Organometallic polysynthons: a novel strategy for selectively polyfunctionalized molecules

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Abstract
An account is given of our exploratory work on metallometalation of unsaturated systems, which relies on: a) Regio- and stereoselective silyl- and stannyl-cupration of N-containing unsaturated molecules such as propargylamines, ynamines, and isocyanates; b) Silyl- and stannyl-cupration of α,β- unsaturated acylsilanes.
The generation and synthetic utility of the nucleophilic polysynthons related to dimetallic adducts, are highlighted and preliminary results on the application of this methodology in chemo-, regio- and stereoselective reactions is presented.

INTRODUCTION

The types of organometallics used in organic synthesis have expanded in the past decade from classical organoalkali and Grignard reagents to organometallics containing less electropositive metals such as Si, Sn, Cu, B, Al, Zn. Simple vinyl organometallics, accessible through hydrometalation and carbometalation of 1-alkynes and based on these metals are, for example, synthons for preparing regio- and stereodefined olefins.

Compared to hydro- and carbometalation, metallometalation reactions have been studied less and so far mainly Si or Sn organometallics in which the accompanying metal (Li, Mg, Al, Cu, B or Zn) yields an organometallic more reactive than either Si or Sn have been used.

The utility of dimetallic reagents, which are virtually "non basic organometallics" and therefore compatible with polar functional groups, lies in the simultaneous generation, once they are reacted with suitable unsaturated molecules, of two stereo- and regio-defined vinyl organometallics of differential reactivity in the same molecule: stepwise combination of the dimetallic adducts with electrophilic centers, allows one to consider the latter as synthetic equivalents of highly versatile nucleophilic polysynthons.[1]
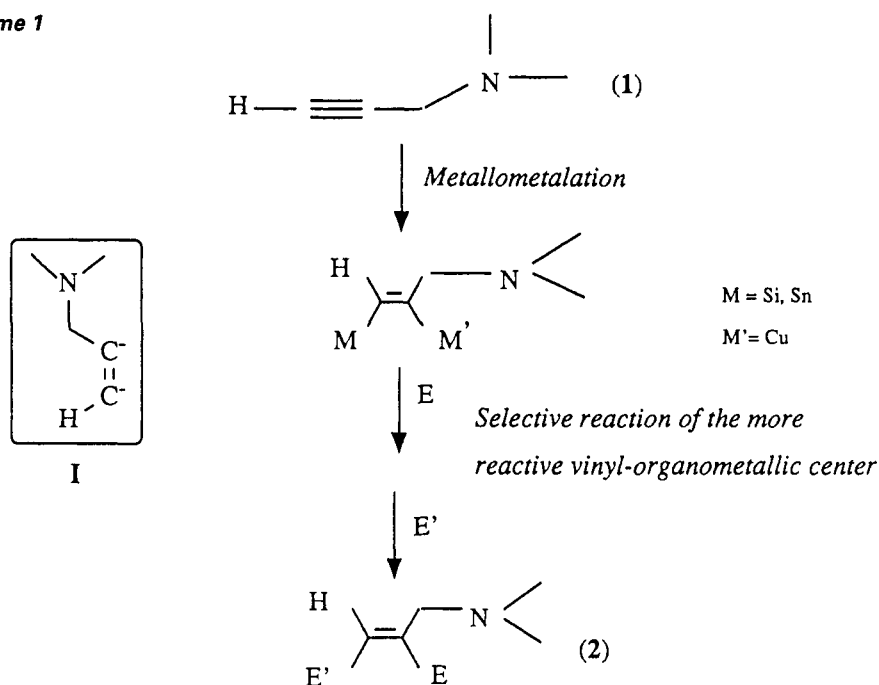
Recent work in our laboratories has been concerned with expanding the synthetic utility of metallometalation by applying this strategy to 1-alkynes bearing -NH_2 or -CO-SiR_3 functionalities as well as to previously unexplored simple organic molecules such as isocyanates. In this paper two selected areas of current interest will be described: a) Stereo- and regiocontrol in silyl- and stannylcupration reactions; b) Exploitation of the synthesis and of the synthetic potential of nucleophilic polysynthons for the development of new synthetic strategies.

