

Cascade Resulting in the Reductive Ethynylation of Aldehydes: Dissection of Its Components

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Abstract: A mild and efficient two-carbon homologation of aldehydes exploiting multiple modes of KO^tBu was developed. This process involves a sequential Peterson allenylation/allene–alkyne isomerization/protodesilylation in a single-flask operation. The differential roles played by the various elements of the process were demonstrated through dissection experiments.

Introduction

The Corey–Fuchs sequence¹ elegantly accomplishes the extension by one carbon of an aldehyde to a terminal acetylene. It also anticipates further functionalization of the alkyne, via the metal acetylide bond present in the concluding phase of the process. In the research described below, we posed a different question, as summarized in Scheme 1. We wondered about the possibility of extending a chain (RC_n, see **1**) by two carbon centers to a terminal ethynyl unit (see target **2**). In principle, there is a well-established method for doing so via a leaving group at the terminus of the C_n moiety (see **3**), which serves as an electrophile for metalated acetylene **4** in an alkylation format.² However, all too often, the formation of a carbon–carbon bond by alkylating a metalated acetylide with a carbon electrophile bearing a leaving group, even at a primary center, is not a straightforward matter, particularly when there is some steric hindrance to attack at the alkylating carbon.³

It was our perception that addition of metalated acetylides, such as **4**, to aldehydes is more widely applicable than is “RX alkylation.” Of course, addition of **4** to aldehyde **5** produces a secondary propargylic alcohol (see **4** → **6**). Progression from **6** to **2** would require site specific deoxygenation.⁴ What we were seeking was implementable chemistry to enable overall *reductive*

ethynylation of an aldehyde (i.e., conversion of aldehyde **5** to a propargyl derivative **2**) by nucleophilic addition of some reagent. We also set as a strong preference that the process be executable by a very simple protocol. A cascade to accomplish this end was designed and its components were dissected and individually demonstrated. As our true carbon nucleophile, we made use of compound **7**,⁵ which is readily obtained by the hydrozirconation of bis-trimethylsilylacetylene. The thought behind the use of **7** was the expectation that carbon-based anion stabilizing groups, such as TMS groups, might accelerate a required allene–alkyne isomerization (*vide infra*).

Results and Discussion

A series of 1,2-bis(TMS)allylic alcohols (see Scheme 2 and Table 1), were prepared via the reaction of **7** with the required aldehydes. We next considered a proposed allenylation by sequential Brook⁶ and Peterson⁷ transformations. It was found that the use of *n*-BuLi, per se, did not accomplish the desired allenylation. Apparently, the relatively covalent alkoxy lithium bond, formed from the deprotonation of the alcohol, is unable to trigger the required Brook–Peterson reaction.⁸ We took note that previous groups had investigated the possibility of using catalytic amounts (ca. 10 mol % of KH) and α-TMS substituted allylic alcohol, seeking to accomplish allenylation. Only low yields of allene products were obtained.^{9–11} Apparently, under

