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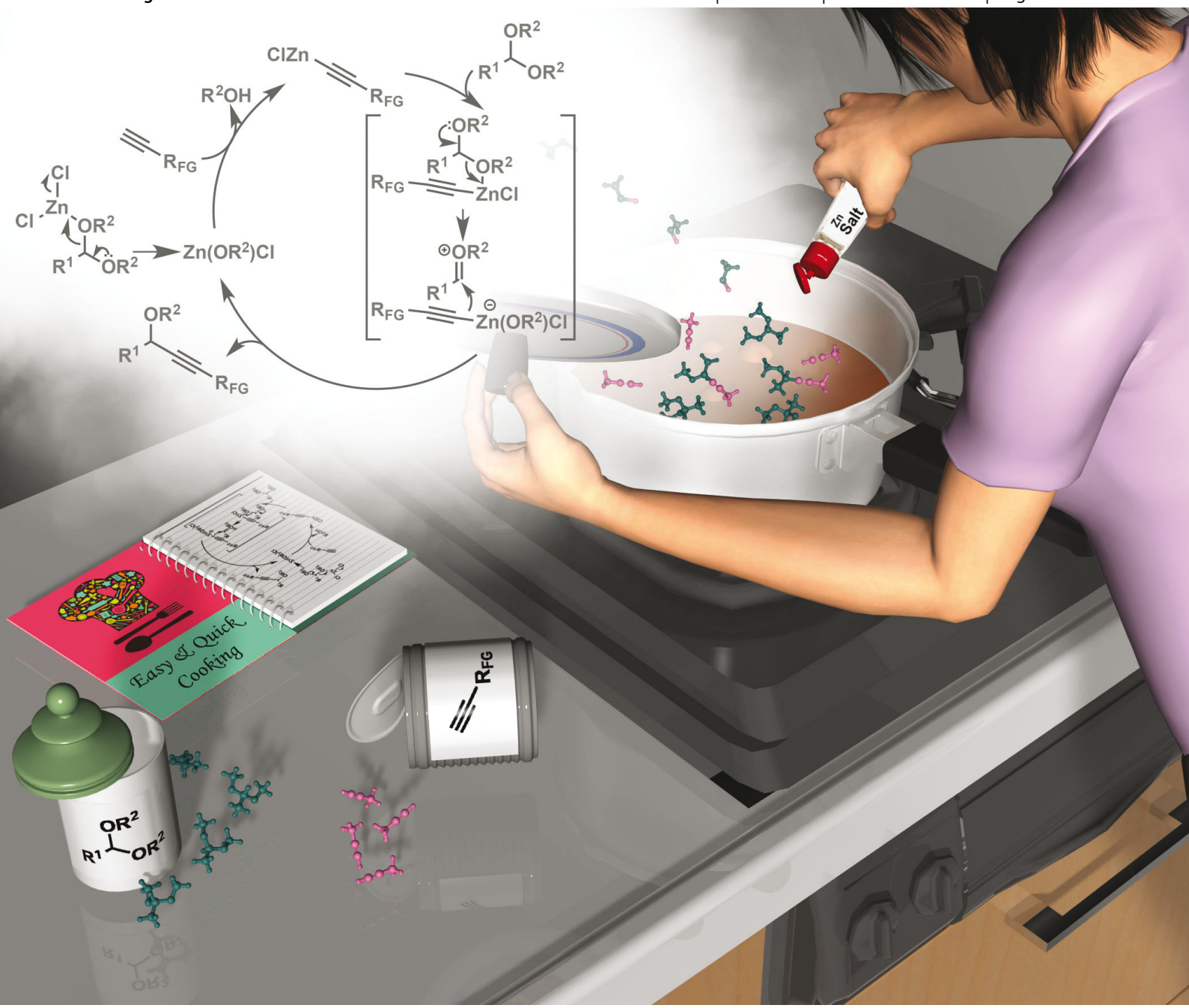



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# Zn(II) chloride-catalyzed direct coupling of various alkynes with acetals: facile and inexpensive access to functionalized propargyl ethers†

