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Zn(II) chloride-catalyzed direct coupling of various alkynes with acetals: facile and inexpensive access to functionalized propargyl ethers
Zn(II) chloride-catalyzed direct coupling of various alkynes with acetals: facile and inexpensive access to functionalized propargyl ethers†

Itaru Suzuki, Makoto Yasuda* and Akio Baba*

The coupling of acetals with various alkynes was achieved using only 1 mol% of inexpensive and mild Lewis acid ZnCl₂, which furnished propargyl ethers. The coupling was catalyzed by Zn(OMe)Cl, which was generated in situ to form an alkynylzinc species. This protocol was allowed to expand to a one-pot subsequent reaction with allylchlorosilane to obtain a 1,4-enyne product.

Alkynylation is a fundamental and valuable method for the preparation of bioactive compounds and charge transport materials. The employment of alkynyl metal agents such as alkynyllithiums, -silanes, -stannanes, and -boranes makes for versatile methods, but these cannot avoid the annoying preparation of, and the incompatibility that results from, various functional groups. To overcome these issues, the direct use of terminal alkynes has been the focus from an environmental point of view.

Our group has reported the direct synthesis of alkynylstannanes from various terminal alkynes and Bu₃SnOMe as catalyzed by ZnBr₂, in which Zn(OMe)Br is generated by transmetalation between Bu₃SnOMe and ZnBr₂ and plays a key role in producing an active alkynylzinc species in situ. We expected the reaction between dimethyl acetals and ZnBr₂ to generate oxonium cations along with Zn(OMe)Br, which may be an alternative formation of Zn(OMe)Br. This idea prompted us to develop the reaction between terminal alkynes and acetals in the presence of ZnBr₂ wherein the generated alkynyl zinc from Zn(OMe)Br was expected to promote the coupling (Scheme 1b). Some examples of coupling between acetals and alkynes have been recently reported, but these generated a cation of metals like Au⁺ for the activation of alkynes or more than one equimolar amount of base for alkynyl metal generation. Fortunately, direct coupling could be promoted by using only a catalytic amount of inexpensive ZnBr₂ or ZnCl₂ to furnish propargyl ethers, and it was a surprise that a weak Lewis acid such as ZnCl₂ worked with no additives.

An investigation into the reaction conditions was commenced. Benzaldehyde dimethyl acetal (1a) did not react with 1-decyne (2a) without a catalyst under toluene refluxing conditions (Table 1, entry 1). The addition of 10 mol% of ZnBr₂ provided the coupling product 3aa in an 81% yield (entry 2). A higher yield was realized when ZnCl₂ was utilized (entry 3). The reaction was completed in 12 h using only 1 mol% loading of ZnCl₂–Et₂O, furnishing 3aa quantitatively (entry 4). ZnI₂ and Zn(OTf)₂ gave moderate yields, and Zn(OAc)₂/C₁₂H₂O, InCl₃, CuCl₂, AlCl₃, BF₃·OEt₂, SnCl₄, and SnCl₄ + ZnCl₂ gave 0% yields.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>ZnBr₂</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>ZnCl₂</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>ZnCl₂–Et₂O</td>
<td>99 (86)</td>
</tr>
<tr>
<td>5</td>
<td>ZnI₂</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>Zn(OTf)₂</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>Zn(OAc)₂·2H₂O</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>InCl₃</td>
<td>55</td>
</tr>
<tr>
<td>9</td>
<td>CuCl₂</td>
<td>65</td>
</tr>
<tr>
<td>10</td>
<td>BiCl₃</td>
<td>40</td>
</tr>
<tr>
<td>11</td>
<td>AlCl₃</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>TiCl₄</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>BF₃·OEt₂</td>
<td>5</td>
</tr>
<tr>
<td>14</td>
<td>SnCl₄</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>SnCl₄ + ZnCl₂</td>
<td>0</td>
</tr>
</tbody>
</table>

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‡ Reaction conditions: 1a (2.0 mmol), 2a (1.0 mmol), and a catalyst (0.10 mmol) were refluxed in toluene (1 mL) for 24 h. ††H NMR yield. The value in parentheses indicates the isolated yield. | Catalyst (0.01 mmol), 12 h.
while Zn(OAc)$_2$ showed no effect (entries 5–7). Employment of mild Lewis acids like InCl$_3$, CuCl$_2$, and BiCl$_3$ gave moderate yields (entries 8–10). In contrast, strong Lewis acids such as AlCl$_3$, TiCl$_4$, BF$_3$, OEt$_2$, or SnCl$_4$ did not promote the reaction at all (entries 11–14). The combined Lewis acid, which was reported as an effective catalyst for the coupling using alkynylosilanes, gave no product (entry 15).

