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# Reaction of Propargylic Substrates with Triorganozincates: A Novel Method for the Preparation of Allenic Zinc Reagents Associated with Carbon–Carbon Bond Formation

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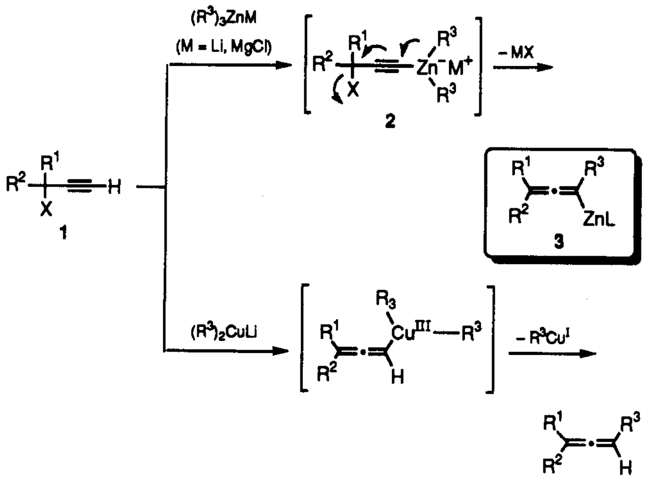
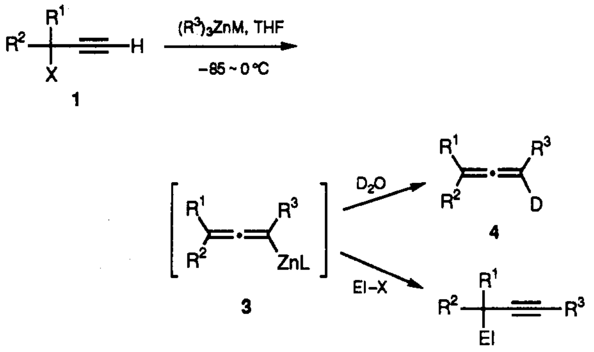
*Summary:* Reaction of propargylic mesylates or chlorides with triorganozincates affords the allenic zinc reagents **3**, which can undergo a second bond forming reaction with a variety of electrophiles regioselectively at the γ-positions.

**Scheme I**



Reaction of propargylic derivatives (**1**)with cuprates is one of the most popular methods for the synthesis of allenes (Scheme I).[1] The reaction is believed to proceed by a mechanism involving S$_N$2′ nucleophilic attack of the Cu(I) atom followed by reductive elimination of the resulting Cu(III) intermediate.[2] We now report that this reaction, with triorganozincates,[3] proceeds through a mechanism different from that observed for cuprates to give allenic zinc reagents **3**. The reagents can undergo a second bond formation regioselectively at the γ-position, providing an efficient one-pot method for the introduction of a nucleophile (R$^3$) and an electrophile (El) to the propargylic substrate at the 1 and 3-positions (eq 1).[3f–h,j,k,4]



(1)

Treatment of mesylate **1a** (R$^1$ = PhCH$_2$CH$_2$, R$^2$ = H, X = MeSO$_2$O) with (Bu)$_3$ZnLi (2.0 equiv) in THF at temperatures from –85 to 0 °C and quench of the reaction mixture with D$_2$O gave deuterioallene **4a** in 97% isolated yield. $^1$H NMR analysis of the product showed regioselective incorporation of a deuterium atom (92% deuterium) at the carbon substituted by the butyl group, demonstrating efficient generation of the corresponding allenic zinc **3**.[5]

