

Allylsilanes and Vinylsilanes from Silylcupration of Carbon–Carbon Multiple Bonds: Scope and Synthetic Applications

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ABSTRACT

Silylcupration of multiple bonds (allenes, acetylenes, dienes, and styrenes) has become one of the most efficient procedures for the synthesis of vinyl- and allylsilanes. These substrates are useful building blocks in organic synthesis since they undergo a great variety of silicon-assisted transformations. The methodology reported has been widely used in the synthesis of different natural products, as well as in the construction of carbo- and heterocycles. In this Account, we wish to illustrate our contribution to this field, as well as to highlight the contributions of others.

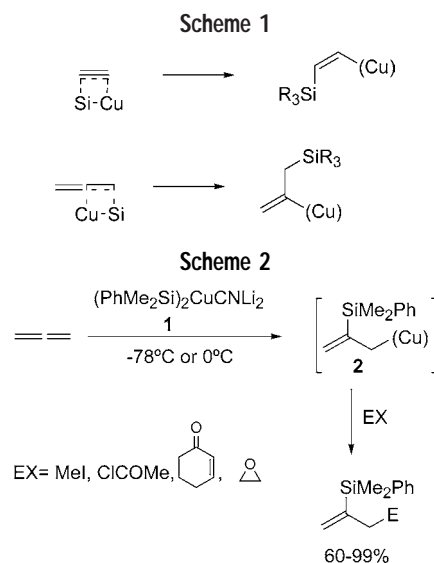
Introduction

Organosilanes are interesting building blocks in organic synthesis due to the large number of transformations that the C–Si bond can undergo.¹ Among them allyl- and vinylsilanes have gained considerable importance as usual synthetic intermediates. Over the last few decades considerable effort has been made to find new routes for the preparation of these derivatives and for their selective reaction with different electrophiles.

Silylmetalation of multiple bonds is one of the most attractive strategies for the efficient synthesis of these compounds.² In particular, the silylcupration of allenes and acetylenes provides an easy entry to the synthesis of

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Francisco J. Pulido was born in Madrid and grew up in Valladolid. He did his undergraduate career of chemistry at the historical University of Valladolid, where he got the doctoral degree in 1979 under the supervision of Professor Angel Alberola. He then was awarded with a Fulbright postdoctoral fellowship, working with Professor Gilbert Stork at the Columbia University during 1982–1983. Later, in 1985, he joined Ian Fleming's research group at Cambridge University supported by a NATO grant. In 1984, he received his tenure at the University of Valladolid (UVA). Soon after, he was promoted to Associate Professor at the UVA where he began his independent scientific research. His interests are the development of new synthetic methodologies in organometallic chemistry and the application of organosilicon and organotin compounds to the synthesis of natural products. He also enjoys teaching organic chemistry to undergraduate and postgraduate students.



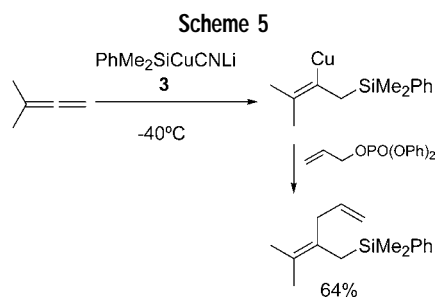
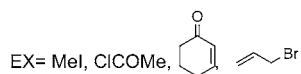
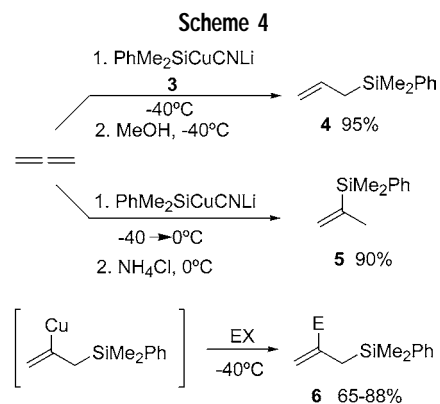
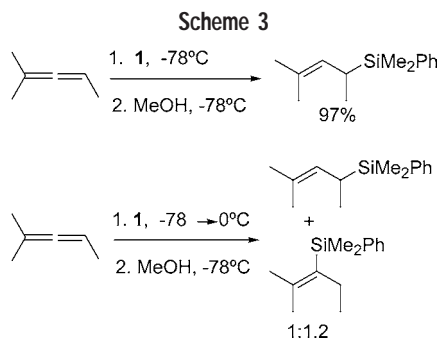
allyl- and vinylsilanes since it allows the introduction of two different metals (Si and Cu) across a C–C multiple bond (Scheme 1). The regio- and stereochemistry of these processes have been abundantly studied and are very well established.