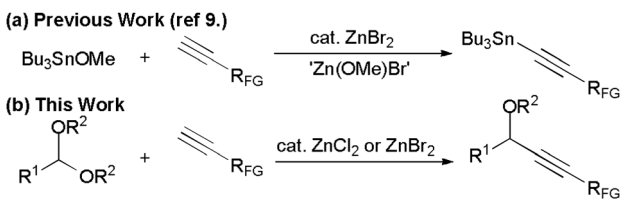
Itaru Suzuki, Makoto Yasuda* and Akio Baba*

**The coupling of acetals with various alkynes was achieved using only 1 mol% of inexpensive and mild Lewis acid $ZnCl_2$, 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[1] for the preparation of bioactive compounds[2] and charge transport materials.[3] The employment of alkynyl metal agents such as alkynyllithiums,[4] -silanes,[5] -stannanes,[6] and -boranes[7] 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.[8]

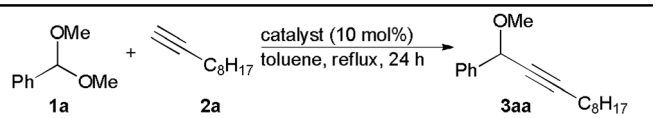
Our group has reported the direct synthesis of alkynylstannanes from various terminal alkynes and $Bu_3SnOMe$ as catalyzed by $ZnBr_2$, in which Zn(OMe)Br is generated by transmetalation between $Bu_3SnOMe$ and $ZnBr_2$ and plays a key role in producing an active alkynylzinc species *in situ* (Scheme 1a).[9] We expected the reaction between dimethyl acetals and $ZnBr_2$ 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 $ZnBr_2$ 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[11] 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 $ZnBr_2$ or $ZnCl_2$ to furnish propargyl ethers, and it was a surprise that a weak Lewis acid such as $ZnCl_2$ 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 $ZnBr_2$ provided the coupling product **3aa** in an 81% yield (entry 2). A higher yield was realized when $ZnCl_2$ was utilized (entry 3). The reaction was completed in 12 h using only 1 mol% loading of $ZnCl_2$–$Et_2O$, furnishing **3aa** quantitatively (entry 4). $ZnI_2$ and $Zn(OTf)_2$ gave moderate yields,




**Scheme 1** Comparison of previous work with this work.

**Table 1** Screening of catalysts[a]




| Entry | Catalyst | Yield[b] (%) |
|---|---|---|
| 1 | None | 0 |
| 2 | $ZnBr_2$ | 81 |
| 3 | $ZnCl_2$ | 90 |
| 4[c] | $ZnCl_2$–$Et_2O$ | 99 (86) |
| 5 | $ZnI_2$ | 76 |
| 6 | $Zn(OTf)_2$ | 50 |
| 7 | $Zn(OAc)_2 \cdot 2H_2O$ | 0 |
| 8 | $InCl_3$ | 55 |
| 9 | $CuCl_2$ | 65 |
| 10 | $BiCl_3$ | 40 |
| 11 | $AlCl_3$ | 0 |
| 12 | $TiCl_4$ | 0 |
| 13 | $BF_3 \cdot OEt_2$ | 5 |
| 14 | $SnCl_4$ | 0 |
| 15 | $SnCl_4$ + $ZnCl_2$ | 0 |

[a] 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. [b] $^1H$ NMR yield. The value in parentheses indicates the isolated yield. [c] Catalyst (0.01 mmol), 12 h.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3cc46570e

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 $AlCl_3$, $TiCl_4$, $BF_3{\cdot}OEt_2$, 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).

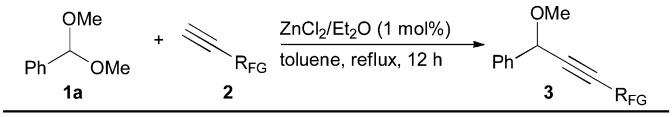
The optimized reaction conditions (Table 1, entry 4) were applicable to the series of terminal alkynes listed in Table 2. Aryl alkynes **2b–d** also afforded the corresponding adducts **3ab–3ad**, but the electron-rich alkyne **2d** was not as effective owing to a low p$K_a$ of the terminal proton. Ester 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.