(a) SILYL- AND STANNYL-CUPRATION OF N-CONTAINING UNSATURATED MOLECULES

(a1) Propargylamines

The silyl- and stannyl-cupration of propargylamines (**1**) performed employing $(Me_3Si)_2Cu(CN)Li_2$[2] and Bu_3Sn-$Cu(Bu)(CN)Li_2$[3] reagents, occurs easily[4,5] at low temperature (-23 °C) leading *(Scheme 1)*, in good to excellent yields, after quenching with a wide range of electrophiles, as the sole or largely predominant products, to (E)-3-(Trimethylsilyl)- and (E)-3-(Trimethylstannyl)-2-substituted-2-propen-1-amines (2), respectively, suitably protected at nitrogen.
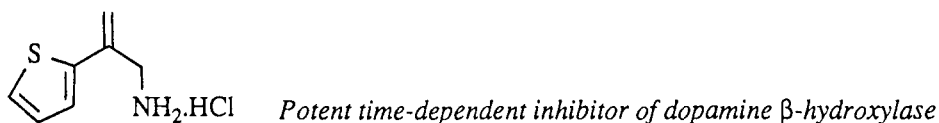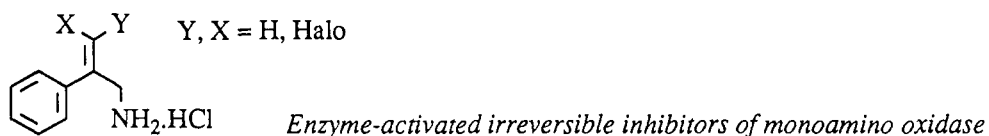
Scheme 1

$$H — ≡ — \diagdown N — \qquad (1)$$

↓ *Metallometalation*

$$\underset{M}{\overset{H}{\diagup}}\diagup — N\diagup\diagdown \qquad M = Si, Sn$$
$$M' = Cu$$

(Structure I boxed)

↓ E

Selective reaction of the more
reactive vinyl-organometallic center

↓ E'

$$\underset{E'}{\overset{H}{\diagup}}\diagdown — N\diagup\diagdown \qquad (2)$$

In this reaction one of the most important aspects which supports the previous findings of Fleming[6], turns out to be the inversion of regioselectivity in the addition of the reagents to the C≡C triple bond with respect to that observed by Corriu et al.[7] for the carbocupration of (1).

As the regiochemical outcome in metallometalation is influenced[1,8] by the catalyst employed, the metals used, the steric bulk of the alkyl groups in the bismetalloids and by the presence of suitable functional groups on the alkyne, an intimate interplay between steric effects exerted by the R_3Si and R_3Sn groups and coordination between Cu and N which might assist in stabilizing intermediate **a** in respect to **b**, could account for the high regioselectivity observed in *Scheme 1*.

(Intermediate structures **a** and **b** with δ⁺, δ⁻ labels, Cu, MR_3, R_3M)
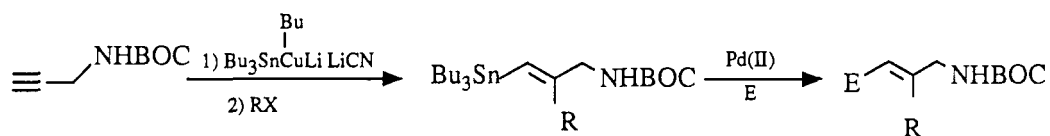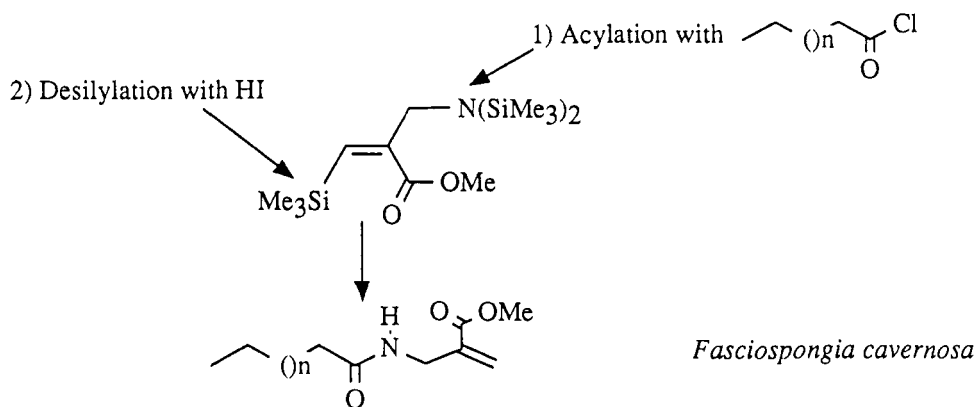
a   b