Silylcupration of C–C Multiple Bonds

It has been shown that the silylcupration of allenes occurs syn stereospecifically³ (Scheme 1) giving rise to the formation of intermediate cuprates, which react with electrophiles to afford either vinyl- or allylsilanes. The regiochemistry of the addition depends on various factors such as the nature of the cuprate, the substitution of the allene, the temperature of the reaction, and the nature of the silyl group. Thus, the reaction of 1,2-propadiene with higher order silylcyanocuprates **1** containing the phenyldimethylsilyl group gives,^{4,5} at any temperature between -78 and 0 °C, a vinylsilane–allylcuprate intermediate **2**, which readily reacts with a wide variety of electrophiles leading to the corresponding vinylsilanes (Scheme 2).

The silylcupration of allenes was confirmed to be reversible from the experience with trimethylallene.⁵ Thus, when the reaction was carried out and quenched at -78 °C, the allylsilane derivative was obtained. Instead, when the intermediate was warmed to 0 °C for 1 h before quenching at -78 °C, the reaction gave a mixture of the allyl- and vinylsilane derivatives in an equimolar ratio (Scheme 3).

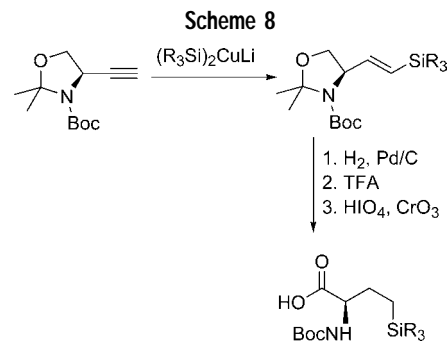
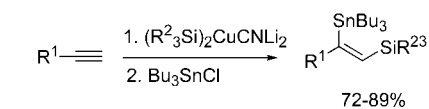
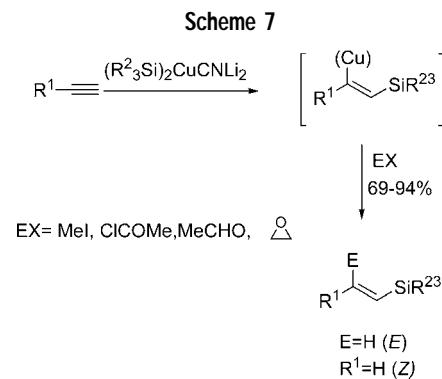
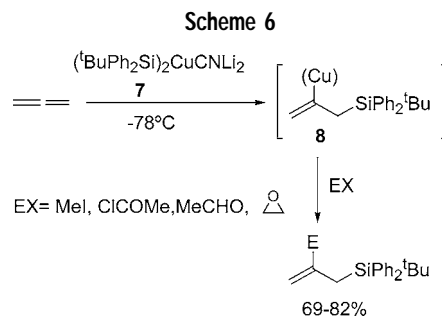
Noteworthy, the use of a lower order cuprate, the phenyldimethylsilylcuprate reagent **3**, in an analogous addition to allene provides a completely different regiochemistry pattern.⁶ The reaction now shows temperature dependence, giving allylsilane **4**, the kinetic product, at -40 °C and vinylsilane **5**, the thermodynamic product, at 0 °C, which again is accounted by the reversibility of the reaction. This result has great interest since it opens a route for the synthesis of functionalized allylsilanes **6**



(Scheme 4). Lately other authors have used our methodology with success in the synthesis of silylated 1,4-dienes,⁷ using allylic phosphates as electrophiles (Scheme 5).

Another factor that greatly influences the regioselectivity of the process is the steric hindrance of the silyl group attached to copper.⁸ Thus the reaction of the higher order cuprate $(^t\text{BuPh}_2\text{Si})_2\text{CuCNLi}_2$, **7**, with allene at -78°C gives rise to an allylsilane–vinylcuprate intermediate **8** where the bulky silyl group prefers the end of the allenic system (Scheme 6). Again the reaction seems to be reversible, since when the intermediate **8** was warmed to 0°C before quenching, the vinylsilane regioisomer was obtained selectively.

