

Design of [1,n]-ambiphiles based on zincate carbenoid chemistry

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Abstract: Treatment of propargyl methanesulfonates, chlorides, and carbamates **4** with lithium triorganozincates **5** generated the corresponding propargylic alkynylzincates **6**, which underwent an S_N2' -type 1,2-ligand migration to form allenylzinc intermediates **7**. On treatment with electrophiles, **7** finally gave propargyl derivatives **8** in which both the nucleophile and electrophile are bound tandem to the 1- and 3-position, respectively. Similar reactions of homopropargyl analogues **15** generated (cyclopropylidene)alkylzinc intermediates **16**, which further reacted with electrophiles to furnish methylenecyclopropanes **18** or **19**. 5-Hexynyl tosylate **20** also afforded (cyclopentylidene)alkylzinc compound **21**.

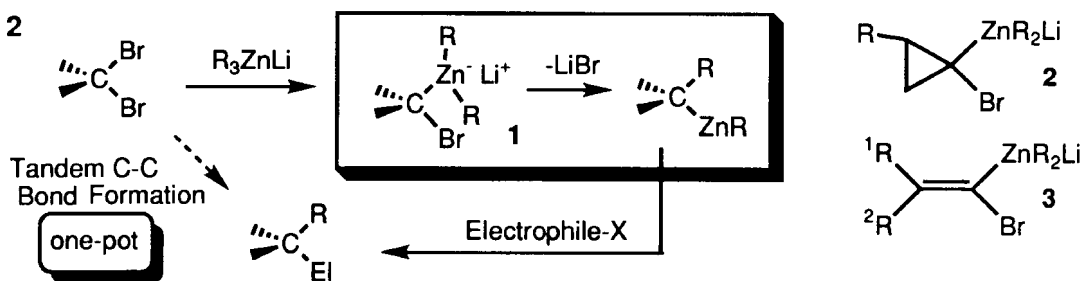
For convergent construction of complex carbon frameworks, it is desirable to develop synthetic methods in which two or more building blocks can be introduced to a substrate successively and selectively by forming more than one carbon-carbon bond in one-pot operation. In this concern, designing novel organometallics on the basis of carbenoid chemistry, not only in the form of [1,1]-ambiphiles but also [1,n]-ambiphiles, seems worth challenging (Scheme 1).

Scheme 1



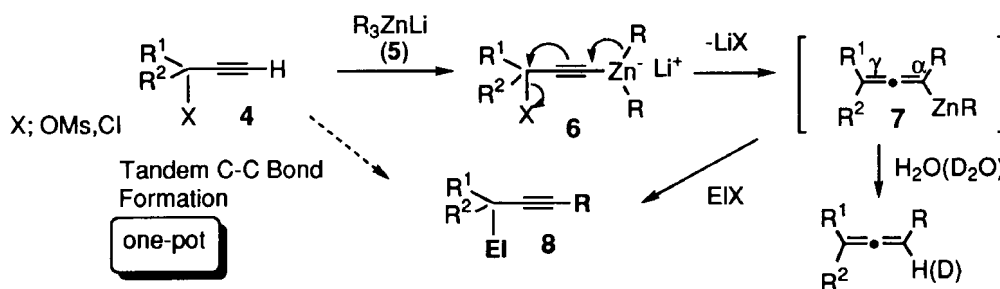
Some organometallic compounds which, after their first carbon-carbon bond forming reaction with nucleophiles, reproduce another type of organometallic intermediates are of significant importance because the intermediates, thus formed, can undergo a second carbon-carbon bond forming reaction with electrophiles. A typical example is the "carbenoids" which can be categorized as α -metallated carbocations or [1,1]-ambiphiles that have potentiality of forming two σ bonds on a single carbon centre more or less in the manner of one-pot operation. While a number of carbenoids, particularly alkali metal-halogen carbenoids, were found labile even at low temperatures so that their controlled bond forming reactions are often far from practical synthetic purposes, several ate-complexed metal carbenoids, such as borate, cuprate, alanate, and zincate carbenoids, have been developed to make up the deficiency. Of particular interest is the utility of zincate carbenoids **1** which were unprecedented when we reported their first preparation and chemical property suitable for convergent bond forming reactions (Scheme 2).

Scheme 2



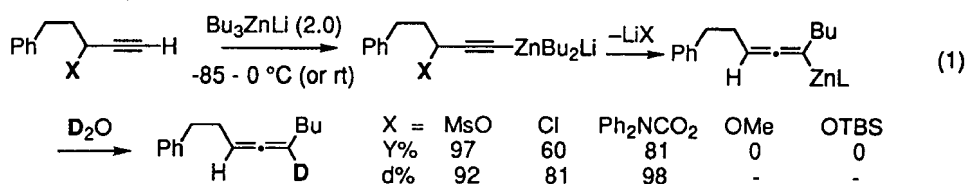
To extend the surpassing characteristics of zincate carbenoids, which were demonstrated by the highly stereoselective tandem C-C bond forming reactions of cyclopropylidene and alkenylidene zincate carbenoids **2** and **3**, we designed propargylic alkynylzincates **6** in the expectation that they may undergo an S_N2' -type conjugate 1,2-ligand migration as shown in Scheme 3.