The metallometalation of propargylamines with silylcupration- and stannylcupration reagents, holds promise as a very convenient and general entry into the not easily accessible class of 2- substituted allylamines[9], which have recently given rise to a great deal of interest due to the presence of this function in many natural products[10] and as enzyme inhibitors[11].

$$\underset{}{\overset{X\diagdown\diagup Y}{}} \qquad Y, X = H, Halo$$
(phenyl ring, CH_2, $NH_2 \cdot HCl$)

Enzyme-activated irreversible inhibitors of monoamino oxidase

(thiophene ring structure with $NH_2 \cdot HCl$)

Potent time-dependent inhibitor of dopamine β-hydroxylase

Desilylation at position 2 can be performed without any difficulty according to the usual procedures by treatment with HI, whereas removal of the Bu_3Sn group is achieved with *Pd II* catalysis. In the latter case Pd-catalyzed cross coupling of the vinylstannane with suitable electrophiles would provide an easy access to allylamines functionalized at position 3.

Two examples are given in *Fig.1* to show how the above described synthetic protocol can be usefully applied to the synthesis of natural products[4] and to "building blocks" such as E,E-dienamines[5] of great interest in the synthesis of complex molecules[12] having biological activity.

Thus metallometalation of propargylamines provides an entry, via dimetallic intermediate adducts to the nucleophilic polysynthon (I) in which the differential reactivity of the two vinyl organometallic centers allows stepwise regio- and stereocontrolled functionalization with electrophiles.

Fasciospongia cavernosa

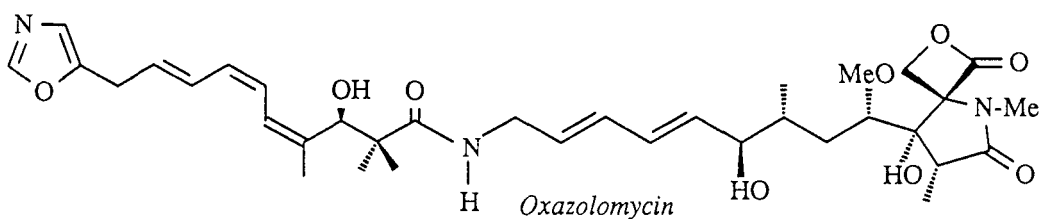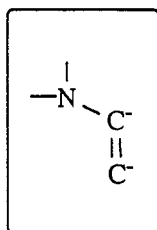| R	E	Pd(II) cat	Product	Yield
H	I_2	$PdCl_2(MeCN)_2$ (5%)	I⌒⌒NHBOC	98%
H	Ph⌒⌒I	$PdCl_2(MeCN)_2$ (5%)	Ph⌒⌒⌒NHBOC	89%
Me	⌒⌒COCl	$BzPdCl(PPh_3)_2$ (5%)	⌒⌒CO⌒⌒NHBOC	71%

Oxazolomycin

Fig. 1

(a2) Ynamines

A great deal of interest in the metallometalation of ynamines stems from the possibility of forming intermediate dimetallic adducts, related to the polysynthon (**II**), through which

(II)

selectively disubstituted enamines can be obtained. Once more the key point of the reaction lies in its regio- and stereochemical outcome.