The metalcupration of triple bonds is also a powerful tool for organic synthesis. The silylcupration of acetylenes shows⁹ high regio- and stereoselectivity leading to *Z* or *E* vinylsilanes, where the Si is usually bonded to the less-substituted carbon of the multiple bond in a syn-addition process. A mechanistic approach to this process has been proposed that involves an oxidative addition step to yield Cu(III) species, followed by reductive elimination to give

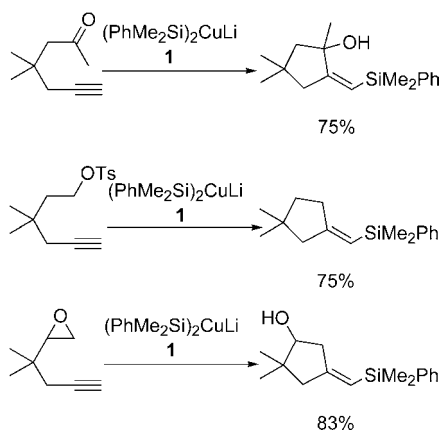


the vinylmetal intermediate. Special interest shows the preparation of bimetalated alkenes (disilylethylenes and silylstannylethylenes) using this methodology (Scheme 7).

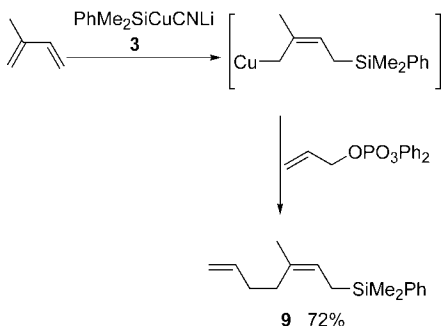
Silylcupration also works with 1-aminoalkynes,¹⁰ propargyl sulfides,¹¹ propargyl ethers,¹² and propargylamines,¹³ the latter used for the synthesis of saturated γ -silyl- α -amino acids (Scheme 8). Intramolecular trapping of the vinylcuprate intermediate allows the synthesis of methylenecyclopentanes.¹⁴ The substrates used for this silylcupration–ring formation have been ω -alkynyl tosylates, mesitates, ketones, and epoxides (Scheme 9).

Recently Bäckvall and colleagues have explored the silylcupration of terminal 1,3-dienes¹⁵ using our low-order cuprate **3** with excellent results. The regioselectivity of the reaction depends on the electrophile used, producing the products of 1,2-addition when the electrophile is carbon dioxide and the products of 1,4-addition when allylic phosphonates are employed. Thus, trapping of the intermediate cuprate with allylic phosphates provides a simple

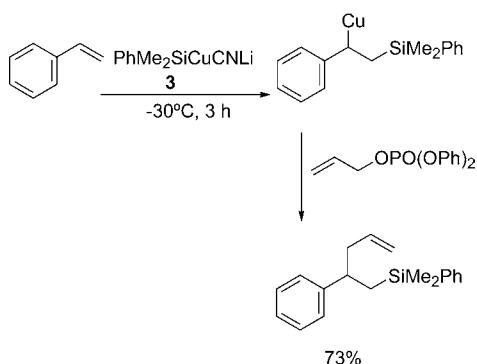
Scheme 9



Scheme 10



Scheme 11



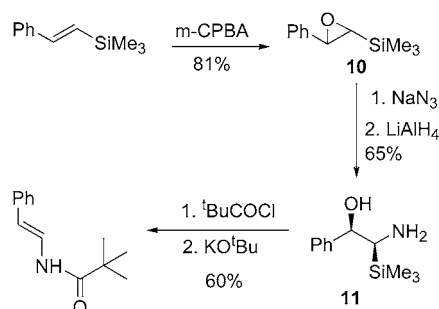
route for the synthesis of silylated 1,5-dienes **9** (Scheme 10), which are useful intermediates in organic chemistry.