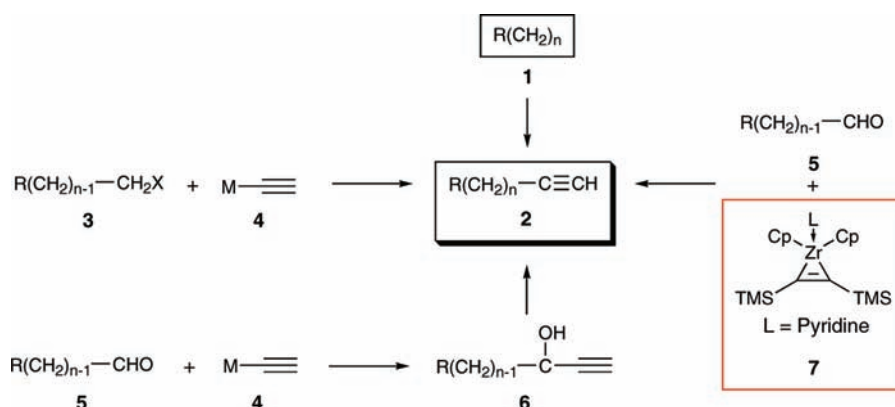
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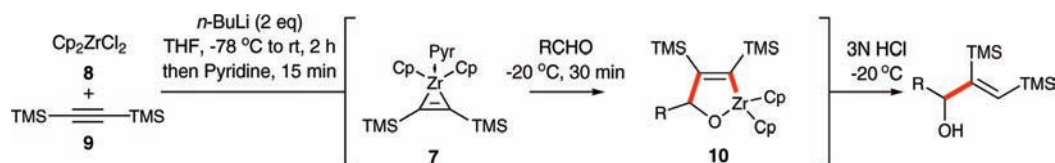
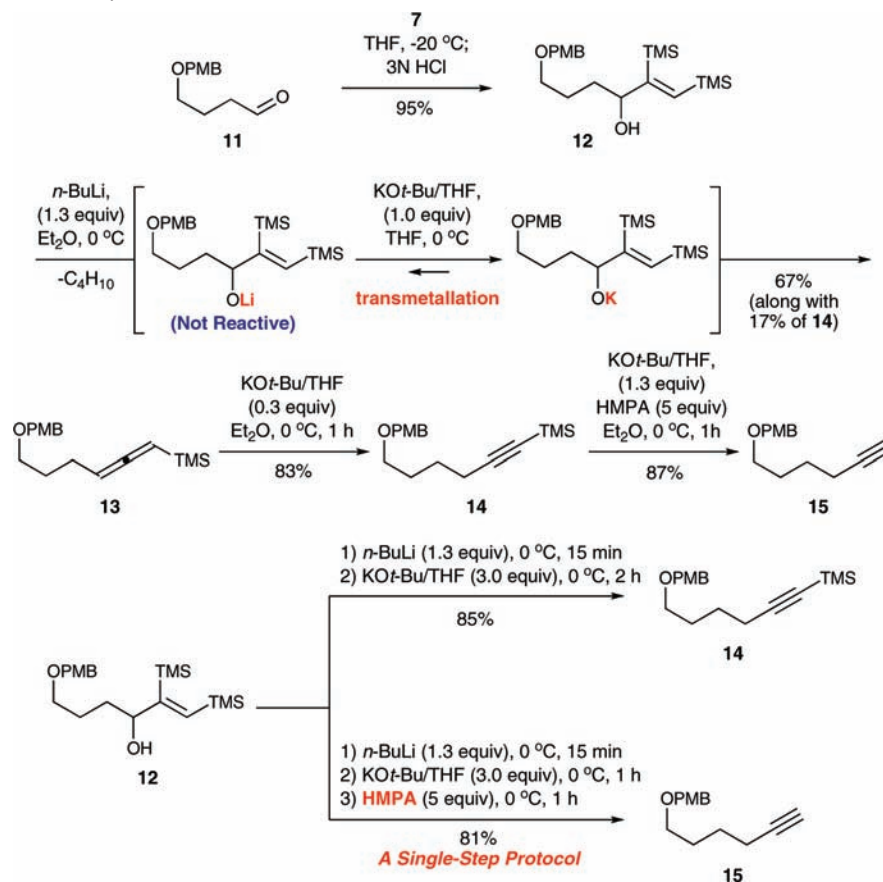
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- (9) Sato, F.; Tanaka, Y.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1983**, 165–166.

Scheme 1



Scheme 2

Scheme 3. KO^tBu Promoted Multiple Transformations

these conditions, the vinyl potassium species arising from the Brook step is protonated by remaining free alcohol. Thus, allyl silyl ethers were obtained from resultant intermediates with the as-yet unreacted alcohol.

We hoped that this problem could be circumvented through the use of *n*-BuLi as the base,¹² thereby leading to high-yielding lithium alkoxide formation (Scheme 3). This lithio alkoxide would not undergo the Brook rearrangement required for Peterson allenylation in a relatively low polarity solvent such

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Table 1. Scope of KO t -Bu Promoted One-Pot Alkynylation

1) n -BuLi (1.3 equiv), 0 °C, 15 min
2) KO t -Bu/THF (3.0 equiv), 0 °C, 1 h
3) HMPA (5 equiv), 0 °C, 1 h

Entry	Aldehyde	Bis(TMS)Allylic Alcohol	Alkyne
1			
2			
3			
4			
5			
6			
7			
		(70%, 33:34 = 4.6:1)	
8			

as Et₂O.^{13,14} We hoped that transmetalation (Li → K),¹⁵ after successful lithium alkoxide formation, could be readily accomplished and that the potassium salt of the allylic alcohol, thus produced efficiently, would undergo high yielding Brook rearrangement. This possibility was investigated, starting with aldehyde **11**, which reacted with **7** to give rise to **12** as shown. Deprotonation of **12** with n -BuLi (1.3 equiv) was followed by addition of 1.0 equiv of KO t -Bu.¹⁶ In Et₂O as the primary

- (13) For the effect of solvent polarity on silyl migration, see: Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron* **1996**, *62*, 503–514.
- (14) In the absence of KO t -Bu, the lithium alkoxide didn't undergo Brook–Peterson allenylation even at room temperature in either Et₂O or THF.
- (15) For the Brook rearrangement with transmetalation of Li → K, see: Smith, A. B., III; Xian, M.; Kim, W.-S.; Kim, D.-S. *J. Am. Chem. Soc.* **2006**, *128*, 12368–12369.
- (16) 1M solution of potassium *tert*-butoxide (KO t -Bu) in THF was purchased from Aldrich Chemical Co.

solvent, a 67% yield of allenylsilane **13**, accompanied by ca. 17% of the corresponding TMS acetylide **14**, was obtained. We next treated the isolated **13** with 0.3 equiv of KO t -Bu, thereby obtaining an 83% yield of **14**. Combining this information, we returned to **12**. When a solution of **12** in Et₂O was treated with 1.3 equiv of n -BuLi and 1.3 equiv of KO t -Bu, an 85% yield of **14** was obtained in a single step. We note parenthetically that, ordinarily, allene → acetylene isomerizations require the use of very strong bases.^{17,18} That it was accomplished here simply with *t*-butoxide reflects the predicted activating effect of the terminal TMS group.