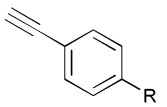
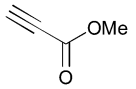
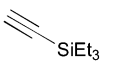
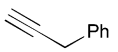
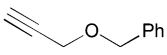
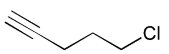
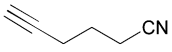
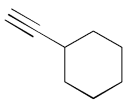
Next, the effect of acetals was investigated (Table 3). Diethyl acetal **1b** gave a high yield upon increasing the amount of catalyst to 0.05 mmol (entry 1). However, no reaction took place when using dihexyl acetal **1c** even with a 5 mol% loading of the catalyst (entry 2). An electron-withdrawing 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 cynnamyl 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). 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 alkynylzinc species, which was proposed in our previous report,[9] the alkynylzinc prepared using alkynylbromide **4** and zinc metal was treated with acetal **1a**.[14] To our delight, the desired coupling product was obtained in a 59% yield (Scheme 3). This result strongly indicates that the reaction contained an alkynyzinc species.

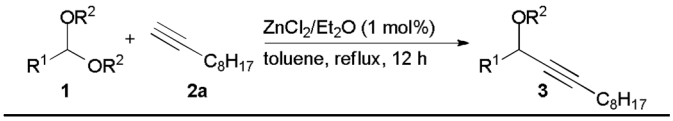
**Table 2** Coupling with various terminal alkynes[a]

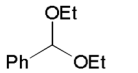
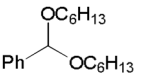
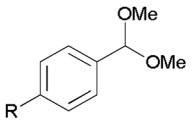
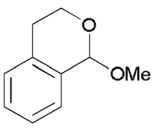
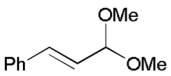
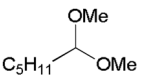



| Entry | Alkyne | | Product | Yield[b] (%) |
|---|---|---|---|---|
| 1[c] |  | **2b** | **3ab** | 93 (86) |
| 2[d] | | **2c** | **3ac** | 69 (43) |
| 3 | | **2d** | **3ad** | 99 (98) |
| 4[c] |  | **2e** | **3ae** | 91 (80) |
| 5[c] |  | **2f** | **3af** | 97 (86) |
| 6 |  | **2g** | **3ag** | 94 (94) |
| 7[c] |  | **2h** | **3ah** | 99 (77) |
| 8 |  | **2i** | **3ai** | 99 (78) |
| 9[c] |  | **2j** | **3aj** | 99 (82) |
| 10 |  | **2k** | **3ak** | 91 (81) |

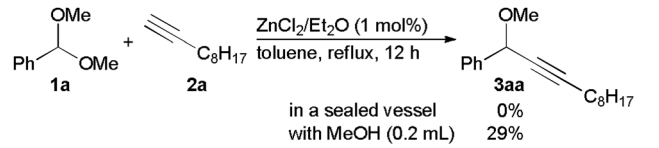
[a] Reaction conditions: **1a** (2.0 mmol), alkyne (1.0 mmol), and a catalyst (0.01 mmol) were refluxed in toluene (1 mL) for 12 h. [b] $^1$H NMR yield. The values in parentheses indicate isolated yields. [c] Catalyst (0.03 mmol). [d] Catalyst (0.05 mmol).

**Table 3** Scope of acetals[a]

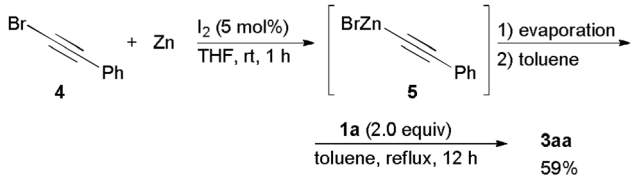



| Entry | Acetal | | Product | Yield[b] (%) |
|---|---|---|---|---|
| 1[c] |  | **1b** | **3ba** | 91 (77) |
| 2 |  | **1c** | | 0 |
| 3 |  R = Me, OMe, Cl | **1d** | **3da** | 92 (89) |
| 4[d] | | **1e** | **3ea** | 99 (85) |
| 5[c] | | **1f** | **3fa** | 99 (90) |
| 6 |  | **1g** | **3ga** | 99 (85) |
| 7[c] |  | **1h** | **3ha** | 99 (78) $E:Z = 66:34$ |
| 8 |  | **1i** | | 0 |

