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New Tandem Zn-Promoted Brook Rearrangement/Ene–Allene Carbocyclization Reactions

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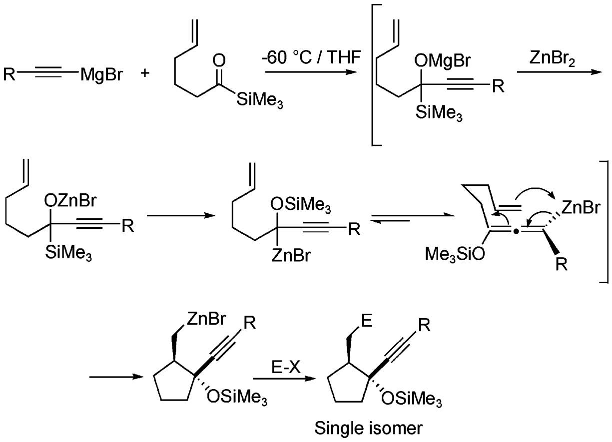
ABSTRACT



A new tandem reaction was developed for the carbocyclization reaction of propargylic zinc reagents. First, we have shown that zinc salt promotes the Brook rearrangement into the carbanionic species followed by a stereospecific Zn–ene–allene carbocyclization reaction to lead to the corresponding cyclopentylmethylzinc derivatives. A single diastereoisomer is formed, even when a tertiary and a quaternary center are linked in the process.

The reversible rearrangement of silyl groups from carbon to oxygen in α-silyl alkoxides, originally recognized and studied by Brook, provides an unusual route to potentially useful carbanions (Scheme 1).[1] The reverse process, namely the intramolecular migration of a silyl group from oxygen to carbon and called the retro-Brook rearrangement, has been investigated in detail by West.[2] A challenge inherent in the implementation of Brook rearrangement-mediated tandem bond formation strategies is the control of the direction and/or rate of the silyl migration.[3] The position of the equilibrium between **1** and **2** is determined by the relative thermodynamic stabilities of the competing species. Consideration of the

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(1) (a) Brook, A. G. *J. Am. Chem. Soc.* **1958**, *80*, 1886. (b) Brook, A. G.; Warner, C. M.; McGriksin, M. E. *J. Am. Chem. Soc.* **1959**, *81*, 981. (c) Brook, A. G.; Schwartz, N. V. *J. Am. Chem. Soc.* **1960**, *82*, 2435. (d) Brook, A. G.; Ischia, B. *J. Am. Chem. Soc.* **1961**, *83*, 827. (e) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77.

(2) West, R.; Lowe, R.; Stewart, H. F.; Wright, A. *J. Am. Chem. Soc.* **1971**, *93*, 282.

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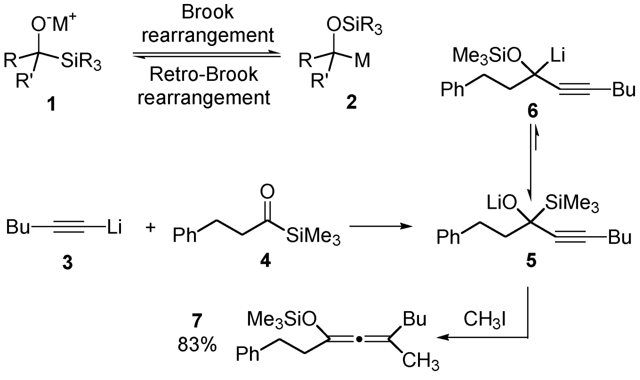
Scheme 1. Brook Rearrangement

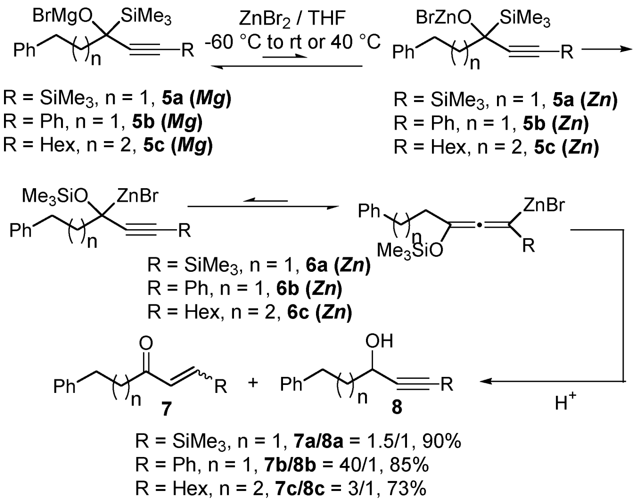


factors that control the stabilities of the species is therefore of primary importance.