Results summarized in Table I demonstrate the wide scope of the reaction of propargylic substrates with triorganozincates. A variety of lithium trialkylzincates were successfully used in the preparation of the corresponding homologated allenic zinc (entries 1–6). Allenic zinc compounds **3** bearing aryl and alkenyl groups were also prepared by using the corresponding lithium zincates (entries 7 and 8). Chloromagnesium zincate prepared by the reaction of BuMgCl with ZnCl$_2$ exhibited a similar reactivity but with slightly lower efficiency than the lithium zincate (entries 2 and 13). Isomerization of allenic zinc **3** to propargylic zinc R$^1$(R$^2$)C(ZnL)C≡CR$^3$ [6] was negligible (<3%) except for **3** with the sterically demanding *sec*- or *tert*-butyl groups as R$^3$ (entries 5 and 6). In the reaction with (Me)$_3$ZnLi, 3.0 equiv of zincates was necessary to obtain **4b** with a satisfactory deuterium content (entries 3 and 4). Propargylic chloride **1e** showed a reactivity comparable to that of the mesylates (entries 12 and 13). Reaction of propargylic ether **1f** (R$^1$ = PhCH$_2$CH$_2$, R$_2$ = H, X = OMe) with (Bu)$_3$ZnLi, however, resulted in recovery of the starting material.

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[•] Abstract published in *Advance ACS Abstracts*, October 1, 1993.

[1] (a) Landor, S. R. *The Chemistry of the Allenes*; Academic Press: New York, 1982. (b) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Chemistry*; Wiley: New York, 1984.

[2] (a) Dollat, J. M.; Luche, J. L.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1977**, 761. (b) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *J. Am. Chem. Soc.* **1990**, *112*, 8042.

[3] For synthetic use of trioganozincates see: (a) Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, 679. (b) Tückmantel, W.; Ohshima, K.; Nozaki, H. *Chem. Ber.* **1986**, 1581. (c) Wakamatsu, K.; Nonaka, T.; Okuda, Y.; Tückmantel, W.; Ohshima, K.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1986**, *42*, 4427. (d) Kjonaas, R. A.; Vawter, E. J. *J. Org. Chem.* **1986**, *51*, 3993. (e) Kjonaas, R. A.; Hoffer, R. K. *J. Org. Chem.* **1988**, *53*, 4133. (f) Harada, T.; Hara, D.; Hattori, K.; Oku, A. *Tetrahedron Lett.* **1988**, *29*, 3821–3824. (g) Harada, T.; Hattori, K.; Katsuhira, T.; Oku, A. *Tetrahedron Lett.* **1989**, *30*, 6039–6040. (h) Harada, T.; Katsuhira, T.; Hattori, K.; Oku, A. *Tetrahedron Lett.* **1989**, *30*, 6035–6038. (i) Takahashi, T.; Nakazawa, N.; Kanoh, M.; Yamamoto, K. *Tetrahedron Lett.* **1990**, *31*, 7349. (j) Harada, T.; Katsuhira, T.; Kotani, Y.; Oku, A. *Tetrahedron Lett.* **1991**, *32*, 1573. (k) Harada, T.; Katsuhira, T.; Hattori, K.; Oku, A. *J. Org. Chem.* **1993**, *58*, 2958.

[4] (a) Negishi, E.; Akiyoshi, K. *J. Am. Chem. Soc.* **1988**, *110*, 646. (b) Kocienski, P.; Wadman. S.; Cooper, K. *J. Am. Chem. Soc.* **1989**, *111*, 2363. (c) Negishi, E.; Akiyoshi, K.; O'Connor, B.; Takagi, K.; Wu, G. *J. Am. Chem. Soc.* **1989**, *111*, 3089. (d) Knochel, P.; Jeong, N.; Rozema, M. J.; Yeh, M. C. P. *J. Am. Chem Soc.* **1989**, *111*, 6474. (e) Knochel, P.; Chou, T.-S.; Chen, H. G.; Yeh, M. C. P.; Rozema, M. J. *J. Org. Chem.* **1989**, *54*, 5202. (f) Rozema, M. J.; Knochel, P. *Tetrahedron Lett.* **1991**, *32*, 1855.

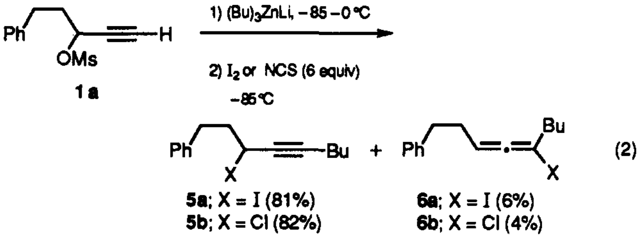
[5] Reaction with 1.25 equiv of (Bu)$_3$ZnLi afforded **4a** with 52% deuterium content in 72% yield.

