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Rhodium(III)-Catalyzed C-H Alkynylation of Azomethine Ylides Under Mild Conditions

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We recently reported with one example the coupling of an azomethine with TIPS-EBX under unoptimized conditions (80 °C),\textsuperscript{10} we felt that the reaction might proceed under even milder conditions because of the high donating ability of the azomethine directing group in C-H activation reactions.\textsuperscript{12} Importantly, the coupled product can undergo facile removal of this DG via simple hydrolysis, leading to ortho-alkynylated aldehydes, which have found wide application in synthetic chemistry.\textsuperscript{13} This represents an indirect process for C-H alkynylation of aryl aldehydes, and has circumvented the issue of poor directing ability of an aldehyde functionality.\textsuperscript{14} Therefore it is necessary to expand the scope of this reaction.

Table 1. Optimization of the reaction conditions\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>additive (mol %)</th>
<th>solvent</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>DCE</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>AgSbF\textsubscript{6} (12)</td>
<td>DCE</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OTf)\textsubscript{2} (12)</td>
<td>DCE</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OTf)\textsubscript{2} (12)</td>
<td>DCE</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>Hg(OTf)\textsubscript{2} (12)</td>
<td>DCE</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>Al(OTf)\textsubscript{3} (12)</td>
<td>DCE</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>Zn(OTf)\textsubscript{2} (12)</td>
<td>DCE</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>Zn(OTf)\textsubscript{2} (12)</td>
<td>DCM</td>
<td>38</td>
</tr>
<tr>
<td>9</td>
<td>Zn(OTf)\textsubscript{2} (12)</td>
<td>MeOH</td>
<td>31</td>
</tr>
<tr>
<td>10</td>
<td>Zn(OTf)\textsubscript{2} (12)</td>
<td>1,4-dioxane</td>
<td>35</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: azomethine (0.2 mmol), TIPS-EBX (0.22 mmol), [RhCp*Cl\textsubscript{2}]\textsubscript{2} (0.006 mol), additive (0.024 mmol), solvent (2
mL), 30 °C, 16 h, under argon. Isolated yield after column chromatography.

We initiated our studies with the screening of the conditions in the coupling of 3-tolyl azomethine (1a) with TIPS-EBX (2a) in the presence of a rhodium catalyst. Azomethine 1a was selected to ensure mono-alkynylation due to the steric blocking of one of the ortho positions (Table 1). It was found that 30 °C can warrant high coupling efficiency when a suitable Lewis acid additive was employed. Consistent with our previous findings, a synthetically useful yield of 3aa was reached when AgSbF₆ was employed as an additive (entry 2), and replacement by Zn(OTf)₂ afforded 3aa in excellent yield, where DCE was established as the optimal solvent. The Lewis acidity of the Zn(OTf)₂ additive may play a dual role by both activating the alkynylation reagent and the rhodium catalysts via reversible removal of the chloride ligand. Other trflate additive proved to be less efficient (entries 3 - 6). Thus under the mild optimal conditions, product 3aa was isolated in 95% yield (entry 7).

Scheme 1. Mild coupling of azomethines with TIPS-EBX

The scope and generality of this coupling were next explored. Azomethines bearing an electron-donating, withdrawing, and halogen group at the meta position of the benzene ring all coupled smoothly with TIPS-EBX. In most cases mono-alkynylation was realized, and the product was isolated in 46-95% yield, where the reaction occurred selectively at the less hindered position, and an electron-withdrawing meta substituent tends to give lower yield. In contrast, both mono- and di-alkynylation products were isolated in similar yields for an azomethine bearing a 3-methoxy group as a result of reduced steric bulkiness of this group (3ka and 3kaa). Introduction of different types of ortho substituents into the benzene ring is well-tolerated and the products were isolated in consistently good to high yield, indicative of tolerance of steric hindrance at the ortho position (3ea-3ha). The coupling of azomethines bearing a para substituent posed complication of mono- versus di-alkynylation. Under the optimal conditions, both mono- and di-alkynylation products were isolated in comparable yields even though the azomethine substrate was used in slight excess. The yield of a dialkynylation product was readily improved by controlling the stoichiometry of the coupling partners. Thus 3maaa was isolated in 90% when an excess (2.1 equiv) of TIPS-EBX was used at a slightly higher temperature. Significantly, the azomethine substrate is not limited to that derived from a benzaldehyde, and those bearing a heteroaryl ring such as furan, thiophene, and indole all underwent smooth coupling in moderate to high yields under the optimal conditions (3pa-3ta).