In the case of the lithium salt **5** of an α-silylpropargylic alcohol, generated by the addition of the lithium acetylide[4] **3** to acylsilane **4**, no substantial Brook rearrangement to **6** was observed.[5] However, upon addition of methyl iodide, the alkylated allenic Brook product **7** was formed in good yield. Thus, **5** must be in equilibrium with minor amounts of the rearranged organolithium that is alkylated more readily than **5**, driving the equilibrium to completion. Other electrophiles such as dialkyl disulfide RSSR, DMF, or a proton (by using an excess of 1-alkyne as proton source) can also be used to drive the equilibrium as well as an elimination reaction in appropriate cases.[6]

However, if one desires to have a carbanionic species in hand for specific subsequent reactions, the addition of the electrophilic partner represents potentially a constraint on the wide applicability of such processes in synthetic chemistry. We were thus interested in overcoming this limitation and developing a strategy for the preparation of carbanionic species equivalent to **6**. One of the most important factors in this silyl migration equilibrium is the basicity of the carbanion and the identity of the counterion. We have recently shown that transmetalation of various metal organic compounds into organozinc derivatives may have different chemical outcomes,[7] and so we decided to investigate the transmetalation and subsequent behavior of α-silylmagnesium carbinols into their zinc counterparts.[8] When zinc bromide is added to **5a**−**c** (**Mg**) (prepared from the reaction between acylsilane **4** and alkynylmagnesium halide)[5] and the solutions warmed to room temperature for **5c** and 40 °C for **5a** and **5b**, evidence of the rearrangement to the corresponding zinc carbanions **6a**−**c** (**Zn**) (in metallotropic equilibrium of the allenyl and propargyl counterparts, Scheme 2) was obtained. After acidic hydrolysis, the enones **7a**−**c**[9] and propargylic alcohols **8a**−**c** were obtained in good isolated yields. It is not surprising that **5Zn** rearranges more readily than **5Mg** given the higher bond dissociation energy of the Mg−O bond (94 kcal/mol) than that of the Zn−O bond (68 kcal/mol).[10]

Scheme 2. Zn-Promoted Brook Rearrangement



Another factor that could also come into play is the stabilization of the allenyl silyl ether and allenylzinc groups in the rearranged organozinc afforded by overlap of the nonbonding electrons of the oxygen atom and the filled d-orbitals of the metal with the π-antibonding orbitals of the carbon−carbon bonds.[11]

We have been able to use this rearrangement for carbocyclization reactions. The additions of propargyl/allenyl organometallic compounds to alkenes and alkynes intramolecu-

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(3) (a) Leroux, F.; Schlosser, M.; Zohar, E.; Marek, I. In *The Preparation of Organolithium Reagents and Intermediates* in *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2004; p 435. (b) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065.

(4) The lithium acetylide should be prepared by deprotonation of acetylene with CH_3Li−LiBr complex; in the absence of lithium halide, only mixtures of oligomeric products are obtained. See ref 6a.

(5) Reich, H. J.; Olson, R. E.; Clark, M. C. *J. Am. Chem. Soc.* **1980**, *102*, 1423.

(6) For representative examples, see: (a) Reich, H. J.; Eisenhart, E. K.; Olson, R. E.; Kelly, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 7791. (b) Reich, H. J.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 5609. (c) Reich, H. J.; Kelly, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 1119. (d) Reich, H. J.; Kelly, M. J.; Olson, R. E.; Holtan, R. C. *Tetrahedron* **1983**, *39*, 949.

