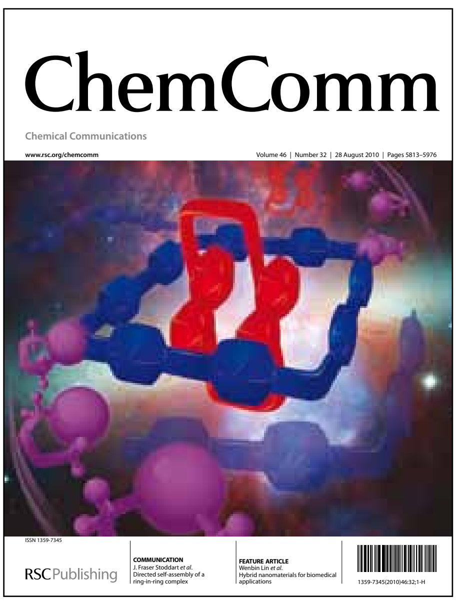
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: I. Suzuki, M. Yasuda and A. Baba, *Chem. Commun.*, 2013, DOI: 10.1039/C3CC46570E.



Dynamic Article Links
View Article Online
DOI: 10.1039/C3CC46570E

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Zn(II) Chloride-Catalyzed Direct Coupling of Various Alkynes with Acetals: Facile and Inexpensive Access to Functionalized Propargyl Ethers

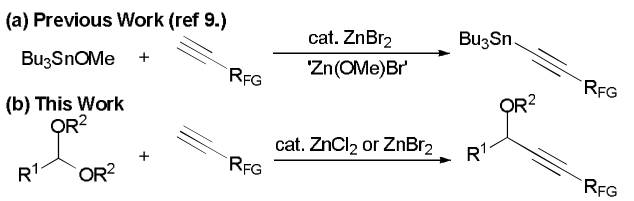
Itaru Suzuki,[a] Makoto Yasuda,[a*] Akio Baba [a*]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

The coupling of acetals with various alkynes was attained 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 alkynyl zinc 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] make 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 acivation of alkynes[11] or more than one equimolar amoumt of base for alkynyl metal generation.[12]

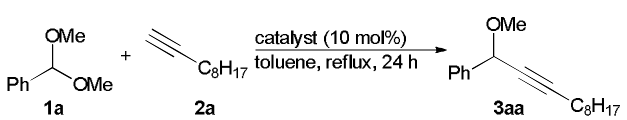


Scheme 1. Comparison of Previous Work with This Work

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, 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 $AlCl_3$, $TiCl_4$, $BF_3 \cdot OEt$, 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).

Table 1. Screening of Catalysts[a]



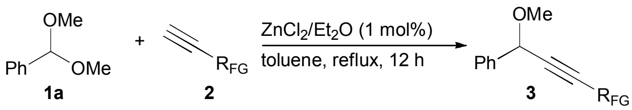
entry	catalyst	yield (%)[b]
1	none	0
2	$ZnBr_2$	81
3	$ZnCl_2$	90
4[c]	$ZnCl_2/Et_2O$	99(86)
5	ZnI_2	76
6	$Zn(OTf)_2$	50
7	$Zn(OAc)_2 \cdot 2H_2O$	0
8	$InCl_3$	55
9	$CuCl_2$	65
10	$BiCl_3$	40
11	$AlCl_3$	0
12	$TiCl_4$	0
13	$BF_3 \cdot OEt_2$	5
14	$SnCl_4$	0
15	$SnCl_4 + ZnCl_2$	0

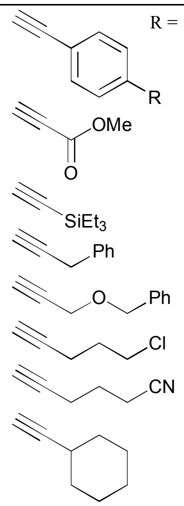
[a] Reaction conditions: **1a** (2.0 mmol), **2a** (1.0 mmol), and a catalyst (0.10 mmol) were refluxed in toluene (1 mL) for 24 h. [b] ^1H NMR yield. The value -in parenthesis indicates an isolated yield. [c] Catalyst (0.01 mmol), 12 h.

 View Article Online
DOI: 10.1039/C3CC46570E

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 with previous methods that were limited to aromatic alkynes.[11,12] The mildness of our method could be the reason for the wide application.

Table 2. Coupling with Various Terminal Alkynes[a]



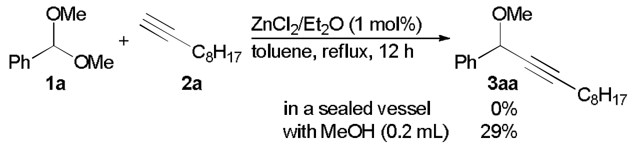


entry	alkyne			product	yield (%)[b]
1[c]	R =	H	2b	3ab	93(86)
2[d]		Me	2c	3ac	69(43)
3		Br	2d	3ad	99(98)
4[c]			2e	3ae	91(80)
5[c]			2f	3af	97(86)
6			2g	3ag	94(94)
7[c]			2h	3ah	99(77)
8			2i	3ai	99(78)
9[c]			2j	3aj	99(82)
10			2k	3ak	91(81)

[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).