The optimized reaction conditions (Table 1, entry 4) were applicable to the series of terminal alkynes listed in Table 2. Aryl alkynes $2b$–$d$ also afforded the corresponding adducts $3ab$–$3ad$, but the electron-rich alkyne $2d$ was not as effective owing to a low pK$_a$ of the terminal proton. Ester and silicon moieties did not disturb the reaction (entries 4 and 5). Alkynes $2g$ and $2h$ bearing active propargyl positions were also effectively coupled with an acetal (entries 6 and 7). Chloro and cyano groups were intact after the reaction (entries 8 and 9). Cyclohexylacetylene (2k) gave the desired product $3ak$ in a high yield. It is noteworthy that a variety of alkynes, including functionalized alkyls, were applicable in contrast to previous methods that were limited to aromatic alkynes. The mildness of our method could be the reason for the wide application.

Next, the effect of acetals was investigated (Table 3). Diethyl acetal $1b$ gave a high yield upon increasing the amount of catalyst to 0.05 mmol (entry 1). However, no reaction took place when using dihexyl acetal $1c$ even with a 5 mol% loading of the catalyst (entry 2). An electron-withdrawing group on an aromatic ring in an acetal decreased the yield of 3 plausibly due to the destabilization of the oxonium cation intermediate (entry 5). Isochroman derivative $1g$ gave an excellent yield (entry 6). The alkynylation of cinnamyl aldehyde dimethyl acetal (1h) was also achieved (entry 7) to give the mixture of regioisomers $3ha$, which also suggested that the reaction proceeded via an oxonium cation species. Unfortunately, no product was obtained from aliphatic acetal $1i$ (entry 8).

To explain the results in entries 1 and 2 in Table 3, the effect of an alcohol that was generated in situ was investigated. No reaction proceeded in a sealed vessel (Scheme 2). Moreover, the addition of 0.2 mL of methanol decreased the yield to 29%. These results indicate the importance of removing the produced alcohol from the reaction media, because the alcohol would hamper the interaction between an acetal and ZnCl$_2$.

To confirm the incorporation of an alkynylic zinc species, which was proposed in our previous report, the alkynylic zinc prepared using alkynylbromide 4 and zinc metal was treated with acetal 1a. To our delight, the desired coupling product was obtained in a 59% yield (Scheme 3). This result strongly indicates that the reaction contained an alkynylic zinc species.
We investigated whether this protocol would allow the alkylation of aldehydes, because the catalytic alkylation of aldehydes with terminal alkynes has been reported.\textsuperscript{15} The fact that there was no reaction of alkyne \textsuperscript{2c} with benzaldehyde (6) (Scheme 4) implies that the active species, Zn(OMe)Cl, generated from dimethyl acetal is essential for the catalytic coupling reaction.

A plausible reaction mechanism is shown in Scheme 5. ZnCl\textsubscript{2} activates the acetal to give zinc species \textsuperscript{8} which interacts with an alkynylzinc \textsuperscript{7} to afford the desired product 7. The kinetic study of the coupling was carried out byVariable 1 catalyst, \([k = 4.06 \times 10^{-2} \text{ mol} \cdot \text{L}^{-1} \cdot \text{s}^{-1}, T = 130 ^\circ \text{C}]\). The result and implication of containing an alkynylzinc as shown in Scheme 3 might indicate that the interaction between an acetal and alkynylzinc \textsuperscript{8} is the rate-limiting step.

The produced propargyl ether \textsuperscript{3aa} was found to subsequently react with allylchlorosilane \textsuperscript{10} in a one-pot treatment, where the alkylation was completed in 30 min at room temperature, yielding 1,5-enyne \textsuperscript{11} (Scheme 6). The isolated \textsuperscript{3aa} did not react with \textsuperscript{10} in the absence of ZnCl\textsubscript{2}, which apparently suggested the catalytic role of ZnCl\textsubscript{2} in the substitution of the OMe moiety to the alkyl one.

In conclusion, we developed an alkylation of acetals with various alkynes including allyls that can be catalyzed by inexpensive ZnCl\textsubscript{2}. This reaction needs no expensive metal catalyst, such as gold,\textsuperscript{11} nor does it need additives.\textsuperscript{12} The product, propargyl ether, was functionalized without isolation, which shows that this reaction is clean enough to effectively undergo further transformation.

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Notes and references

1 For recent reviews on alkylation of carbonyl compounds, see:
[e] H. Dacquet and J.-C. Hirsch, Angew. Chem., Int. Ed., 2007, \textbf{46}, 834. For a review on electrophilic alkylation, see:

[b] M. E. Maier, Synlett, 1995, 13;


10 ZnBr\textsubscript{2} catalyzed reaction of acetals with acetyl chloride was reported.