(7) (a) Sklute, G.; Amsallem, D.; Shibli, A.; Varghese, J. P.; Marek, I. *J. Am. Chem. Soc.* **2003**, *125*, 11776. (b) Varghese, J. P.; Zouev, I.; Aufauvre, L.; Knochel, P.; Marek, I. *Eur. J. Org. Chem.* **2002**, 4151. (c) Deng, K.; Chalker, J.; Yang, A.; Cohen, T. *Org. Lett.* **2005**, *7*, 3637. (d) Klein, S.; Marek, I.; Normant, J. F. *J. Org. Chem.* **1994**, *59*, 2925. (e) Norsikian, S.; Marek, I.; Klein, S.; Poisson, J. F.; Normant, J. F. *Chem. Eur. J.* **1999**, *5*, 2055. (f) Marek, I. *Tetrahedron* **2002**, *58*, 9463.

(8) If alkynyllithium derivatives are used, the Brook rearrangement is much slower even after the addition of zinc salt. This effect is not clearly understood, but the combination magnesium halide/zinc salt exerts an influence on the rate and equilibrium of the C to O silyl rearrangement. Without zinc salt, no rearrangement of the magnesium alcoholate was detected.

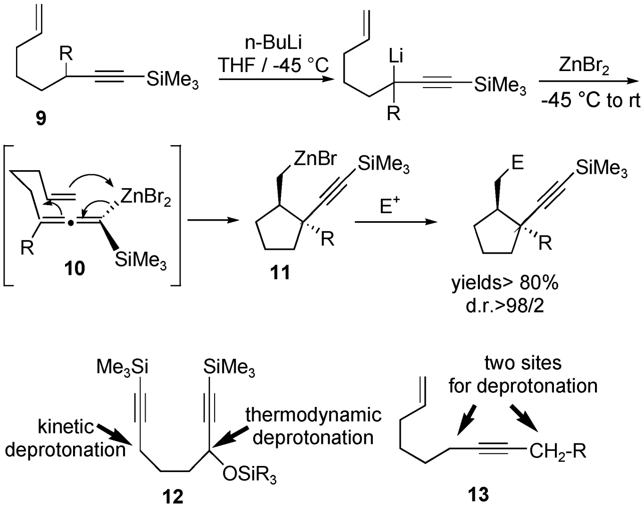
(9) No attempts were made to isolate its siloxyallenyl precursor.

(10) *Lange's Handbook of Chemistry*, 15th ed. (on line); Dean, J. A., Ed.; McGraw-Hill: New York, 1999.

(11) The products of electrophilic capture of propargylic/allenic organozincs can be explained by assuming that the equilibria between propargylzincs and allenylzincs lie far in favor of the latter. (a) Zweifel, G.; Hahn, G. *J. Org. Chem.* **1984**, *49*, 4565. (b) Poisson, J. F.; Normant, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4639. (c) Lorthiois, E.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1996**, *37*, 6693. (d) Lorthiois, E.; Marek, I.; Meyer, C.; Normant, J. F. *Tetrahedron Lett.* **1996**, *37*, 6689. (e) Poisson, J. F.; Chemla, F.; Normant, J. F. *Synlett.* **2001**, 305. (f) Poisson, J. F.; Normant, J. F. *J. Org. Chem.* **2000**, *65*, 6553. (g) Harada, T.; Katsuhira, T.; Osada, A.; Iwazaki, K.; Maejima, K.; Oku, A. *J. Am. Chem. Soc.* **1996**, *118*, 11377.