Scheme 2. Coupling using other alkynylation reagents and DGs

a Reaction conditions: azomethine (0.2 mmol), R-EBX (0.22 mmol), [RhCp*Cl₂]₂ (0.006 mmol), Zn(OTf)₂ (0.024 mmol), DCE (2 mL), 30 °C, 16 h, under argon. Isolated yield after column chromatography.

b TIPS-EBX 2a (0.42 mmol) was used, T=50 °C.

The coupling partner is not restricted to TIPS-EBX. Variation of the alkynylation reagent to those bearing different alkynyl substituents has little influence, and the product was isolated in consistently high yield. Significantly, when Ph-EBX was employed, the alkynylation product was also isolated in high yield (3af). This stands in contrast to previous reports where bulky alkynyl substituents are necessary for efficient coupling.10,11 In addition to using azomethine bearing a gem-
dimethyl group, omission of one of the methyl groups led to a much less efficient coupling (3aa).

\[
\text{NaOH (2.0 equiv)} \text{ MeOH:H}_{2}O (10:1) \text{ rt, 3h} \quad 4, 81\%
\]

The directing group in the coupled product can be readily cleaved as demonstrated in the simple hydrolysis of 3aa under basic conditions (eq 1), under which the silyl group remains intact. This result indicates that the current method offers an efficient process for the C-H alkylation of benzaldehyde via a sequence of DG installation (condensation), C-H alkylation, and hydrolysis.

Several experiments have been performed to probe the mechanism. To explore the relevancy of C-H activation, a chelometalated Rh(III) complex (5) was prepared and was designated as a catalyst in the presence of Zn(OtBu). Under these conditions, the coupling of 1a and 2a afforded the product in 90% yield (eq 2), a yield comparable to that of the catalytic system using [Rh(Cp*Cl)]. In addition, a small amount of 31aa was also detected as a result of the functionalization of the chelating ligand in complex 5. Since C-H activation is very likely involved, KIE was next studied. An intermolecular competitive coupling between azomethines derived from benzaldehyde and benzaldehyde-d5 at a low conversion afforded a mixture of isotopologues. 1H NMR analyses revealed a KIE value of 3.8, and this suggests that C-H activation is probably involved in the rate-limiting step.

**Scheme 3 Mechanistic Proposals**

Given the relevance of the azomethine and the 2-phenylpyridine substrates and our previous mechanistic studies on the alkylation of the 2-phenylpyridine system, a plausible mechanism has been proposed to account for this transformation (Scheme 3). Cyclometalation of an azomethine affords a rhodacyclic intermediate, and subsequent oxidative addition of the hypervalent iodine reagents leads to the formation of a Rh(V) alkylnyl intermediate. C(sp2)-C(sp2) reductive elimination furnishes the coupled product together with the formation of a Rh(III) benzoate intermediate, protonolysis of which regenerates the active Rh(III) catalyst and closes the catalytic cycle.

**Conclusions**

In summary, we have examined the rhodium-catalyzed C-H alkylation of azomethines under rhodium catalysis. A broad scope of azomethine substrates has been established, and the coupling occurred under mild conditions with high efficiency for azomethines bearing various aryl and heteroaryl rings under assistance of an ortho directing group. In most cases, monoalkylation was observed when a meta blocking group was introduced into the arene ring. In contrast, both mono- and di-alkynlation products were generated when both ortho positions are sterically accessible. Preliminary mechanistic studies have been performed and this coupling reaction can provide a method for the ortho C-H alkylation of aryl aldehydes, and may find applications in the synthesis of related structures.

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**Notes and references**

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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Rh(III) complexes catalyzed the ortho C-H alkynylation of azomethine imine, which acts as a masked aldehyde group.