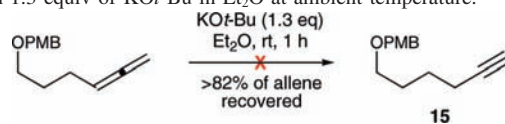
We then probed the possibility that nucleophile-induced desilylation of the terminal acetylide could be accomplished by KO t -Bu in a more polar solvent (such as HMPA). This possibility was explored with substrate **14**. Indeed, as shown, the reaction thus conducted gave rise to **15** in 87% yield. Combining these informatics, a one step protocol, leading from **12** to **15** in 81% yield, was implemented. The high yielding cascade involves cooperativity between n -BuLi to achieve clean deprotonation of **12**, and transmetalation with KO t -Bu to accomplish Brook rearrangement. This is followed by elimination, allene → acetylide isomerization enabled by the terminal TMS group and exposure to the nucleophilicity enhancing character of HMPA (to enable desilylation).

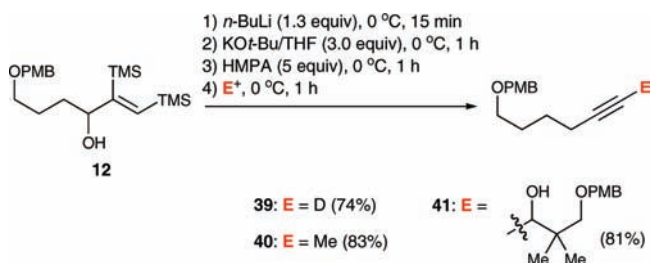
Informed by these dissection experiments, we investigated the scope of the cascade type reaction. As shown in Table 1, the reductive ethynylation chemistry was found to be compatible with a range of alkyl-substituted allylic alcohols, obtained from the reactions of the appropriate aldehydes with **7** (entries 1–6). We were particularly pleased to observe that the sterically hindered *neo*-pentyl alcohols, **26** and **29** (entries 5 and 6), derived from their hindered aldehyde precursors, readily entered into the cascade to provide the corresponding alkynes **27** and **30** in good yields.

We also investigated application of this sequence to a conjugated enal (see **31**). In this case, while the chemistry described above worked, a three-component mixture of products *E,Z*-**33** and **34** was obtained. This result is understood in terms of the ambident protonation possibilities of **35**, generated in the course of the allenyl silane → ethynylsilane isomerization. Also not surprising was the finding that attempted application of the reductive ethynylation protocol to **37** led to **38**. The formation of the latter is seen to reflect late-stage tautomerization of the initially produced terminal alkyne, facilitated by the aryl group of the primary product.

Finally, we sought to extend this chemistry to a multicomponent setting, wherein the ultimate alkynyl anion would be trapped by an electrophilic species (Scheme 4). We first

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- (18) Terminal allene (see below) didn't undergo allene-alkyne isomerization with 1.3 equiv of KO t -Bu in Et₂O at ambient temperature.



Scheme 4. KO t -Bu Promoted One-Pot Multicomponent Approach

examined this concept in the context of a deuterium oxide quench. Thus, sequential treatment of the lithium alkoxide generated from alcohol **12** with KO t -Bu (3 equiv), HMPA (5 equiv), and finally D₂O, provided the deuterated alkyne **39**¹⁹ in 74% overall yield. This type of quenching experiment was found to be feasible with other electrophiles. For instance, trapping by either MeI or, indeed, by aldehyde **25**, led to the formation of **40** and **41**, respectively, as shown.

Conclusion

In conclusion, we have developed a mild and efficient process which exploits multiple reactivity modes within a single one-

(19) Deuterium incorporation was greater than 95%.

flask sequence. The key components of the cascade include Brook–Peterson allenylation, allene–alkyne isomerization, and protodesilylation or other means of trapping the ultimate potassium acetylide. Overall, the transformation results in two-carbon homologation of aldehydes to provide the corresponding terminal alkynes, or other trapping products. The differential roles played by the various elements of the process were demonstrated through dissection experiments. Further studies of the scope and application of these findings are in progress.

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Supporting Information Available: General experimental procedures, including spectroscopic and analytical data for new compounds along with copies of ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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