Rhodium(III)-Catalyzed Synthesis of Pyridines from α,β-Unsaturated Ketoximes and Internal Alkynes

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Abstract: A method for the synthesis of highly substituted pyridines from α,β-unsaturated ketoximes and internal alkynes has been developed using [Cp*RhCl2]2–CsOPiv as the catalyst system. The present transformation is carried out by a redox-neutral sequence of vinylic C–H rhodation, alkyne insertion, and C–N bond formation of the putative vinyl rhodium intermediate with the oxime nitrogen, where the N–O bond of oxime derivatives could work as an internal oxidant to maintain the catalytic cycle.

Key words: pyridines, oximes, alkynes, rhodium, C–H activation

Among nitrogen-containing heterocycles (azaheterocycles), pyridines are one of the most prevalent motifs in numerous natural products, potent pharmaceutical drugs, and synthons for functional materials. Although diverse approaches toward synthesis of pyridines have been developed, there remains a demand for versatile methodologies to construct pyridines with selective control of substitution patterns from readily accessible building blocks.

Synthetic transformation via C–H bond functionalization by transition-metal catalysts is an ideal process in organic synthesis in terms of atom- and step-economical points of view. Commonly, suitable heteroatoms are utilized as a directing group to activate the specific proximal C–H bond, where an sp2-imino/amido nitrogen atom has been employed in numerous examples of the C–H bond activation.

Recently, redox-neutral catalytic strategies using the N–O bond attached in the nitrogen directing group have been developed for the synthesis of azaheterocycles via the sequence of ortho C–H activation and C–N bond formation, where the N–O bond works as an internal oxidant to maintain catalytic turnover. For example, Guimond and Fagnou disclosed the synthesis of isoquinoline derivatives with internal alkynes (Scheme 1). Based on these backgrounds, our attention has been drawn to the use of readily available α,β-unsaturated ketoximes for vinylic C–H fission/functionalization. Herein we wish to report rhodium(III)-catalyzed synthesis of highly functionalized pyridines from α,β-unsaturated ketoximes and internal alkynes under mild reaction conditions (Scheme 2).

First, we screened the reaction conditions for synthesis of pyridine 3aa from (E)-4-phenylbut-3-ene-2-one oxime derivatives 1a and diphenyl acetylene 2a (Scheme 2). Using 2.5 mol% of [Cp*RhCl2]2 and 30 mol% of metal carboxylates as an additive in MeOH (Table 1). As expected, the reactions of O-acetyloxime 1a proceeded to give desired pyridine 3aa, the highest yield of which was provided by running with CsOPiv as an additive (10 h, 77% yield, Table 1, entry 3). The reaction with Cu(OAc)2, however, did not give the desired pyridine 3aa, resulting in decomposition of oxime acetate (Table 1, entry 4). Using the [Cp*RhCl2]2–CsOPiv system, the effect of the substituent X was next examined. Although the yield of pyridine 3aa from oxime acetate 1a was moderate (Table 1, entry 5), the reactions of oxygen-free oxime 1a resulted in the smooth reaction, affording pyridine 3aa in 79% yield within seven hours (Table 1, entry 6). The reaction under a N2 atmosphere...
was found to be sluggish, indicating that the presence of air (oxygen) has a crucial role to maintain and accelerate the catalytic turnover (Table 1, entry 7). Use of 1.5 equivalents of oxime 1a with diphenyl acetylene (2a) gave 86% yield of pyridine 3a (based on acetylene 2a), while longer reaction time (24 h) was required (Table 1, entry 8).

Table 1 Optimization of Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Additive</th>
<th>Time (h)</th>
<th>Yield of 3aa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a X = Ac</td>
<td>NaOAc</td>
<td>24</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>1a X = Ac</td>
<td>CsOAc</td>
<td>24</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>1a X = Ac</td>
<td>CsOPiv</td>
<td>10</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>1a X = Cu</td>
<td>Cu(OAc)₂</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>1a’ X = Piv</td>
<td>CsPiv</td>
<td>19</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>1a” X = H</td>
<td>CsPiv</td>
<td>7</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>1a” X = H</td>
<td>CsPiv</td>
<td>24</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>1a” X = H</td>
<td>CsPiv</td>
<td>24</td>
<td>86</td>
</tr>
</tbody>
</table>

a Unless otherwise noted, reactions were carried out using 0.5 mmol of oxime 1a and 1.2 equiv of alkyne 2a with 2.5 mol% of [Cp*RhCl₂]₂ and 30 mol% of additive in MeOH at 60 °C under an air atmosphere.
b Isolated yields were recorded above.
c The reaction was conducted under a N₂ atmosphere.
d The reaction was conducted using 0.5 mmol of alkyne 2a and 1.5 equiv of oxime 1a”, and the yield of 3aa was calculated based on alkyne 2a.

