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Silyl-Cupration of an Acetylene Followed by Ring-Formation

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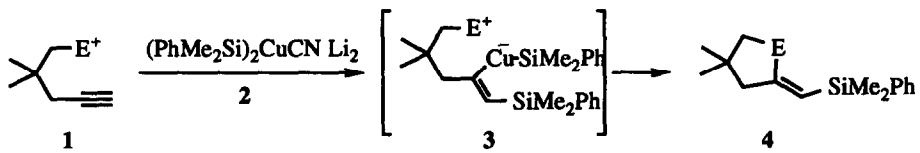
Abstract The acetylenes **1a-e** undergo silyl-cupration followed by cyclisation, the acetylenes **1f-1h** react with the silyl-cuprate reagent more rapidly at the alternative electrophilic site, and the acetylenes **1i, 1j** and **21** give relatively low yields of cyclic products amongst others. Ring-formation is, unusually, a not particularly favourable pathway.

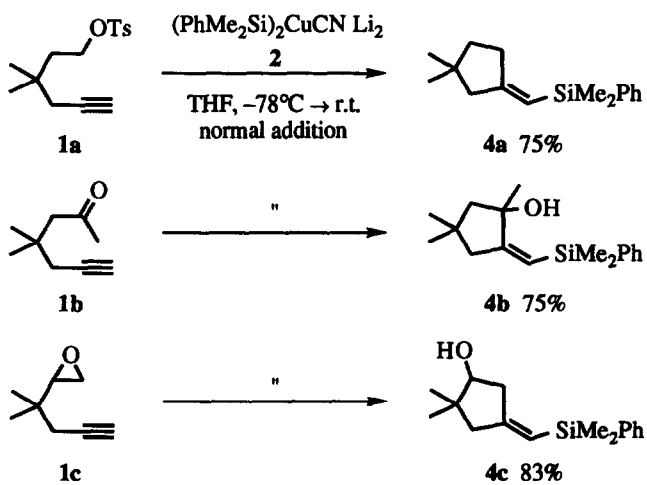
We have earlier established that the phenyldimethylsilyl-cuprate reagent **2** reacts with acetylenes,[1] allenes,[2] allylic acetates[3] and a variety of αβ-unsaturated enone systems,[4] and others have established that the same or similar silyl-cuprate reagents react with acid chlorides,[5,6] allylic chlorides,[7] a vinyl iodide,[8] epoxides,[6,9] a primary alkyl bromide,[9] an imminium ion,[10] a vinyl sulfone,[11] vinyl sulfoxides,[12] and a few



1 **3** **4**

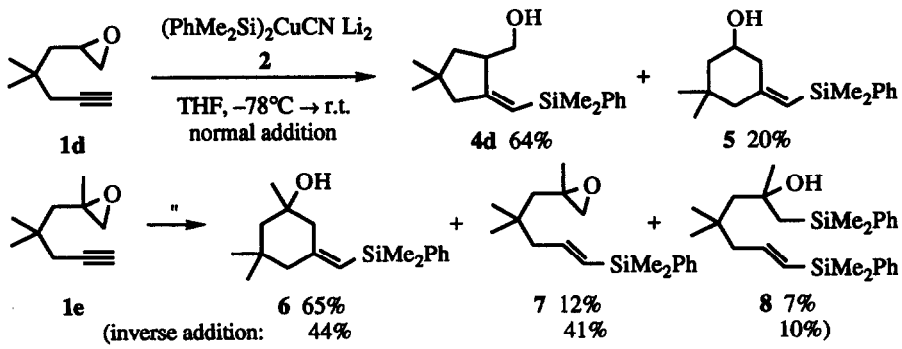
other, probably less general, functional groups.[13] However, no one has established the *relative* reactivity of these substrates.[14,15] We have now investigated the relative reactivity of the terminal acetylene group with respect to some of the other substrates, labelled E+, using compounds **1** that contain both, with some hope[15] that carbocyclic rings **4** might be formed from an intermediate vinyl-cuprate **3**.

When we carried out the reaction in the more convenient way, referred to here as normal addition, by adding the substrates **1**[16] to the cold silyl-cuprate solution, the *p*-toluenesulfonate **1a**,[17] the ketone **1b**,[18] and



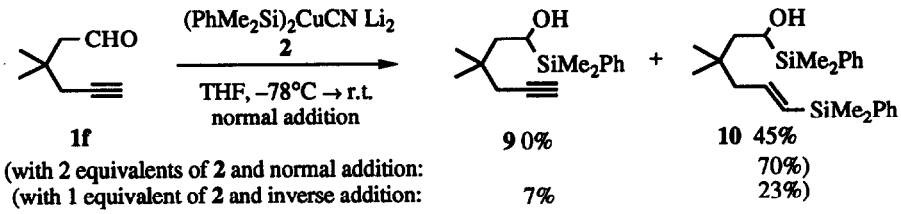
the epoxide **1c**[17] behaved well, giving the cyclopentanes **4a-4c** as the only identifiable products. Clearly a primary alkyl tosylate, not surprisingly, in view of Oshima's work,[15] a ketone group, and a terminal epoxide are relatively unreactive towards the silyl-cuprate reagent **2**.