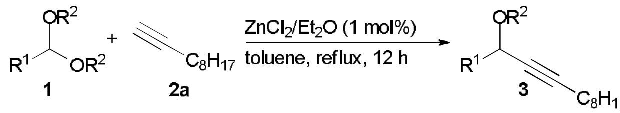
Next, the effect of acetals was investigated (Table 3). Diethyl acetal **1b** gave a high yield by increasing the amount of catalyst to 0.05 mmol (entry 1). However, no reaction took place when using dihexyl acetal **1c** even with a 5 mol% loading of catalyst (entry 2). An electron-withdrawing group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

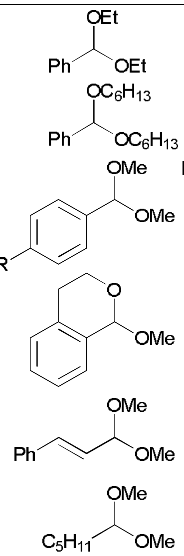
To explain the results in entries 1 and 2 and in Table 3, the effect of an alcohol that was generated *in situ*, plausibly as a by-product, was investigated. No reaction proceeded in a sealed vessel (Scheme 2). Moreover, the addition of 0.1 mL of methanol decreased the yield to 29%. These results indicate the importance of removing the produced alcohol from the reaction media, because the alcohol would hamper the interaction between an acetal and $ZnCl_2$.



Scheme 2. Disturbing Effect of an Alcohol By-Product

Table 3. Scope of Acetals[a]

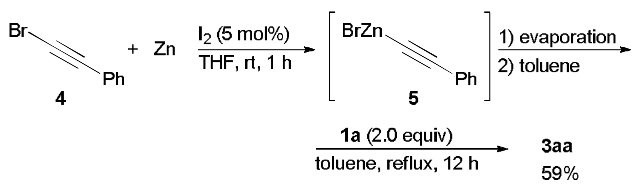




entry	acetal		product		yield (%)[b]
1[c]			1b	3ba	91(77)
2			1c		0
3		R = Me	1d	3da	92(89)
4[d]		OMe	1e	3ea	99(85)
5[c]		Cl	1f	3fa	99(90)
6			1g	3ga	99(85)
7[c]			1h	3ha	99(78) *E*:*Z* = 66:34
8			1i		0

[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).

To confirm the incorporation of an alkynylzinc species, which was proposed in our previous report,[9] the alkynylzinc prepared by 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.

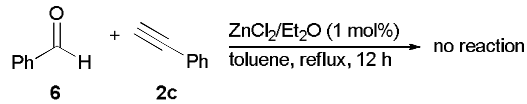


Scheme 3. Reaction of Alkynylzinc **5** with Acetal **1a**

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

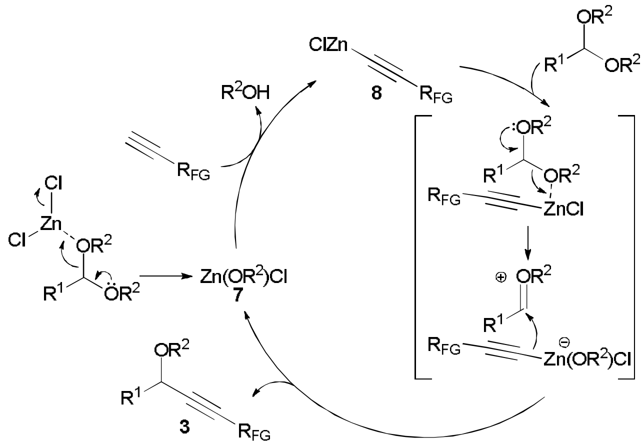
View Article Online
DOI: 10.1039/C3CC46570E

coupling reaction.



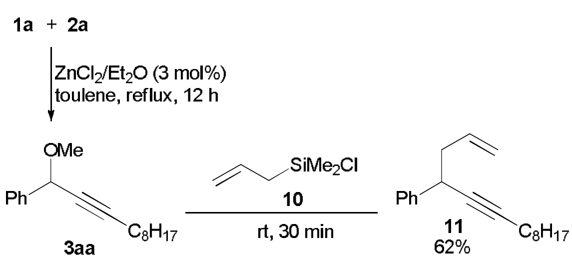
Scheme 4. Reaction of Aldehyde **6** with Alkyne **2c**

A plausible reaction mechanism is shown in Scheme 5. $ZnCl_2$ acivates 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 and 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 Supporting Information) and showed that the reaction was dependent on the first order of each component ($v = k$[**1a**][**2a**][catalyst], k; 4.06 x 10^{-2} $mol^{-2}L^{2}s^{-1}$, T = 130 °C). The result and implication of containing an alkynylzinc as shown in Scheme **3** might indicate that the interaction between an acetal and alkynylzinc **8** is a rate-limiting step.



Scheme 5. Plausible Reaction Mechanism

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 tempelature, 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 catalyst role of $ZnCl_2$ in the substitution of the OMe moiety to allyl one.