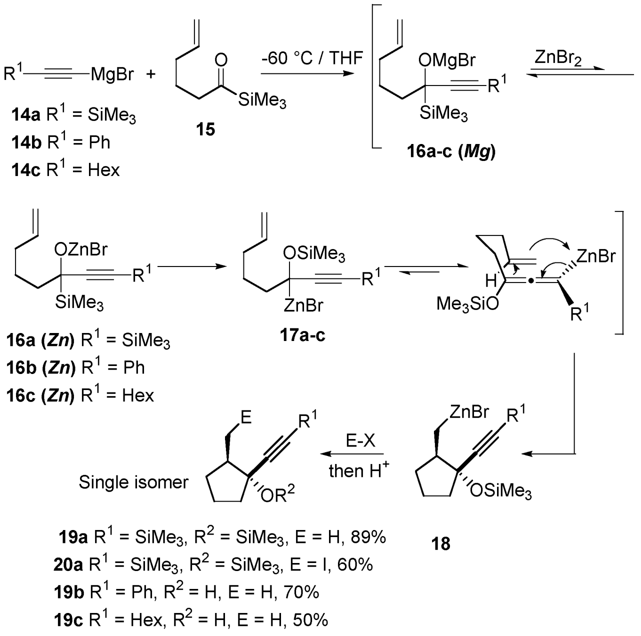
larly are considered metallo−ene−allene and metallo−yne−allene carbocyclization reactions, respectively.[12] Previously, these reactions were performed by an initial lithiation step at the propargylic position of enynes **9** followed by a transmetalation reaction leading to the corresponding zinc reagents **10**. During the warming to room temperature, a fast carbocyclization reaction occurred leading to the corresponding cyclopentylmethylzinc derivatives **11**. These cyclizations are stereospecific and a single diastereoisomer of **11** was formed (for R = H, alkyl, OMe).[12] Interestingly, the direct metalation of propargylic silyl ether (R = $OSiMe_3$) gave none of the cyclic product but instead a triene coming from translocation of the metal and an allylic proton.[13] Moreover, as a metalation step is initially required, problems of regioselectivity may arise when two acidic sites are present in the molecule (i.e., kinetic versus thermodynamic metalation reactions, see metalation of **12** for the yne−allene cyclization)[12a] or between two nearly equivalent acidic sites (i.e., metalation of **13**) (Scheme 3).

Scheme 3. Zn−Ene−Allene Carbocyclization Reaction



These two limitations should be easily overcome if we were to use the Zn-promoted Brook rearrangement as a new source of propargylic/allenic zinc derivatives. Deprotonation of various terminal alkynes with organomagnesiums generates alkynylmagnesium bromides **14** [R^1 = $SiMe_3$ (**14a**) R^1 = Ph (**14b**), R^1 = Hex (**14c**)], and after slow addition of acylsilane **15** over a period of 30 min, the corresponding magnesium alkoxides **16a−c** (**Mg**) were obtained. The addition of zinc salt and warming the mixture to room temperature for **16a** (**Zn**) and reflux for **16b**,**c** (**Zn**) led first to the corresponding Zn−Brook rearrangement product **17a−c** followed by the Zn−ene−allene carbocyclization reaction as depicted in Scheme 4.

Scheme 4. Tandem Zn-Promoted Brook Followed by the Zn−Ene−Allene Carbocyclization Reaction



Hydrolysis of the reaction mixture afforded **19a−c** in 89, 70, and 50% yields, respectively. The Zn−ene−allene carbocyclization is faster for **17a** than for **17b** and **17c**.[14] The cis configuration between the methyl groups and the alkynyl moieties was determined by comparison with literature data for **19a** and assigned by analogy for all the other compounds.[12b,15] The formation of a discrete organometallic species **18** was checked by iodinolysis as depicted in Scheme 4 (formation of **20a**). The unique stereochemistry of the reaction is rationalized by a zinc−ene−allene transition state in which the allenylmetal moiety plays the role of the ene partner and fixes the cis relationship of the two substituents.

Therefore, a stereoselective construction of a polysubstituted five-membered ring is now possible via this one-pot tandem Zn−Brook rearrangement/ene−allene carbocyclization reaction in which a quaternary and a tertiary center are created as single isomers. This new strategy solves the problems related to the more classical Zn−ene−allene reaction described in Scheme 3.