In view of the exploratory character of this unprecedented reaction, N-ethynyl-N-phenyl-aniline (3) has been selected as the substrate of choice: addition of the trimethylsilylcupration reagent occurs[13] in a highly regio- and stereocontrolled fashion *(Scheme 2)* and only enamine (4) with E configuration bearing the trialkylsilyl group at the terminal position, is isolated in 75% yield after quenching with MeOH and a non-aqueous workup. The similarity encountered in the propargylamino and ynamino series confirms the general and determinant role played by the N heteroatom in driving the regiochemistry of addition of the dimetallic reagents.
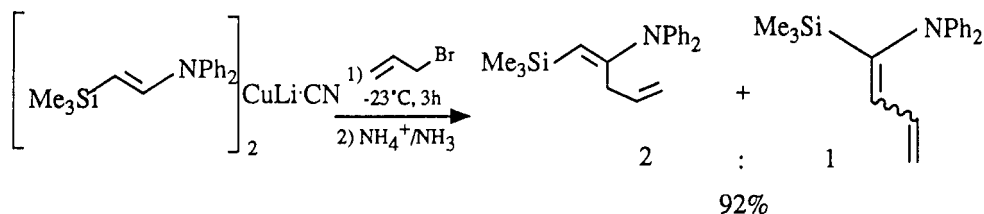
Scheme 2
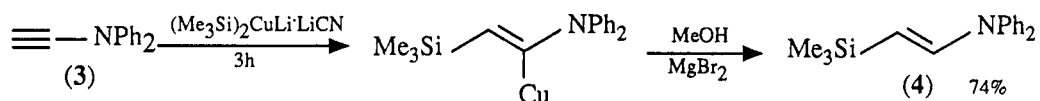
Quenching with representative electrophiles other than a proton, performed in order to further exploit the synthetic potential of (**II**), shows *(Table 1)* besides functionalization at position 2, easy removal of the Me_3Si group, which was not totally unexpected in view of the known tendency of the enamines to react with electrophiles at position 3 enhanced in this particular case by the presence of a good leaving group.

Table 1

	Ratio Ynam./E⁺	Reaction Product	
		Before the workup	After the workup
CH_3I	1:1		
CH_3I	1:2		
1) CO_2 2) Me_2SO_4	excess		

Interestingly the expected product from allylation of the intermediate cuprate *(Scheme 3)* slowly isomerizes to the dienammino derivative.

Scheme 3

92%

Noteworthy compounds in *Table 1* and in *Scheme 3*, contain combinations of a functionalized enamino skeleton with a reactive vinylsilane function or of a dienammino system with an allylsilane function which make them highly reactive and versatile "building blocks" whose synthetic potential is now being exploited in our laboratories.

(a3) Isocyanates

The interest in extending the previous findings related to the reactivity of ynamines and propargylamines coupled with preliminary observations showing a certain degree of unreactivity under normal conditions of nitriles and isonitriles prompted us to search for more reactive N-containing unsaturated compounds to be tested for the reactivity with silylcupration and stannylcupration reagents. Our choice fell on isocyanates whose high reactivity has been widely reported with a series of organic and organometallic derivatives. Furthermore the presence of the -N=C= and =C=O frameworks opens up interesting problems in terms of regio- and ·chemo-selectivity due to the different structures which might be generated.

Metallometalation of isocyanates has not been previously reported and amongst the additions of organometallic reagents hydrostannylation[14] appears to be the most important in connection with the present study. Even though stannylcupration of PhNCO **(5)** occurs at an appreciable rate under mild conditions without catalyst, attempts at isolating the reaction products after quenching met insurmountable difficulties due to the lability of the resulting stannylated derivative. On the other hand when PhNCO was subjected to trimethylsilylcupration in the presence of HMPA, after quenching with electrophiles, urea-type derivatives PhN(E)CO(E)NPh were isolated as the main products of the reaction probably arising from a competing side reaction of the dimetallic adduct with a second molecule of PhNCO. To overcome this difficulty and taking advantage of a recent literature report[15] dealing with the dramatic acceleration of the conjugate addition of organocuprates using the R_3SiX/HMPA system, addition of the trimethylsilylcupration reagent to PhNCO in the presence of equimolar amounts of Me_3SiCl was performed. This led[16] after quenching with representative electrophiles and non-aqueous workup *(Scheme 4)* to the N-substituted carbamylsilane **(6)** in 65-70 % yield.
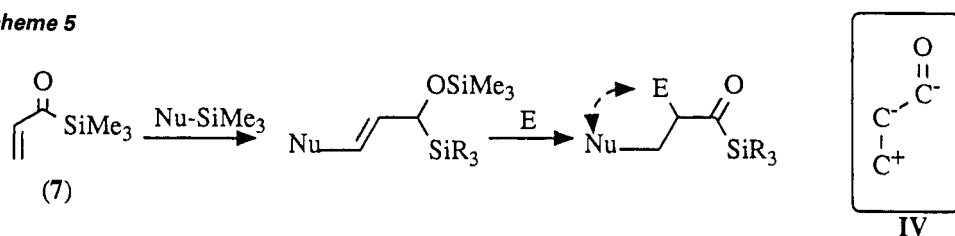
Scheme 4
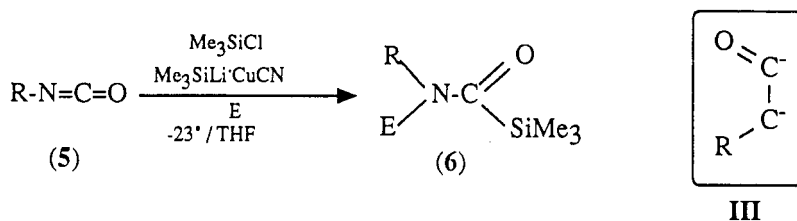
This chemistry which envisions a new useful route to the almost unknown class of carbamylsilanes[17] points out the possibility of obtaining, through metallometalation of **(5)**, the carbamyl polysynthon **(III)** whose chemistry is now being actively investigated.