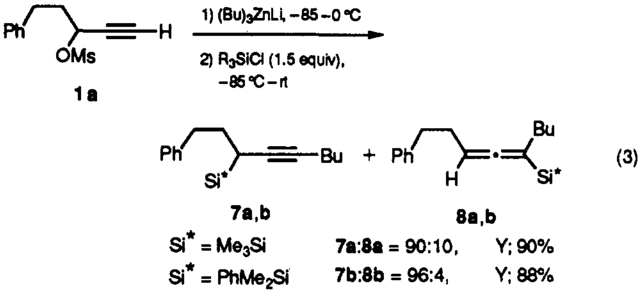
[6] Moreau, J.-L. In *The Chemistry of Ketenes, Allenes, and Related Compounds*; S. Patai, Ed.; Wiley: New York, 1980; pp 363–414.

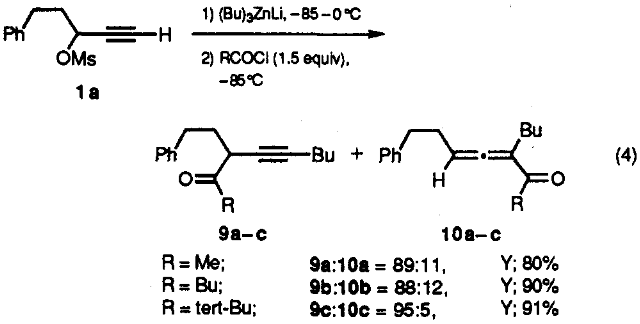
0022-3263/93/1958-6166$04.00/0

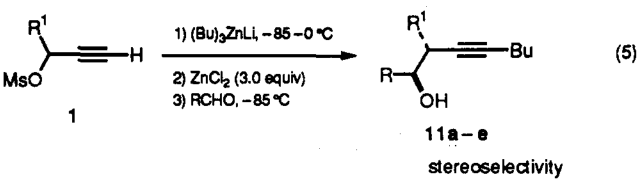
It has been reported that allenic zinc species were prepared by lithiation of the corresponding allenes[7] or alkynes ($R^1CH_2C{\equiv}CR^3$)[8] followed by transmetalation. Application of the method to the preparation of 1,3-disubstituted derivatives **3** ($R^2$ = H) would unavoidably result in nonselective formation of a mixture of the regioisomers. The present reaction allows such allenic zinc species to be prepared in a regiospecific manner.

Allenic zinc reagent **3**, thus generated, underwent an $S_E2'$-type reaction with a variety of electrophiles providing a useful one-pot transformation of propargylic derivatives.[9] Halogenation of **3** with $I_2$ and NCS proceeded regioselectively at the $\gamma$ position to give propargylic halides **5a,b** (eq 2).









| | | stereoselectivity |
|---|---|---|
| **11a**; $R^1$ = Me, R = *iso*-Pr | Y; 89% | 98:2 |
| **11b**; $R^1$ = $C_8H_{17}$, R = *iso*-Pr | Y; 85% | 99:1 |
| **11c**; $R^1$ = $C_8H_{17}$, R = $PhCH_2CH_2$ | Y; 86% | 95:5 |
| **11d**; $R^1$ = *c*-Hex, R = Et | Y; 89% | 97:3 |
| **11e**; $R^1$ = $(MeO)_2CH(CH_2)_4$, R = *iso*-Pr | Y; 88% | 98:2 |

Propargylsilanes **7a,b** were obtained in high yields by the reaction with chlorosilanes (eq 3). The reaction with acyl chlorides also proceeded regioselectively at the $\gamma$ position, affording alkynones **9a-c** (eq 4). Finally, treatment of **3** with $ZnCl_2$ (3.0 equiv) followed by the reaction of the resulting allenic zinc chloride with aldehydes yielded *threo* alcohols **11a-e** with high regio- and stereoselectivities (eq 5).[7,8,10,11]