The same tandem strategy was applied to the Zn−yne−allene carbocyclization. In this case, two different alkynylmagnesium halide derivatives **14a** and **14b** were, respectively, added to the new acylsilane **21**, holding an electrophilic trimethylsilyl acetylene unit. After the acylation reaction, zinc

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[12] (a) Meyer, C.; Marek, I.; Normant, J. F.; Platzer, N. *Tetrahedron Lett.* **1994**, *35*, 5645. (b) Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J. F. *J. Org. Chem.* **1995**, *60*, 863. (c) Lorthiois, E.; Marek, I.; Meyer, C.; Normant, J. F. *Tetrahedron Lett.* **1995**, *36*, 1263. (d) Meyer, C.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1996**, *37*, 857. (e) Lorthiois, E.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1997**, *38*, 89. (f) Lorthiois, E.; Marek, I.; Normant, J. F. *Bull. Chem. Soc. Fr.* **1997**, *134*, 333.

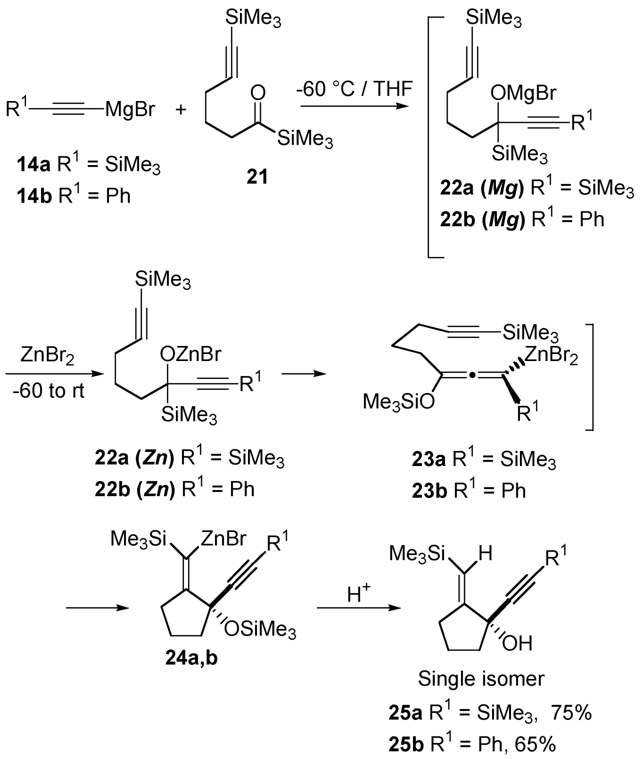
[13] Courtemanche, G.; Normant, J. F. *Tetrahedron Lett.* **1991**, *32*, 5317.

[14] The carbocyclization reaction to **19c** was incomplete leading to the isolation of the hydrolysis product of **17c**.

[15] (a) Battioni, J. P.; Capmau, M. L.; Chodkiewicz, W. *Bull. Soc. Chim. Fr.* **1969**, *3*, 976. (b) Battioni, J. P.; Chodkiewicz, W. *Bull. Soc. Chim. Fr.* **1969**, *3*, 981. (c) Cannone, P.; Bernatchez, M. *J. Org. Chem.* **1986**, *51*, 2147.

salt was added to **22** to promote the Brook rearrangement which subsequently led to the cyclic product via the yne-allene carbocyclization (Scheme 5).

Scheme 5. Tandem Zn-Promoted Brook Followed by the Zn−Yne−Allene Carbocyclization Reaction



The propargyl/allenylzinc bromides **23** (Scheme 5) undergo a regiospecific 5-exo-dig cyclization to give the cyclic organozinc bromides **24**. The pure *E*-configuration of the vinyl silanes **25** clearly shows that the carbocyclization proceeds in a totally stereoselective fashion to give the configurationally stable Z-alkenylzinc bromides **24**.[12a]

The discovery of the Zn-promoted Brook rearrangement allows the preparation of propargylic/allenyl organozinc species. The resulting organometallic derivative can be used synthetically for effective zinc−ene−allene and zinc−yne−allene carbocyclization reactions. This new tandem methodology represents a unique and straightforward way to generate polysubstituted cyclopentylmethylzinc and cyclopentylidenemethylenezinc derivatives under mild conditions. We are currently investigating some extensions of this work such as the preparation of more challenging organometallic species as well as applications to new carbocyclization reactions.

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Supporting Information Available: Experimental procedures with a description of ^{1}H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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