### (b) CARBO-, SILYL- AND STANNYL CUPRATION OF α,β UNSATURATED ACYLSILANES

Further advances in the development of nucleophilic polysynthons start from the observation[18,19] that propenoylsilanes **(7)** *(Scheme 5)* and propynoylsilanes **(8)** *(Scheme 6)* undergo 1,4-conjugated Michael type addition with silylated nucleophiles without any added catalyst and under neutral and very mild conditions.

Scheme 5

In all cases the reactions turn out to be chemo- and regiospecific and highly (>95:5) stereoselective.
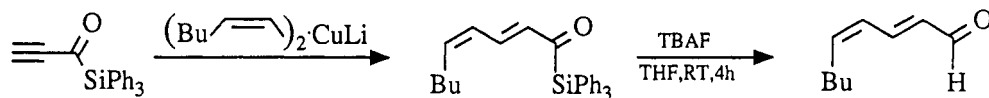
Scheme 6
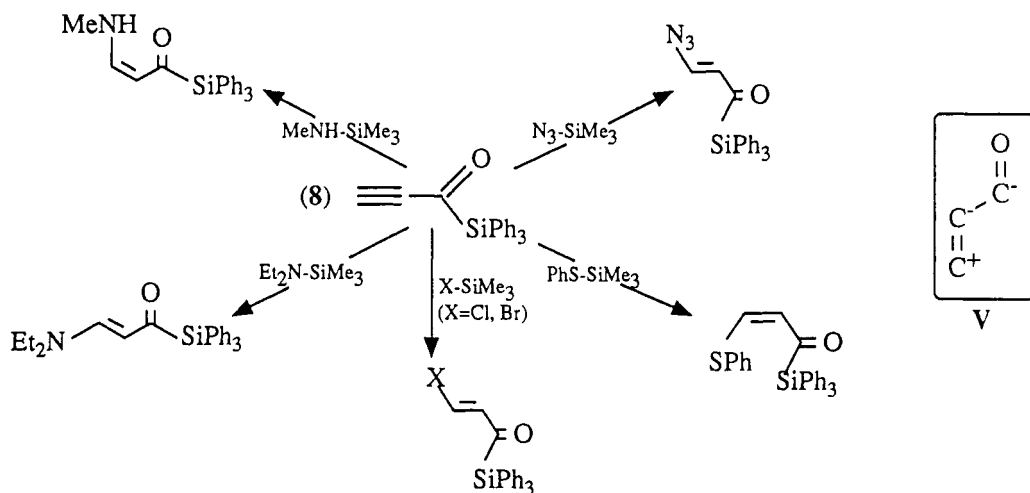
This behaviour makes compounds (7) and (8) synthetic equivalents of the polyfunctional synthons **IV** and **V** respectively.