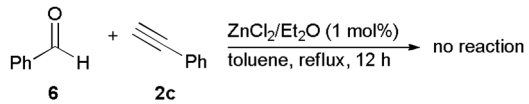
[a] Reaction conditions: **1** (2.0 mmol), **2a** (1.0 mmol), and catalyst (0.01 mmol) were refluxed in toluene (1 mL) for 12 h. [b] $^1$H NMR yield. Values in parentheses indicate isolated yields. [c] Catalyst (0.05 mmol). [d] Catalyst (0.03 mmol).




**Scheme 2** Disturbing effect of an alcohol by-product.



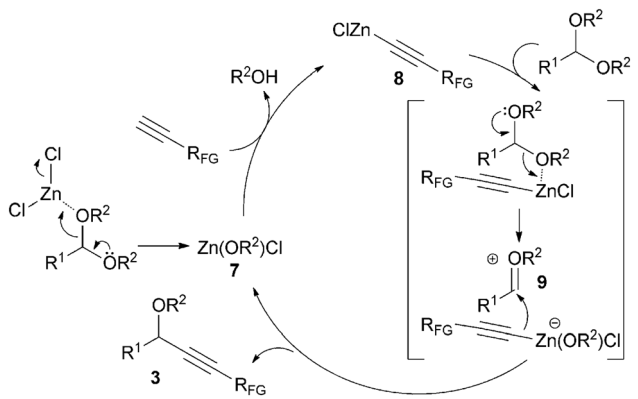

**Scheme 3** Reaction of alkynylzinc **5** with acetal **1a**.



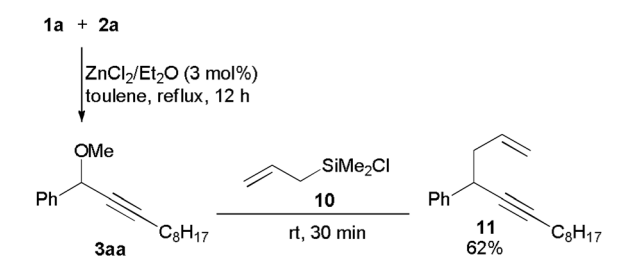

**Scheme 4** Reaction of aldehyde **6** with alkyne **2c**.

We investigated whether this protocol would allow the alkynylation of aldehydes, because the catalytic alkynylation of aldehydes with terminal alkynes has been reported.[15] The fact that there was no reaction of alkyne **2c** with benzaldehyde (**6**) (Scheme 4) implies that the active species, Zn(OMe)Cl, generated from dimethyl acetals is essential for the catalytic coupling reaction.

A plausible reaction mechanism is shown in Scheme 5. $ZnCl_2$ activates the acetal to give zinc species **7**, which interacts with an alkyne and leads to the formation of alkynylzinc **8**. The alkynylzinc **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 ($v = k$[**1a**][**2a**][catalyst], $k$; $4.06 \times 10^{-2}$ mol$^{-2}$ L$^2$ s$^{-1}$, $T$ = 130 °C). The result and implication of




**Scheme 5** Plausible reaction mechanism.




**Scheme 6** One-pot allylation of the product **3aa**.

containing an alkynylzinc 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 allylation was completed in 30 min at room temperature, yielding 1,5-enyne **11** (Scheme 6). The isolated **3aa** did not react with **10** in the absence of $ZnCl_2$, which apparently suggested the catalytic role of $ZnCl_2$ in the substitution of the OMe moiety to the allyl one.

In conclusion, we developed an alkynylation of acetals with various alkynes including alkyls that can be catalyzed by inexpensive $ZnCl_2$. This reaction needs no expensive metal catalyst, such as gold,[11] nor does it need additives.[12] The product, propargyl ether, was functionalized without isolation, which shows that this reaction is clean enough to effectively undergo further transformation.

This work was supported by the Ministry of Education, Culture, Sports, Science and Technology (Japan) and the Shorai Foundation for Science and Technology.

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