Scheme 5. One-pot Allylation of the Product **3aa**

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, propargy ether, was funcionallized 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.

Notes and references

[a] *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; Fax: +81-6-6879-7387; Tel: +81-6-6879-7386*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ 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.

1 For recent reviews of alkynylation of carbonyl compounds, see; (a) S. Guillarme, K. Plé, A. Banchet, A. Liard, A. Haudrechy, *Chem. Rev.*, 2006, **106**, 2355. (b) B. M. Trast, A. H. Weiss, *Adv. Synth. Catal.*, 2009, **351**, 963. For a transition metal catalyzed cross coupling, see; (c) K, Sonogashira, *J. Organomet. Chem.*, 2002, **653**, 46. (d) E.-i. Negishi, L. Anastasia, *Chem. Rev.*, 2003, **103**, 1979. (e) H. Doucet, J.-C. Hierso, *Angew. Chem. Int. Ed.*, 2007, **46**, 834. For a review of electrophilic alkynylation, see; (f) J. P. Brand, J. Waser, *Chem. Soc. Rev.*, 2012, **41**, 4165.

2 (a) K. C. Nicolau, W.-M. Dai, *Angew. Chem.*, 1991, **103**, 1453; *Angew. Chem. Int. Ed.*, 1991, **30**, 1387. (b) M. E. Maier, *Synlett*, 1995, 13. (c) A. L. K. Shi Shu, R. R. Tykwinski, *Angew. Chem. Int. Ed.*, 2006, **45**, 1034. (d) R. E. Minto, B. J. Blacklock, *Prog. Lipid. Res.*, 2008, **47**, 233. (e) B. W. Gung, *C. R. Chimie*, 2009, **12**, 489.

3 (a) A. Harriman, R. Ziessel, *Chem. Commun.*, 1996, 1707. (b) N. J. Long, C. K. Williams, *Angew. Chem. Int. Ed.*, 2003, **42**, 2586. (c) K. A. Green, M. P. Cifuentes, M. Samoc, M. G. Humphrey, *Cood. Chem. Rev.*, 2011, **255**, 2530. (d) K. A. Green, M. P. Cifuentes, M. Samoc, M. G. Humphrey, *Cood. Chem. Rev.*, 2011, **255**, 2025. (e) G. Bottari, D. D. Díaz, T. Torres, *J. Porphyrins Phthalocyanines*, 2006, **10**, 1083. (f) F. Silvestri, A. Marrocchi, *Int. J. Mol. Sci.*, 2010, **11**, 1471.

4 G. Wu, M. Huang, *Chem. Rev.*, 2006, **106**, 2596.

5 S. E. Denmark, M. H. Ober, *Aldrichimica Acta*, 2003, **36**, 75.

6 S. Pascual, A. M. Echavarren, In *Tin Chemistry*; A. G. Davies, Ed.; John Wiley & Sons Ltd.: Chichester, 2008; pp 579-606.

7 J. Jiao, Y. Nishihara, *J. Organomet. Chem.*, 2012, **721-722**, 3.

8 (a) N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.*, 2001, **123**, 9687. (b) R. Takita, Y. Fukuta, R. Tsuji, T. Ohshima, M. Shibasaki, *Org. Lett.*, 2005, **7**, 1363. (c) R. Takita, K. Yakura, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 13760.

9 K. Kiyokawa, N. Tachikake, M. Yasuda, A. Baba, *Angew. Chem. Int. Ed.*, 2011, **50**, 10393.

10 $ZnBr_2$ catalyzed reaction of acetals with acetyl chloride was reported. See: M. A. Berliner, K. Belecki, *J. Org. Chem.*, 2005, **70**, 9618.

11 (a) C. Li, F. Mo, W. Li, J. Wang, *Tetrahedron Lett.*, 2009, **50**, 6053. (b) M. Zhang, Y. Wang, Y. Yang, X. Hu, *Adv. Synth. Catal.*, 2012, **354**, 981.

12 P. Maity, H. D. Srinivas, M. P. Watson, *J. Am. Chem. Soc.* 2011, **133**, 17142.

13 M. Hayashi, A. Inubushi, T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 4037.

14 G. M. R. Tombo, E. Didier, B. Loubinoux, *Synlett*, 1990, 547.

15 (a) J.-i. Ito, R. Asai, H. Nishiyama, *Org. Lett.*, 2010, **12**, 3862. (a) P. K. Dhondi, J. D. Chisholm, *Org. Lett.*, 2006, **8**, 67. (b) Y. Asano, K. Hara, H. Ito, M. Sawamura, *Org. Lett.*, 2007, **9**, 3901. (c) T. Ishikawa, T. Mizuta, K. Hagiwara, T. Aikawa, T. Kudo, S. Saito, *J. Org. Chem.*, 2001, **68**, 3702. (e) M. Yamashita, K.-i. Yamada, K. Tomioka, *Adv. Synth. Catal.*, 2005, **347**, 1649. (f) T. Weil, P. R. Schreiner, *Eur. J. Org. Chem.*, 2005, 2213. Also see; ref 8.