Scheme 3

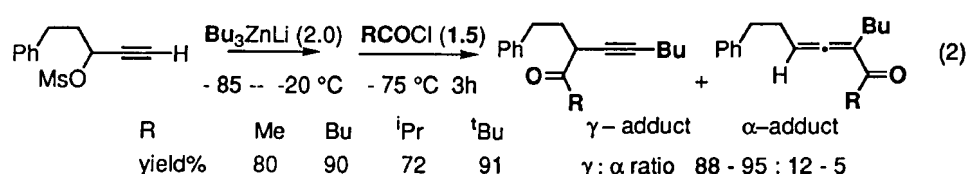


The reaction of propargyl methanesulfonate, chloride, or carbamate of type **4** (Scheme 3) with triorganozincates **5** produced propargylic alkynylzincates **6** bearing both electropositive (Zn) and electronegative group at the 1- and 3-position, respectively. They are [1,3]-ambiphiles, or may be called [1,3]-carbenoids, whose thermal stability depends on the kind of leaving group X. They undergo ligand transfer from the metal to the adjacent acetylide carbon to form a C-C, a characteristic feature of hitherto known ate-complexed metal carbenoids but unique for the conjuncted S_N2' -type transformation to give allenylzinc intermediate **7**. Again, **7** can function as another type of organozinc reagent to form a second C-C bond with an electrophile regioselectively at either 1- or 3-position. Except protonation which selectively occurred at the 1-position, other electrophiles selectively attacked the 3-position. All the procedures can be carried out successively in one-pot operation, thus providing an efficient method of introducing a nucleophile (R) and an electrophile (EI) one after another, to the 1,3-positions of propargylic substrates **8**. Some typical reactions are shown in Equations 1 - 4.

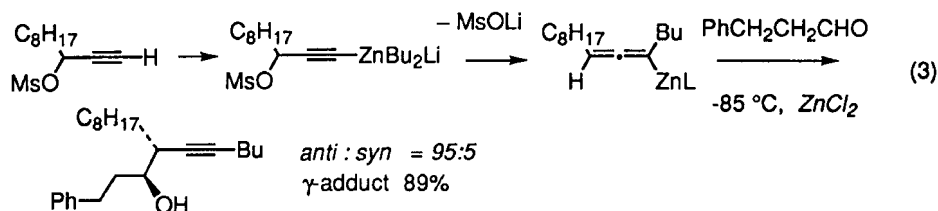
1-Deuterio-1-alkylallenes:



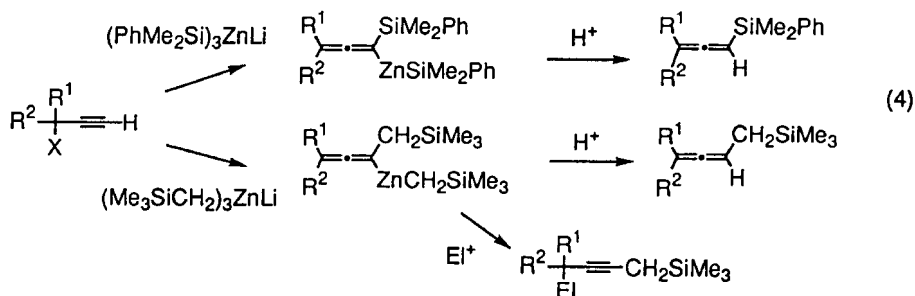
1-Alkyl-3-acylalkynes:



Homopropargyl alcohol:

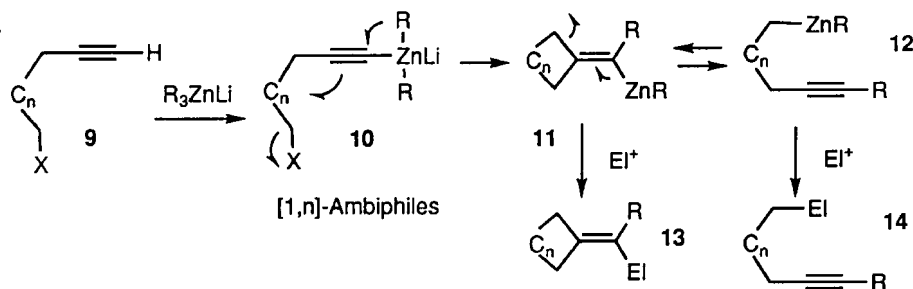


Allenylsilanes, allenylmethylsilanes, and propargylsilanes:

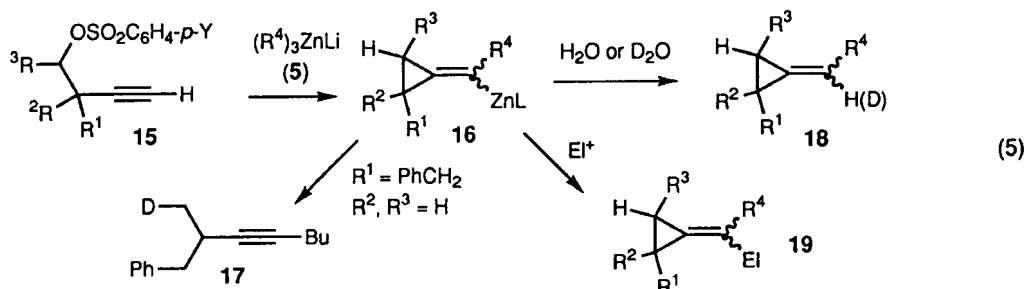


The successful one-pot transformation of **6** to 1,3-disubstituted alkynes, initiated by the 1,2-alkyl ligand migration, tempted us to extend the idea to a similar [1,4]-ambiphile system. First, homopropargyl sulfonates **9** ($n = 0$, $X = \text{SO}_3\text{Ar}$) were investigated in hope of establishing an access to 1-(cyclopropylidene)alkylzinc compounds **11** starting from the formation of homopropargylic alkynylzincates **10**, i.e. a [1,4]-ambiphile (Scheme 4, $n = 0$). Treatment of tosylate **15** with

Scheme 4

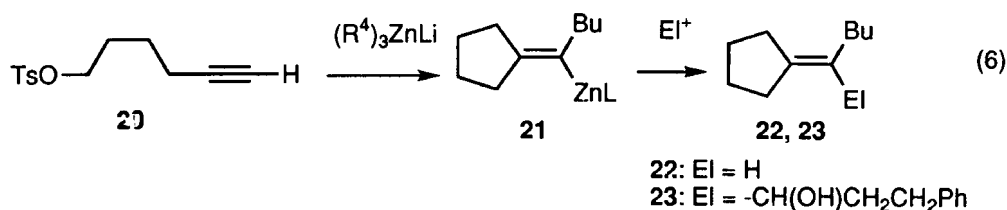


Bu_3ZnLi (2.0 equiv) in THF at 0°C for 1 h followed by quenching with D_2O gave methylenecyclopropane **18** ($R = \text{Bu}$, 75%, $E : Z = 1.9 : 1$) and alkyne **17** (8%) (Eq. 5). Deuterium was incorporated into the olefinic carbon of **18** (98%) demonstrating the generation of 1-(cyclopropylidene)pentylzinc **16**. Deuterium was also incorporated into the methyl group of **17** (68%) indicating that it was produced via the ring-opening of **16**. Indeed, the yield of **17** increased to 42% in the reaction at 0°C , whereas it was suppressed completely at -20°C . Finally, efficient generation of **16** was achieved by employing less nucleophilic leaving groups, e.g. *p*-Cl- and *p*-F-benzenesulfonyloxy group, with which **18** was obtained nearly quantitatively.



Organozinc reagents **16** underwent coupling reactions with carbon electrophiles to furnish functionalized methylenecyclopropanes **19**. In the reaction with aldehydes, **16** underwent a selective transfer of the 1-(cyclopropylidene)alkyl group in preference to the other ligand $L (= \text{Bu})$. For example, treatment with 2-methylpropanal (1.2 equiv) of the reaction mixture obtained from **15** ($R^1 - R^3 = \text{H}$) with **5** (2.0 equiv) at -80°C afforded **19** ($\text{El} = -\text{CH}(\text{OH})^i\text{Pr}$) in 69% yield. The higher reactivity of the cyclopropylidenealkyl ligand than the Bu in **16** is attributable to the reversible formation of ate-complexed **16** ($\text{ZnL} = \text{Zn}(\text{Bu})_2\text{Li}$), a more reactive species than the $\text{Zn}(2)$ species, in the presence of remaining **5**.

It should be noted that the design of [1,6]-ambiphiles in the form of **10** ($n = 2$), which can be prepared from 5-hexynyl tosylate **20**, was also successful to realize a similar cyclization (Scheme 4, $n = 2$). Treatment of **20** with **5** (2 equiv) at a room temperature gave pentylidenecyclopentane **22** together with a minor amount of endo-cyclization product 1-butylcyclohexene in 65% (5.6 : 1, Eq. 6). The intermediate 1-(cyclopentylidene)pentylzinc **21**, upon treatment with 3-phenylpropanal, gave the hydroxyalkylated adduct **23** in 59% yield.



To summarize, characteristic features of the present tandem C-C bond forming reaction are: (1) the reaction procedure is very simple, (2) the reaction is versatile with respect to both propargylic substrates and organozincates, (3) a variety of propargylic compounds can be prepared by the reaction of the intermediate allenic zinc compounds with appropriate electrophiles, (4) the basic idea for the [1,3]-ambiphile system can be extended further to elongated [1, n]-ambiphile systems.

References:

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