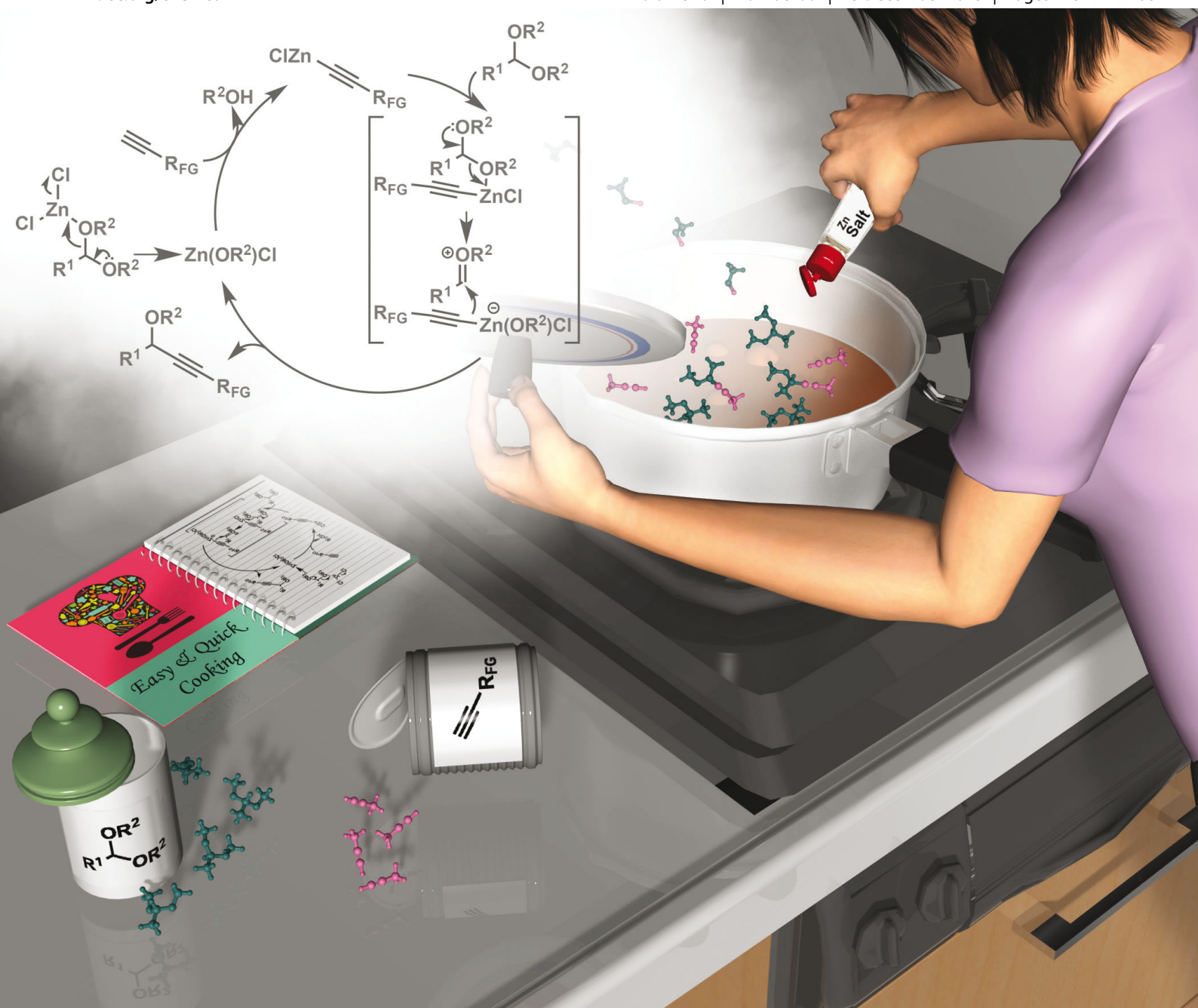


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Zn(II) chloride-catalyzed direct coupling of various alkynes with acetals: facile and inexpensive access to functionalized propargyl ethers



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

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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.

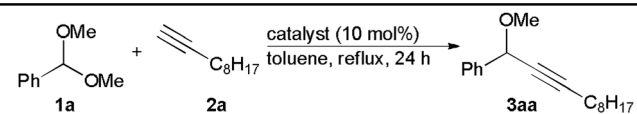
Alkynylation is a fundamental and valuable method¹ for the preparation of bioactive compounds² and charge transport materials.³ The employment of alkynyl metal agents such as alkynyllithiums,⁴ -silanes,⁵ -stannanes,⁶ and -boranes⁷ makes for versatile methods, but these cannot avoid the annoying preparation 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 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* (Scheme 1a).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

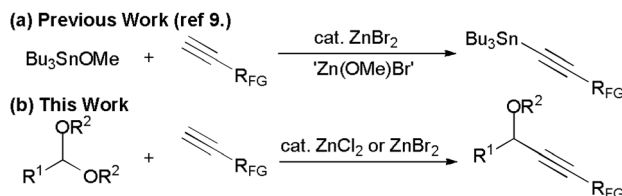
expected to promote the coupling (Scheme 1b). Some examples of coupling between acetals and alkynes have been recently reported, but these generated a cation of metals like Au⁺ for the activation of alkynes¹¹ or more than one equimolar amount of base for alkynyl metal generation.¹² Fortunately, direct 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,

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 ₂ O	99 (86)
5	ZnI ₂	76
6	Zn(OTf) ₂	50
7	Zn(OAc) ₂ ·2H ₂ O	0
8	InCl ₃	55
9	CuCl ₂	65
10	BiCl ₃	40
11	AlCl ₃	0
12	TiCl ₄	0
13	BF ₃ ·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.