Extension of this chemistry to organocuprates when applied to (8) exhibits the same regio-, chemo- and stereochemical outcome and can be usefully applied, with an appropriate choice of the organocopper reagent, for preparing a series of stereochemically defined and not easily accessible dienoylsilanes *(Scheme 7)*. Their synthetic equivalence to the corresponding aldehydes can be easily
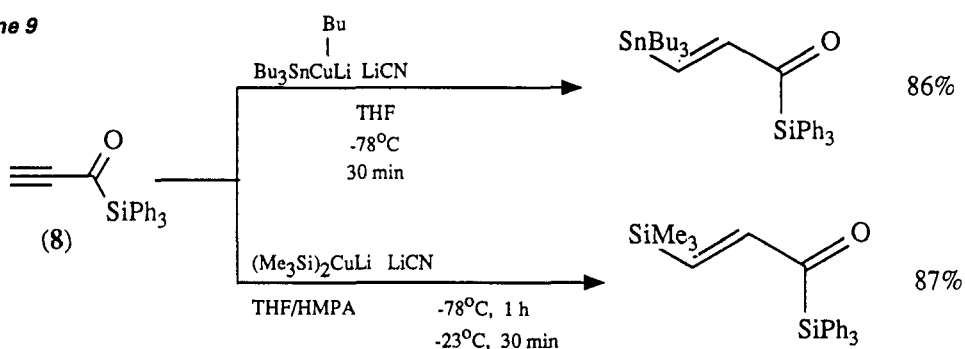
Scheme 7

exploited. This leads to a new route, highly competitive with respect to the most recent methods[20], for obtaining 99% stereochemically pure polyenals. Combination of this chemistry with the Wittig reaction results *(Scheme 8)* in a new exciting synthetic protocol[21] for the stereocontrolled synthesis of E,E,-dienes and E,E,Z-trienes starting from (8).

Scheme 8
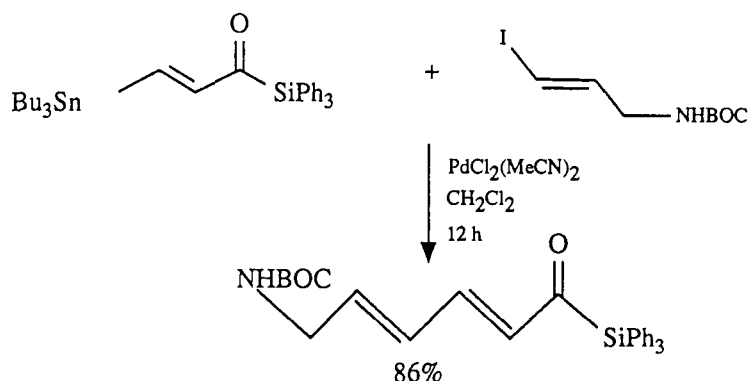

R = Bu, Bu /==\ , ==\
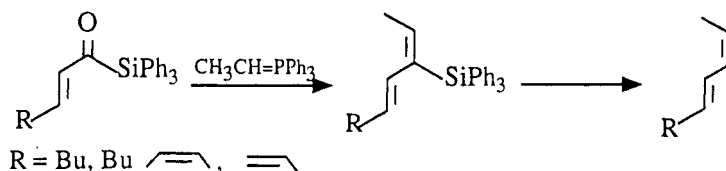
Silylcupration and stannylcupration reagents add equally well to (8) according to *Scheme 9*.

Scheme 9

The formation of a new vinyl organometallic center at C-4, allows further functionalization at this position particularly in the case of the stannylated derivative *(Scheme 10)*.

Scheme 10

In situ quenching of the intermediate mixed cuprate with electrophiles other than protons, gives rise *(Scheme 11)* to very efficient substitution at position 2 of the enoylsilane moiety leaving the vinylstannane function unaffected. This approach leads, amongst others, to 1,3-diketones of high synthetic interest. According to the above results reaction of (8) with metallometalation reagents

Scheme 11

E = COMe, COOMe, CH₂-CH=CH₂
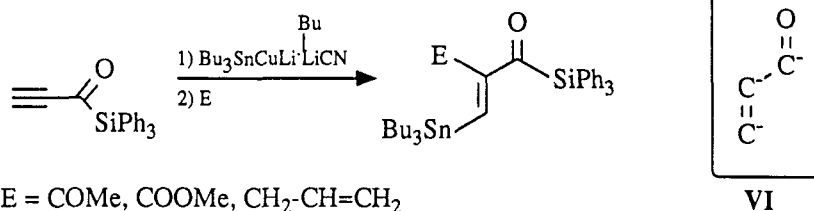
makes this acylsilane the synthetic equivalent of the polysynthon **VI** in which an *"umpolung"* of the charge at C 4 can be observed with respect to **V**.

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