Ataru Suzuki, Makoto Yasuda and Akio Baba

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.9 We expected the reaction between dimethyl acetals and ZnBr2 to generate oxonium cations along with Zn(OMe)Br,10 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 alkynes11 or more than one equimolar amount of base for alkynyl metal generation.12 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/C2H2O, InCl3, CuCl2, BiCl3, AlCl3, TiCl4, BF3·OEt2, SnCl4, SnCl4 + ZnCl2, SnCl4 + ZnI2, SnCl4 + Et3AlCl, SnCl4 + AlCl3, SnCl4 + BF3·OEt2, and SnCl4 + ZnI2 gave very low or no yields.

Table 1  Screening of catalysts

| Entry | Catalyst | Yield (%) |
|-------|----------|-----------|
| 1     | None     | 0         |
| 2     | ZnBr2    | 81        |
| 3     | ZnCl2    | 90        |
| 4c    | ZnCl2–Et2O | 99 (86)  |
| 5     | ZnI2     | 76        |
| 6     | Zn(OTf)2 | 50        |
| 7     | Zn(OAc)2 | 0         |
| 8     | InCl3    | 55        |
| 9     | CuCl2    | 65        |
| 10    | BiCl3    | 40        |
| 11    | AlCl3    | 0         |
| 12    | TiCl4    | 0         |
| 13    | BF3·OEt2 | 5         |
| 14    | SnCl4    | 0         |
| 15    | SnCl4 + ZnCl2 | 0     |
| 15    | SnCl4 + ZnI2 | 0     |
| 15    | SnCl4 + Et3AlCl | 0     |
| 15    | SnCl4 + AlCl3 | 0     |
| 15    | SnCl4 + BF3·OEt2 | 0     |
| 15    | SnCl4 + ZnI2 | 0     |
| 15    | SnCl4 + ZnCl2 | 0     |
| 15    | SnCl4 + ZnI2 | 0     |
| 15    | SnCl4 + Et3AlCl | 0     |
| 15    | SnCl4 + AlCl3 | 0     |
| 15    | SnCl4 + BF3·OEt2 | 0     |
| 15    | SnCl4 + ZnI2 | 0     |
| 15    | SnCl4 + ZnCl2 | 0     |
| 15    | SnCl4 + ZnI2 | 0     |
| 15    | SnCl4 + Et3AlCl | 0     |
| 15    | SnCl4 + AlCl3 | 0     |
| 15    | SnCl4 + BF3·OEt2 | 0     |
| 15    | SnCl4 + ZnI2 | 0     |
| 15    | SnCl4 + ZnCl2 | 0     |

* 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. *1H NMR yield. The value in parentheses indicates the isolated yield. * Catalyst (0.01 mmol), 12 h.

Scheme 1  Comparison of previous work with this work.

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka, 565-0871, Japan.
E-mail: yasuda@chem.eng.osaka-u.ac.jp, baba@chem.eng.osaka-u.ac.jp;
Fax: +81-6-6879-7387; Tel: +81-6-6879-7386
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3cc46570e

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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 alkynylsilanes,$^{13}$ 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.$^{11,12}$ 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, plausibly as a by-product, was investigated. No reaction proceeded in a sealed vessel (Scheme 2).

To confirm the incorporation of an alkynylzinc species, which was proposed in our previous report,$^9$ the alkynylzinc prepared using alkynylbromide 4 and zinc metal was treated with acetal 1a.$^{11}$ To our delight, the desired coupling product was obtained in a 59% yield (Scheme 3). This result strongly indicates that the reaction contained an alkynylzinc species.

![Scheme 2 Disturbing effect of an alcohol by-product.](image-url)
We investigated whether this protocol would allow the alkylation of aldehydes, because the catalytic alkylation of aldehydes with terminal alkynes has been reported. The fact that there was no reaction of alkyn 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. ZnCl2 activates the acetal to give zinc species 7, which interacts with an alkyn and leads to the formation of alkynylzinc 8. The alkylnzinc 8 reacts with acetal 1 via an oxonium cation 9 and a zincate complex to afford the desired product 3 along with the regeneration of 7. The kinetic study of the coupling was carried out by GC (see ESI†) and showed that the reaction was dependent on the first order of each component (v = 4[1a][2a][catalyst], k: 4.06 × 10⁻² mol⁻² L⁻¹ s⁻¹, T = 130 °C). The result and implication of containing an alkylnzinc as shown in Scheme 3 might indicate that the interaction between an acetal and alkynylzinc 8 is the rate-limiting step.

The produced propargyl ether 3aa was found to subsequently react with allylchlorosilane 10 in a one-pot treatment, where the alkylation was completed in 30 min at room temperature, yielding 1,5-enzyme 11 (Scheme 6). The isolated 3aa did not react with 10 in the absence of ZnCl2, which apparently suggested the catalytic role of ZnCl2 in the substitution of the OMe moiety to the allyl one.

In conclusion, we developed an alkylation of acetals with various alkynes including aliphatic carbonyl compounds catalyzed by inexpensive ZnCl2. This reaction needs no expensive metal catalyst, such as gold, nor does it need additives. 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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