Internal alkyne $PhCH_2CH_2CH(OSO_2CH_3)C{\equiv}CCH_3$ did not react with $(Bu)_3ZnLi$ at all under similar reaction conditions. Lithium triorganozincates are basic enough to abstract an acetylenic proton. Thus, $D_2O$ quench of the reaction mixture of propargylic ether **1f** ($R^1$ = $PhCH_2CH_2$, $R^2$ = H, X = $OCH_3$) and $(Bu)_3ZnLi$ afforded **1f**-*d* containing >99% deuterium at the terminal acetylenic carbon. These results suggest that the formation of the allenic zinc species **3** proceeds through a mechanism involving abstraction of the acetylenic proton by the triorganozincate and subsequent 1,2-alkyl migration of the resulting alkynylzincate **2** with liberation of $X^-$ (Scheme I).[13] A similar 1,2-migration of an alkynylboron ate complex has been reported previously.[14]

In order to detect intermediate alkynylzincate **2**, the reaction mixture of **1** and $(Bu)_3ZnLi$ (2 equiv) was trapped with DCl–$D_2O$ before full conversion of the starting material. The reaction of mesylate **1a** (–60 °C for 0.5 h) afforded allene **4a** (90% yield, 93% deuterium) and the starting material **1a** (5% yield) with no deuterium incorporation. The reaction of chloride **1e** (–40 °C for 0.5 h) gave allene **4j** (66% yield, 91% deuterium) and recovered **1e** (33% yield) containing 10% deuterium at the acetylenic carbon. The results suggest that the rate of proton abstraction by zincates is slower, as in the reaction of mesylate **1a**, or comparable, as in the reaction of chloride **1e**, to that of 1,2-migration of the resulting alkynylzincate **2**.[15]

In summary, we have developed a simple and general method for the preparation of allenic zinc reagents associated with carbon–carbon bond formation by the reaction of propargylic substrate **1** with triorganozincates. The allenic zinc reagents were found to react with a variety of electrophiles regio- and/or stereoselectively to give propargylic halides, silanes, ketones, and homopropargylic alcohols. Examination of the full scope of the process and

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[7] Zweifel, G.; Hahn, G. *J. Org. Chem.* **1984**, *49*, 4565.

[8] Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225.

(9) Typical Procedure. Preparation of homopropargyl alcohol **11a**: To a solution of $ZnCl_2$ (1.42 g, 10.4 mmol) in THF (31 mL) was added BuLi (1.62 M in hexane, 19.3 mL, 31.2 mmol) at 0 °C. After being stirred for 15 min, the mixture was cooled at –85 °C. A THF (5 mL) solution of **1a** (772 mg, 5.21 mmol) was added to the resulting solution of $(Bu)_3ZnLi$. The mixture was allowed to warm to 0 °C during a 5-min period and then cooled back to –85 °C. A THF solution of $ZnCl_2$ (1 M, 15.6 mL, 15.6 mmol) was slowly added, and the mixture was stirred for 1 h at –85 °C. After addition of 2-methylpropanal (563 mg, 7.81 mmol), the mixture was allowed to warm to rt during a 2-h period. The mixture was poured into 1 N HCl and extracted twice with ether. The combined organic layers were washed with aq $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography ($SiO_2$, eluting with 10–15% ethyl acetate in hexane) afforded a 98:2 mixture of *threo*- and *erythro*-**11a** (847 mg, 89% yield).

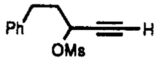
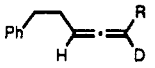
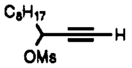
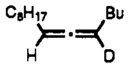
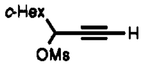
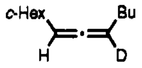
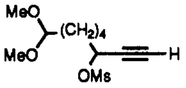
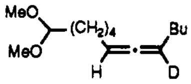
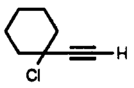
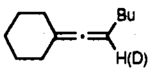
(10) Direct reaction of allenic zinc **3** with aldehydes gave raise to nonregio- and nonstereoselective formation of the $\gamma$- and $\alpha$-adducts. Thus, for example, reaction of allenic zinc **3** ($R^1$ = $C_8H_{17}$, $R^2$ = H, $R^3$ = Bu) with $PhCH_2CH_2CHO$ gave *threo*- and *erythro*-**11b** (54:46, 77%) together with allenic alcohol $PhCH_2CH_2CH(OH)C(C_4H_9)C{=}C{=}CH(C_8H_{17})$ (12%).