Scheme 1 Comparison of previous work with this work.

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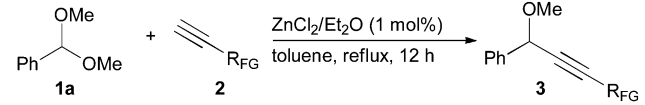


while $\text{Zn}(\text{OAc})_2$ showed no effect (entries 5–7). Employment of mild Lewis acids like InCl_3 , CuCl_2 , and BiCl_3 gave moderate yields (entries 8–10). In contrast, strong Lewis acids such as AlCl_3 , TiCl_4 , $\text{BF}_3 \cdot \text{OEt}_2$, or SnCl_4 did not promote the reaction at all (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.

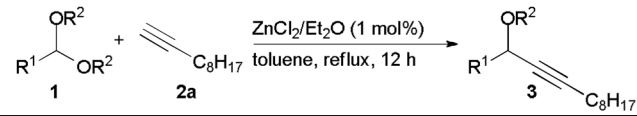
Next, the effect of acetals was investigated (Table 3). Diethyl acetal **1b** gave a high yield upon increasing the amount of catalyst to 0.05 mmol (entry 1). However, no reaction took place when using dihexyl acetal **1c** even with a 5 mol% loading of the catalyst (entry 2). An electron-withdrawing 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**

Table 2 Coupling with various terminal alkynes^a

			
Entry	Alkyne	Product	Yield ^b (%)
1 ^c		3ab	93 (86)
2 ^d		3ac	69 (43)
3		3ad	99 (98)
4 ^c		3ae	91 (80)
5 ^c		3af	97 (86)
6		3ag	94 (94)
7 ^c		3ah	99 (77)
8		3ai	99 (78)
9 ^c		3aj	99 (82)
10		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 ¹H 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

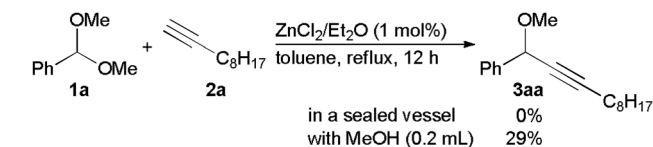
			
Entry	Acetal	Product	Yield ^b (%)
1 ^c		3ba	91 (77)
2		1c	0
3		1d	3da 92 (89)
4 ^d		1e	3ea 99 (85)
5 ^c		1f	3fa 99 (90)
6		1g	3ga 99 (85)
7 ^c		1h	3ha 99 (78) <i>E:Z</i> = 66:34
8		1i	0

^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 ¹H NMR yield. Values in parentheses indicate isolated yields. ^c Catalyst (0.05 mmol). ^d Catalyst (0.03 mmol).

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).

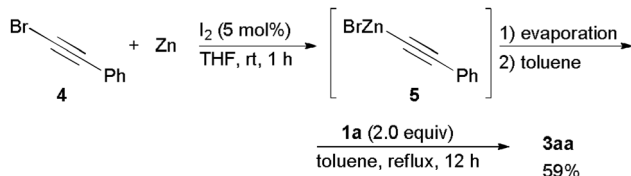
To explain the results in entries 1 and 2 in Table 3, the effect of an alcohol that was generated *in situ*, plausibly as a by-product, was investigated. No reaction proceeded in a sealed vessel (Scheme 2). Moreover, the addition of 0.2 mL of methanol decreased the yield to 29%. These results indicate 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 alkynylzinc species.

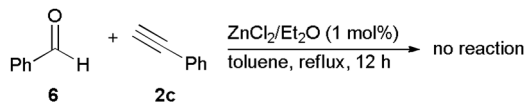


Scheme 2 Disturbing effect of an alcohol by-product.





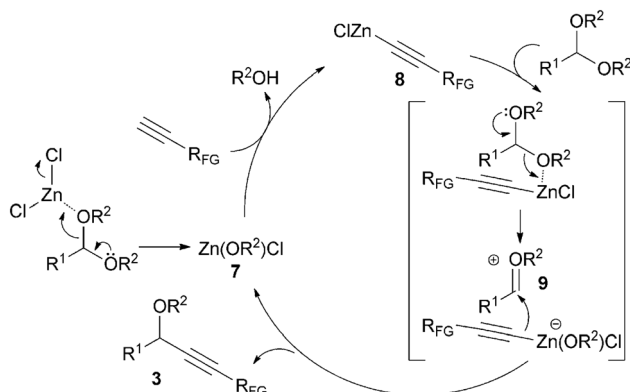
Scheme 3 Reaction of alkynylzinc **5** with acetal **1a**.



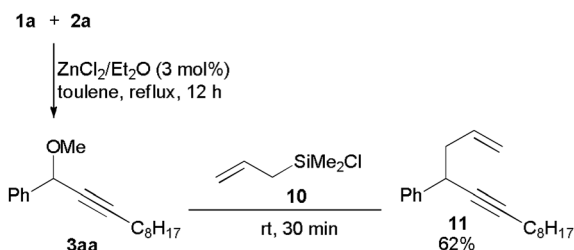
Scheme 4 Reaction of aldehyde **6** with alkyne **2c**.

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, $\text{Zn}(\text{OMe})\text{Cl}$, 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 ($v = k[1a][2a][\text{catalyst}]$; k ; $4.06 \times 10^{-2} \text{ mol}^{-2} \text{ L}^2 \text{ s}^{-1}$, $T = 130^\circ \text{C}$). 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.

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