of 1.28 and

0.43, respectively, which infers that the C-H metalation step may not be the rate-determining step.

Scheme 2. Deuterium labeling experiments



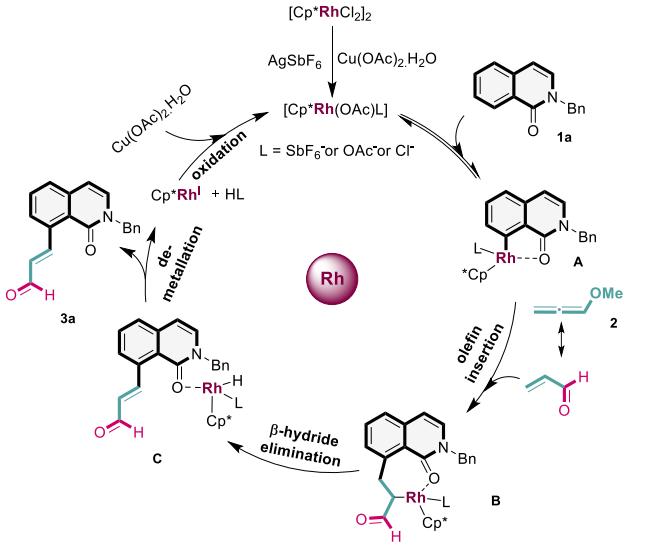
Scheme 3. Control experiment



Next, we evaluated whether the current protocol could serve as a C(sp^2)–H alkenylation platform with other coupling partners (Scheme 3). We hypothesize the involvement of *α,β*-unsaturated carbonyl functionality generated *in situ* from its reacting precursor. To explore this hypothesis, we envisioned that *α,β*-unsaturated carbonyl unit in methyl vinyl ketone **2a** could deliver the corresponding alkenylated product **3aa**[20] under optimized conditions. Indeed, we were pleased to accomplish the installation of such moiety on **1a**, indicating that this method could provide rapid access to *α,β*-unsaturated carbonyl compounds.

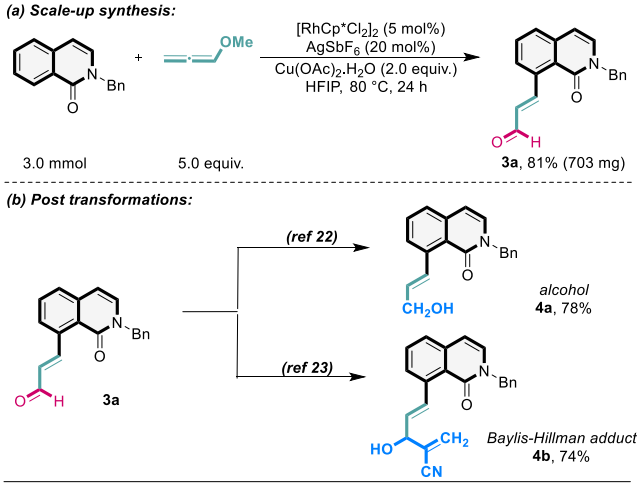
Based on previous literature and experimental results, a plausible mechanism is outlined in scheme 4.[11-13, 21] The reaction starts with the generation of active rhodium(III) species in the presence of $AgSbF_6$ and oxidant. Then, this active Rh(III) species facilitated the C-H activation of *N*-benzylisoquinolone, yielding the rhodacycle **A**. The rhodacycle **A** could further undergo 1,2-olefin migratroy insertion step to produce the intermediate **B**, followed by *β*–hydride elimination to afford intermediate **C**. Next, the de-metallation step leads to the formation of the desired alkenylated product **3a** and Rh(I) species, which is oxidized to Rh(III) species in the presence of $Cu(OAc)_2.H_2O$ to continue the catalytic cycle.

Scheme 4. Plausible Mechanistic Cycle



To magnify the potential merit of the current protocol, we assessed the scale-up synthesis and post-transformations as illustrated in scheme 5. A scale-up reaction of **1a** was conducted under standard conditions to provide the product in 81% yield (703 mg). In post-transformations, selective functionalization of aldehydic moiety of **3a** was carried out to get the corresponding alcohol (**4a**) in 78% yield.[22] Moreover, the functionalized alkene nitrile (**4b**) was also synthesized through the derivatization of **3a** with acrylonitrile.[23]

Scheme 5. Synthetic applicability of the current methodology



We have devised a rhodium-catalyzed protocol for accessing isoquinolone aldehyde scaffolds. The present transformation highlights the intrinsic reactivity of methoxyallene and the explicit role of oxidant in enabling the regioselective alkenylation of a diverse range of isoquinolones *via* a directing group approach. Methoxyallene was utilized as an operationally simple and comparatively safer surrogate of acrolein. Furthermore, streamlining the conversion of aldehydic group of the product into alcohol and synthesis of baylis Hillman adduct showcased the usefulness of this valuable

building block. Kinetic studies and controlled experiments revealed that the current reaction involves *in situ* conversion of methoxyallene into acroline, which undergoes insertion with rohaldacycle (**A**)and finally delivers the alkenylated product *via* the *β*-hydride elimination step.

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

The authors are grateful to the Director, CSIR-IHBT for providing the necessary facilities AT thanks UGC, Delhi for the SRF fellowship. The CSIR-IHBT communication number for this manuscript is 0000.

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