The epoxides **1d** and **1e** were only slightly more complicated, giving a mixture of regioisomers **4d** and **5** in the former case, and a mixture of three products in the latter: the major product was the six-membered ring cyclisation product **6**, but there were minor amounts of the product **7** of silyl-cupration without cyclisation, and of the product **8** of reaction at both sites. The proportion of reaction taking place at both sites should be reduced



by inverse addition, although this is somewhat less convenient to carry out, and runs a small risk of losing, through decomposition, some of the silyl-cuprate reagent as it is transferred by cannula into the cold solution of the substrate. However, inverse addition in the reaction with the epoxide **1e** did not increase the amount of the cyclic product **6**.

In contrast, the aldehyde **1f** gave no cyclic product. When we used one equivalent of the bissilyl-cuprate **2**, the only recognisable product **10** (45%), apart from some recovered aldehyde, was the result of attack at both groups. With two equivalents of the cuprate, the yield of this product was quite good (70%). Using

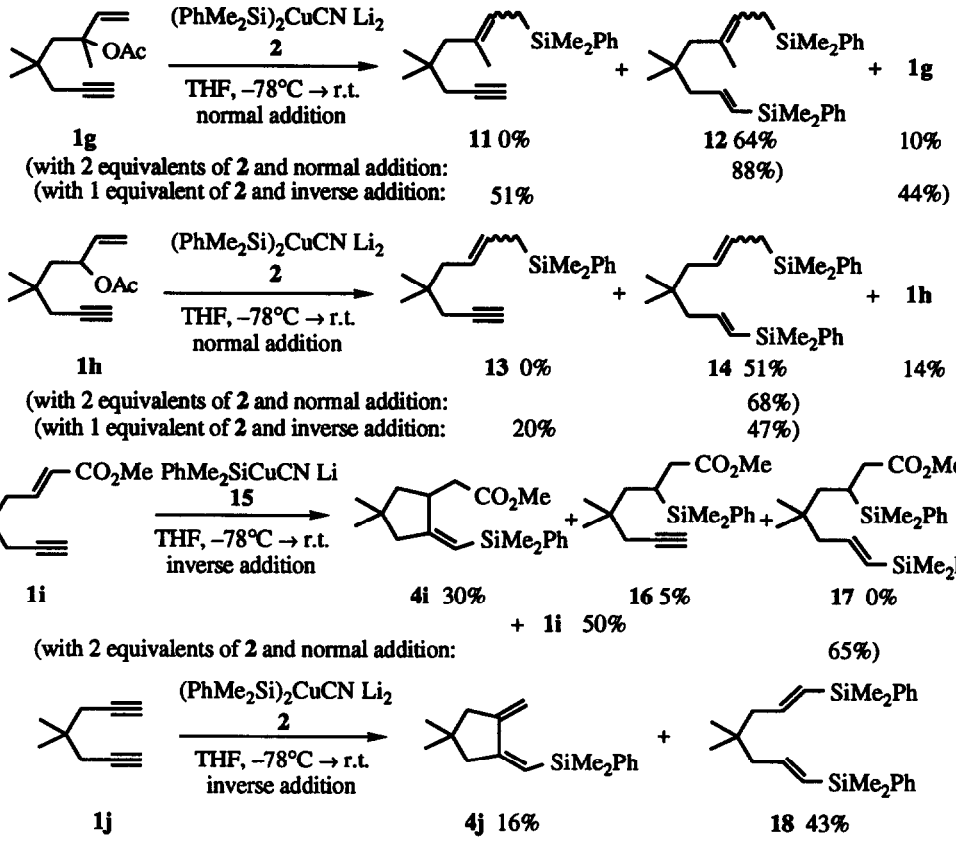


inverse addition, we were able to isolate a small amount of the product **9**, showing that the aldehyde group was more reactive than the acetylene group, and using our mixed cuprate,[19] with both a methyl and a silyl group, the yield of this product was increased to 25%.