(11) The stereochemistry of **11a** was determined by converting it into (2*R**,3*S**)-2,4-dimethyl-1,3-pentanediol:[12] (i) $CH_3OCH_2Cl$, *i*-$Pr_2NEt$, (ii) $H_2$, Lindlar cat., (iii) $O_3$, $NaBH_4$, (iv) aqueous HCl, MeOH.

(12) Harada, T.; Matsuda, Y.; Uchimura, J.; Oku, A. *J. Chem. Soc., Chem. Commun.* **1989**, 1429.

(13) An alternative mechanism involving the initial formation of allene **4** followed by regioselective metalation by zincates was excluded by the following experiment. Treatment of the nondeuterioallene **4a** with $(Bu)_3ZnLi$ (2.0 equiv) at 0 °C for 1 h followed by $D_2O$ quench resulted in the recovery of the starting material (98%) without deuterium incorporation.

**Table I. Reaction of Propargylic Derivatives 1a-e with Lithium and Chloromagnesium Triorganozincates**[a]

| entry | substrate | reagent | product | yield[b] % (deuterium content) (%)[c] |
|---|---|---|---|---|
| 1 |  <br>**1a** | (Bu)$_3$ZnLi |  | 97 (92) |
| 2 | | (Bu)$_3$ZnMgCl | **4a**; R = Bu | 66 (86) |
| 3 | | (Me)$_3$ZnLi | **4b**; R = Me | 92 (56) |
| 4[d] | | | | 90 (75) |
| 5 | | (*s*-Bu)$_3$ZnLi | **4c**; R = *s*-Bu | 96[e] (94) |
| 6 | | (*t*-Bu)$_3$ZnLi | **4d**; R = *t*-Bu | 76[f] (93) |
| 7 | | (Ph)$_3$ZnLi | **4e**; R = Ph | 77 (81) |
| 8 | | (CH$_2$=C(Me))$_3$ZnLi | **4f**; R = CH$_2$=C(Me) | 77 (72) |
| 9 |  <br>**1b** | (Bu)$_3$ZnLi |  <br>**4g** | 97 (92) |
| 10 |  <br>**1c** | (Bu)$_3$ZnLi |  <br>**4h** | 95 (91) |
| 11 |  <br>**1d** | (Bu)$_3$ZnLi |  <br>**4i** | 91 (100) |
| 12 |  <br>**1e** | (Bu)$_3$ZnLi |  <br>**4j** | 95[g] (86) |
| 13 | | (Bu)$_3$ZnMgCl | | 79[g] (81) |

[a] Unless otherwise indicated, all reactions were performed in THF by using 2.0 equiv of zincates at temperatures from −85 to 0 °C. [b] All new compounds are fully characterized by IR, NMR, MS, HRMS, and/or elemental analyses. [c] Unless otherwise noted, yields refer to isolated yields of analytically pure products. [d] 3.0 equiv of zincates was used. [e] A combined yield of **4c** (86%) and 3-methyl-8-phenyl-4-octyne (10%). [f] A combined yield of **4d** (60%) and 2,2-dimethyl-7-phenyl-3-heptyne (16%). [g] GC yield.

extension of the 1,2-alkyl migration of alkynylzincates to related substrates are in progress.

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**Supplementary Material Available:** Experimental procedures and spectral data for all products (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(14) (a) Leung, T.; Zweifel, G. *J. Am. Chem. Soc.* **1974**, *96*, 5620. (b) Midland, M. M. *J. Org. Chem.* **1977**, *42*, 2650. (c) Zweifel, G.; Backlund, S. J.; Leung, T. *J. Am. Chem. Soc.* **1978**, *100*, 5561.

(15) It is probable that, in the course of the reaction, initially formed allenic zinc **3** (L = Bu) reacts reversibly with (R$^3$)$_3$ZnLi to form allenic zincate **3** (L = Zn(R$^3$)$_2$Li). Protonation of the allenic zincate by remaining propargylic substrate **1** may explain the byproduct formation of the protonated allene. Employment of 2 or more equiv of zincates may effectively retard the undesirable pathway especially in the later phase of the reaction.