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. Owing to their vibrant chemistry and high reactivity associated with the centered carbon of the cumulated diene render their diversity in natural products, organic materials, and pharmaceuticals. Based on the stereoelectronically 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.

The direct functionalization of simple C-H bonds with allenes via transition metal catalysis has been extensively studied. However, these protocols are exploited mainly for allylation, allenylation, dienylation, and annulation. 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. Later, Rueping’s group reported C-H alkenylation of indole with electronically biased allenoles under manganese catalysis. In 2017, Ackermann’s group disclosed a nickel-catalyzed directing group-free approach for C-H alkenylation of purines with disubstituted allene. Furthermore, electronically biased allenes, especially alkoxycyclohexynes, are highly versatile C3 building blocks. Moreover, it is well known that methoxyallene can be utilized as safer acrolein equivalents because acrolein has a toxic profile. 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. Isoquinolone is an important scaffold and plays an essential role in organic synthesis, owing to its abundance in natural alkaloids and biologically active molecules. In continuation of our ongoing efforts to expand the scope of isoquinolones C-H functionalization, herein, methoxyallene has been used as a safe and operationally simple acrolein surrogate in the rhodium catalyzed C-H alkenylation of N-benzyisoquinolone to produce the corresponding alkenylated product 3a (Scheme 1b).

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

Initially, N-benzyisoquinolone (1a) and methoxyallene (2, 1.5 equiv.) were reacted in the presence of [Ru(p-cymene)Cl2]/AgSbF6 combination, Cu(OAc)2.H2O (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*Cl2]/AgSbF6 with HFIP as the best combination (Table 1, entry 3-5). Control experiment without Cu(OAc)2.H2O 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

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Variation from standard condition</th>
<th>yield (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>92 (91)*</td>
</tr>
<tr>
<td>2</td>
<td>[Ru(p-cymene)Cl2]2 complex</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>[IrCl2]2 &amp; CO2 in place of Ru complex</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>[RhCl2]2 / AgSbF6, PhCl solvent</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>HFIP as solvent</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>without Cu(OAc)2·H2O</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>Anhydrous Cu(OAc)2, H2O</td>
<td>44</td>
</tr>
<tr>
<td>8</td>
<td>O2 as an oxidant in place of Cu(OAc)2·H2O</td>
<td>n.d.</td>
</tr>
<tr>
<td>9</td>
<td>12 h</td>
<td>62</td>
</tr>
<tr>
<td>10</td>
<td>36 h</td>
<td>66</td>
</tr>
<tr>
<td>11</td>
<td>60 °C</td>
<td>37</td>
</tr>
<tr>
<td>12</td>
<td>120 °C</td>
<td>52</td>
</tr>
</tbody>
</table>

*reaction conditions: 1a (0.05 mmol), 2 (5.0 equiv.), [RhCl2]2 (5.0 mol%), AgSbF6 (20 mol%), Cu(OAc)2·H2O (2.0 equiv.), HFIP (0.2 M), 24 h. +2 (1.5 equiv.), Cu(OAc)2·H2O (1.0 equiv.). *GC yield (n-decane as an internal standard). aIsolated yield in parenthesis. n.d.: not detected.

The optimal conditions were then implemented to explore the scope of isoquinolones for C(sp2)-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 disubstituted 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 phenanthroline 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(sp2)-H alkenylation of diversely substituted isoquinolones

<table>
<thead>
<tr>
<th>Reaction conditions: 1a-1p (0.2 mmol), 2 (5.0 equiv.), [RhCl2]2 (5.0 mol%), AgSbF6 (20 mol%), Cu(OAc)2·H2O (2.0 equiv.), HFIP (0.2 M), 80 °C, 24 h.</th>
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<tr>
<td><img src="https://doi.org/10.26434/chemrxiv-2024-z65f0" alt="Diagram of reaction" /></td>
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<tr>
<td><img src="https://orcid.org/0000-0002-7693-8690" alt="Table of products" /></td>
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</tbody>
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However, C7-substituted isoquinolones were found unsuitable for this reaction (1q-1r), which might be due to steric factors. Unfortunately, N-benzylisoquinolone (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 methoxallylene was included in H/D experiment, 8% deuteration was observed on the aldehyde 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, gave kinetic isotope values of 1.28 and
0.43, respectively, which infers that the C-H metation step may not be the rate-determining step.

Scheme 2. Deuterium labeling experiments

(a) Deuterium Labeling Experiment without Methoxallene:

\[
\begin{array}{c}
\text{MeOD} \\
\text{Cu(OAc)}_2 (2.0 \text{ eqv}) \\
\text{DCE, 80 °C, 3 h}
\end{array}
\]

\[
\begin{array}{c}
1a \text{, 0.1 mmol} \\
1a-d_2 65\% \text{-D}
\end{array}
\]

(b) Deuterium Labeling Experiment with Methoxallene:

\[
\begin{array}{c}
\text{MeOD} (10.0 \text{ eqv}) \\
\text{Cu(OAc)}_2 (2.0 \text{ eqv}) \\
\text{DCE, 80 °C, 3 h}
\end{array}
\]

\[
\begin{array}{c}
1a, 0.1 \text{ mmol} \\
1a-d_2 55\% \text{-D}
\end{array}
\]

(c) Kinetic Isotopic Effect Study:

\[
\begin{array}{c}
\text{KIE = 1.28 (parallel rxn)} \\
\text{KIE = 0.43 (competitive rxn)}
\end{array}
\]

\[
\begin{array}{c}
1a-d_2, 0.05 \text{ mmol} \\
1a \text{ and } 1a-d_2 \\
3a \\
3a-d_2
\end{array}
\]

Next, we evaluated whether the current protocol could serve as a C(sp²)-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 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 AgSbF₆ 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- reductive 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·H₂O to continue the catalytic cycle.

Scheme 3. Control experiment

\[
\begin{array}{c}
\text{MeOD} \\
\text{Cu(OAc)}_2 (2.0 \text{ eqv}) \\
\text{DCE, 80 °C, 24 h}
\end{array}
\]

\[
\begin{array}{c}
1a \text{, 5.0 mmol} \\
2a \text{, 5.0 mmol} \\
3a, 61\%
\end{array}
\]

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 4. Plausible Mechanistic Cycle

Scheme 5. Synthetic applicability of the current methodology

(a) Scale-up synthesis:

\[
\begin{array}{c}
\text{MeOH} \\
\text{Cu(OAc)}_2 (2.0 \text{ eqv}) \\
\text{HFP, 80 °C, 24 h}
\end{array}
\]

\[
\begin{array}{c}
1a \text{, 3.0 mmol} \\
5.0 \text{ equiv.} \\
3a, 81\% (703 mg)
\end{array}
\]

(b) Post transformations:

\[
\begin{array}{c}
\text{Cu(OAc)}_2 (2.0 \text{ eqv}) \\
\text{HFP, 80 °C, 24 h}
\end{array}
\]

\[
\begin{array}{c}
\text{4a, 78%} \\
\text{4b, 74%}
\end{array}
\]

We have devised a rhodium-catalyzed protocol for accessing isoquinolone aldehyde scaffolds. The present transformation highlights the intrinsic reactivity of methoxallene and the explicit role of oxidant in enabling the regioselective alkenylation of a diverse range of isoquinolones via a directing group approach. Methoxallene was utilized as an operationally simple and comparatively safer surrogate of acrolein. Furthermore, streamlineing 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 methoxyllallene 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.

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