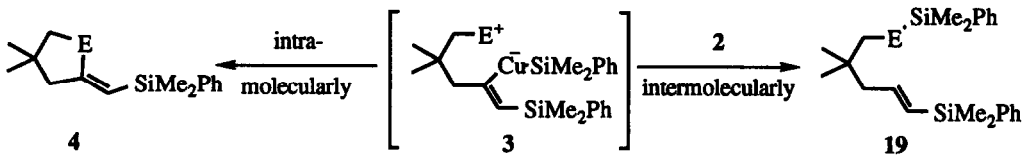
Similarly, the allylic acetates **1g** and **1h**, with either one or two equivalents of the cuprate reagent **2**, gave largely the allylsilanes **12** and **14**, as mixtures of geometrical isomers, from attack at both sites. Using inverse addition, we were able to isolate the mixtures of allylsilanes **11** and **13**, respectively, in which no reaction had occurred at the acetylene groups, showing that allylic acetates are more reactive than a terminal acetylene. Again, the mixed cuprate[19] gave these two compounds in better yield (65% and 72%). There was no sign in any of these experiments of any significant quantities of cyclic products. There is therefore little hope of using an aldehyde or an allylic acetate for ring formation by this method.

Finally, the αβ-unsaturated ester **1i** and the acetylene **1j** gave some cyclisation. The cyclopentane **4i** was present in the product mixture of every variant that we tried, except when we used two equivalents of the cuprate **2** and normal addition, when we obtained the product **17** of addition at both sites.[20] The best yield of the cyclisation product **4i** was a mere 30% (60% based on starting material consumed) obtained using one equivalent of the 1:1 silyl-cuprate reagent **15**, and in this case inverse addition did increase the proportion of

cyclisation. It appears that the unsaturated ester group is nearly as reactive as the acetylene group, as shown by the formation of some of the product **16** of reaction only at that site. The yield of **4j** was 34% using the mixed cuprate.[19]

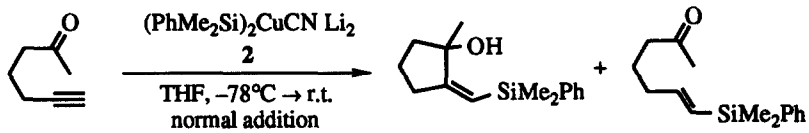


Why do we see here such a limited range of substrates undergoing cyclisation, when five-membered ring formation is normally faster than intermolecular reactions? We believe that silyl-cuprates are inherently more reactive than carbon-based cuprates. In consequence, the intramolecularity of the cyclisation step **3** → **4** must compensate for the relatively high reactivity of silyl-cuprates in the intermolecular reaction **3** → **19**. We expected therefore that cyclisation might not always occur, even when the acetylene was the first group to be attacked by the silyl-cuprate reagent.



Because we forsaw that cyclisation might not be easy, we incorporated gem dimethyl groups in all the substrates **1** above, in order to benefit from the Thorpe-Ingold effect. In Oshima's reaction, similar to **1a** → **4a** but with no gem dimethyl group, cyclisation had been easy, but we reasoned that this was an especially

favourable situation. That it had been a wise precaution for our other reactions became evident when we repeated the second of our most successful reactions without that advantage. In contrast to the ketone **1b**, the ketone **21** gave two recognisable products **22** and **23**.[17] The alcohol **22** was only a minor component under normal conditions, and not even the only product using inverse addition, although the yield was raised substantially. Ring-formation clearly needs all the help it can get.



21 **22** 11% **23** 55%

(with inverse addition: 37% 33%)

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14. Allyl crotonate gave conjugate addition of the silyl-cuprate reagent to the enone system and only a little crotonic acid (Fleming, I.; Sarkar, A. K. *J. Chem. Soc., Chem. Commun.* **1986**, 1199-1201), but allyl cinnamate gave largely cinnamic acid (Hill, J. H. M. unpublished result). αβ-Unsaturated esters and primary allylic acetates would appear to be comparable in reactivity.
15. Oshima has observed 3-6-membered ring-formation from a range of primary and secondary 1-alkyn-n-yl methanesulfonates and tosylates, using the copper-catalysed addition of $PhMe_2SiMgMe$ to the terminal acetylene (Okuda, Y.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 2483-2486).
16. All the substrates **1** were prepared from the ketone **1b** using standard reactions to be described in a full paper. The ketones **1b** and **21** were prepared following Schreiber, J.; Felix, D.; Eschenmoser, A.; Winter, M.; Gautschi, F.; Shulte-Elte, K. H.; Sundt, E.; Ohloff, G.; Kalvoda, J.; Kaufmann, H.; Wieland, P.; Anner, G. *Helv. Chim. Acta* **1967**, *50*, 2101-2108; Felix, D.; Schreiber, J.; Ohloff, G.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 2806-2912.
17. We thank Klaus Breuer for carrying out this reaction as a summer visitor.
18. We thank Helen Hailes for first carrying out this reaction as an undergraduate project.
19. Fleming, I.; Newton, T. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1805-1808.
20. There is some of the regioisomer with the silyl group attached to the internal carbon atom of the acetylene in this product.

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