During optimization of the reaction conditions (Table 1), in addition to the desired pyridine 3aa generated via 1:1 coupling of oxime 1a and alkyne 2a, the formation of 2-naphthylpyridine 4aa (1:3 coupling of 1a and 2a) was observed as a minor side product (less than 10% yield) in most of the entries. The naphthyl moiety of 4aa was presumably constructed from 3aa via catalytic multiple C–H bond cleavage and insertion of two more equivalents of alkyne 2a. Indeed, treatment of oxime 1a” with excess amounts (5 equiv) of alkyne 2a under the present reaction conditions delivered 2-naphthylpyridine 4aa in 56% yield after 54 hours along with 32% yield of 3aa (Scheme 3).

With the optimized reaction conditions using oxygen-free oxime 1a” (Table 1, entry 6), generality of the substituents on internal alkynes was investigated (Table 2). Symmetrical diaryl acetylenes bearing various substituents reacted smoothly, affording the corresponding pyridines 3 in good yields (Table 2, entries 1–3). Similarly, the reactions of dialkyl acetylenes 2e and 2f also proceeded smoothly (Table 2, entries 4 and 5). Insertion of unsymmetrical alkynes 2g–i occurred somehow in regioselective manner, albeit in moderate selectivity (Table 2, entries 6–8).

Scheme 3 A proposed catalytic pathway

The present process showed wide substrate tolerance with α,β-unsaturated oxime derivatives 1 by the reactions with alkynes 2a or 2e (Table 3). By varying the substituent on the β-carbon, benzene rings bearing electron-donating groups (Table 3, entries 1–3) and a bromine atom (Table 3, entry 4) as well as naphthyl and thienyl groups (Table 3, entries 5–8) could be introduced, leading to the formation of the corresponding pyridines 3 in good to moderate yields. The reaction of dibenzylideneacetone oxime (1i) with diphenyl acetylene (2a) proceeded smoothly to give 6-styrylpyridine 3ia in 81% yield (Table 3, entry 9). When the substituent of R₁ of oxime 1a” was replaced from methyl to isopropyl, the stereosemetry of the N–O bond of oxime 1j became a mixture of E- and Z-isomers in a 55:45 ratio. The reaction of oxime 1j afforded pyridine 3ja in 40% yield with 25% recovery of Z-isomer (Table 3, entry 10). Pentasubstituted pyridines 3ka and 3la could be synthesized smoothly in good yields (Table 3, entries 11 and 12). When 3-benzylbut-3-en-2-one oxime (1m) without the β-substituent was employed, the reaction took place in a shorter reaction time (2 h), affording 2,3,5,6-tetrasubstituted pyridine 3ma in 88% yield (Table 3, entry 13).

A proposed catalytic reaction pathway of the present pyridine formation was outlined in Scheme 4. It commences with vinyclic C–H activation of α,β-unsaturated oxime 1a” with the aid of the oxime sp²-nitrogen to give vinyl rhodium intermediate A. Insertion to alkynes 2a with A affords seven-membered-ring rhodacylic iminium cation intermediate B, which undergoes concerted redox processes of C–N reductive elimination and regeneration of rhodium(III) species to give pyridine 3aa.
Table 2  Scope of Internal Alkynes\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne</th>
<th>R\textsuperscript{4}</th>
<th>R\textsuperscript{5}</th>
<th>Time (h)</th>
<th>Yield of 3 (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b</td>
<td>4-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>4-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>24</td>
<td>3ab 61</td>
</tr>
<tr>
<td>2</td>
<td>2c</td>
<td>4-TMSC\textsubscript{6}H\textsubscript{4}</td>
<td>4-TMSC\textsubscript{6}H\textsubscript{4}</td>
<td>10</td>
<td>3ac 60\textsuperscript{c}</td>
</tr>
<tr>
<td>3</td>
<td>2d</td>
<td>3-BrC\textsubscript{6}H\textsubscript{4}</td>
<td>3-BrC\textsubscript{6}H\textsubscript{4}</td>
<td>10</td>
<td>3ad 77</td>
</tr>
<tr>
<td>4</td>
<td>2e</td>
<td>n-Pr</td>
<td>n-Pr</td>
<td>8</td>
<td>3ae 75</td>
</tr>
<tr>
<td>5</td>
<td>2f</td>
<td>TBSOCH\textsubscript{2}</td>
<td>TBSOCH\textsubscript{2}</td>
<td>30</td>
<td>3af 69</td>
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<tr>
<td>6</td>
<td>2g</td>
<td>Me</td>
<td>Ph</td>
<td>8</td>
<td>3ag 97 (60:40)</td>
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<tr>
<td>7</td>
<td>2h</td>
<td>CO\textsubscript{2}Et</td>
<td>Ph</td>
<td>24</td>
<td>3ah 45 (60:40)</td>
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<tr>
<td>8</td>
<td>2i</td>
<td>4-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>4-F\textsubscript{3}CC\textsubscript{6}H\textsubscript{4}</td>
<td>24</td>
<td>3ai 87 (70:30)</td>
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</tbody>
</table>

\textsuperscript{a} Unless otherwise noted, reactions were carried out using 0.5 mmol of oxime 1\textsuperscript{a} and 1.2 equiv of alkyne 2 with 2.5 mol\% of \([\text{Cp}^*\text{RhCl}_2]\)\textsubscript{2} and 30 mol\% of CsOPiv in MeOH at 60 °C under an air atmosphere.

\textsuperscript{b} Isolated yields were recorded above.

\textsuperscript{c} Oxime 1\textsuperscript{a} was recovered in 32% yield.

Table 3  Scope of \(\alpha,\beta\)-Unsaturated Oximes\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oximes 1</th>
<th>Alkynes 2a or 2e</th>
<th>Time (h)</th>
<th>Pyridines 3</th>
<th>Yield (%)\textsuperscript{b}</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>2e</td>
<td>20</td>
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<tr>
<td>2</td>
<td>1c</td>
<td>2e</td>
<td>30</td>
<td>3ce 63</td>
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<tr>
<td>3</td>
<td>1d</td>
<td>2a</td>
<td>30</td>
<td>3da 68</td>
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<tr>
<td>4</td>
<td>1e</td>
<td>2a</td>
<td>12</td>
<td>3ea 87</td>
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\textsuperscript{a} Unless otherwise noted, reactions were carried out using 0.5 mmol of oxime 1\textsuperscript{a} and 1.2 equiv of alkyne 2 with 2.5 mol\% of \([\text{Cp}^*\text{RhCl}_2]\)\textsubscript{2} and 30 mol\% of CsOPiv in MeOH at 60 °C under an air atmosphere.

\textsuperscript{b} Isolated yields were recorded above.

\textsuperscript{c} Oxime 1\textsuperscript{a} was recovered in 32% yield.
Table 3  Scope of α,β-Unsaturated Oximes (continued)

![Diagram of reaction]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oximes 1</th>
<th>Alkynes 2a or 2e</th>
<th>Time (h)</th>
<th>Pyridines 3</th>
<th>Yield (%)$^b$</th>
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<td>2a</td>
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<tr>
<td>13</td>
<td><img src="1m" alt="Image" /></td>
<td>2a</td>
<td>2</td>
<td><img src="3ma" alt="Image" /></td>
<td>3ma 88</td>
</tr>
</tbody>
</table>

$^a$ Unless otherwise noted, reactions were carried out using 0.5 mmol of oxime 1 and 1.2 equiv of alkyne 2 with 2.5 mol% of [Cp*RhCl$_2$], and 30 mol% of CsOPiv in MeOH at 60 °C under an air atmosphere.

$^b$ Isolated yields were recorded above.

$^c$ The reaction was conducted using 1 equiv of alkyne 2a.

$^d$ The Z isomer of oxime 1j was recovered in 25% yield.
In summary, we have developed a synthetic method of highly substituted pyridines from α,β-unsaturated oximes and internal alkenes using [Cr^III(η^5-C_5H_5)Cl_2]_2-CsOPiv as the catalyst system. Further investigation on application of this methodology for the synthesis of other types of heterocycles are currently under way.

Supporting Information for this article is available online at https://www.thieme-connect.com/ejournals/soc/synlett.

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References and Notes


(12) The formation of 4aa could result in generation of rhodium(I) species, which should be re-oxidized to rhodium(III) by air (O2) to maintain the catalytic turnover.

(13) Although E/Z isomerization of the N–O bond of oxime 1k might be possible in the present reaction conditions, we are not certain whether the Z-isomer of 1k was converted into pyridine via its isomerization to E-isomer during this reaction. For isomerization of the oxime N–O bonds, see: Johnson, J. E.; Silk, N. M.; Nalley, E. A.; Arfan, M. J. Org. Chem. 1981, 46, 546.

(14) General Procedure (Table 1, Entry 6)
To a MeOH solution (2.5 mL) of (2E,3E)-4-phenylbut-3-en-2-one oxime (1a, 80.5 mg, 0.50 mmol) and diphenylacetylene (2a, 106.9 mg, 0.60 mmol) were added [Cp*RhCl2]2 (7.7 mg, 0.0125 mmol) and CsOPiv (35.1 mg, 0.15 mmol), and the reaction mixture was stirred at 60 °C under air for 7 h. After cooled to r.t., the solvent was removed in vacuo, and the resulting crude material was subjected to flash column chromatography (hexane–EtOAc = 90:10) to afford 6-methyl-2,3,4-triphenylpyridine (3aa, 126.4 mg, 0.393 mmol) in 79% yield.