The same authors have reported the silylcupration of substituted and unsubstituted styrenes,^{16a} though this reaction is much slower than that of acetylenes or allenes. The copper intermediate obtained can be easily trapped by different electrophiles, including allylic phosphonates. An anionic mechanism involving a copper(III) intermediate seems to be plausible^{16b} (Scheme 11).

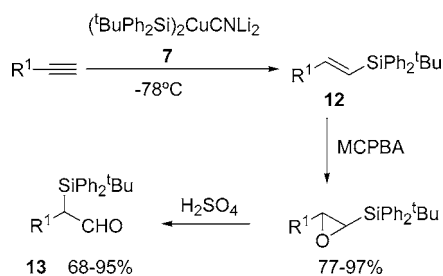
Synthetic Applications

The methodology reported so far establishes a simple and convenient route for the introduction of silicon in organic molecules, thus providing a useful entry to the synthesis of small silicon synthons of wide synthetic applications. The vinyl- and allylsilanes formed are extremely useful intermediates in organic synthesis.

Scheme 12



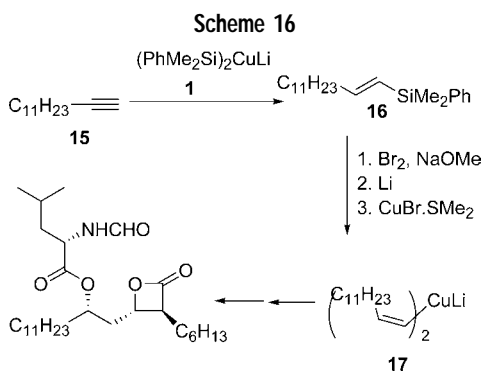
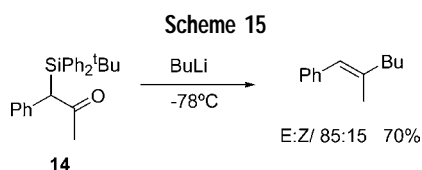
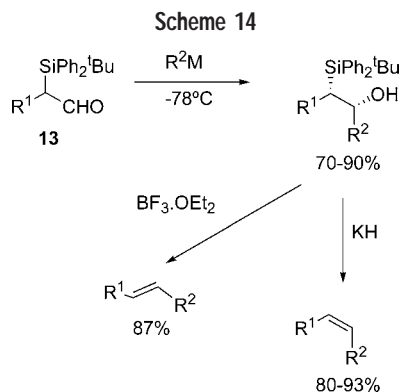
Scheme 13



Reactivity of Vinylsilanes. The stereochemistry of the enamide moiety of a potent cytotoxic agent (salicylhalamide) has been controlled¹⁷ using *E*-vinylsilanes obtained by silylcupration of alkynes. Silicon-directed ring opening of the silyl epoxide **10** with NaN_3 furnished, after reduction, amino alcohol **11** with high stereoselectivity. Reaction with pivaloyl chloride followed by Peterson elimination of the resulting β -hydroxysilane provided cleanly the *E*-enamide (Scheme 12).

Vinylsilanes containing the *tert*-butyldiphenylsilyl group¹⁸ **12** have been used in our group for the preparation of α -silyl-substituted aldehydes **13** and ketones **14**, compounds that play an important role as crucial structures in organic synthesis.^{19,20} The introduction of the bulky *tert*-butyldiphenylsilyl group α to a carbonyl group helps to overcome some of the difficulties associated with the lability of these compounds,²¹ since only α -silyl aldehydes bearing crowded silyl groups are stable enough to be isolated.²² Preparation of these compounds has been achieved in three steps involving silylcupration of acetylenes, epoxidation of the resulting vinylsilanes, and subsequent acid-catalyzed rearrangement of the corresponding epoxysilanes.^{23a} Experimental evidence indicates that the mechanism of the rearrangement involves cleavage of the C–O bond β to the silicon and migration of the silyl group^{23b} (Scheme 13).

One of the most interesting synthetic applications of these α -*tert*-butyldiphenylsilyl aldehydes **13** lies in their ability to get converted into *Z* and *E* alkenes.¹⁸ Thus, nucleophilic addition of organolithium and Grignard reagents to these carbonyl compounds provides β -hydroxysilanes, according to the Felkin–Anh model. The addition takes place with a high degree of diastereoselectivity to form exclusively anti- β -hydroxysilanes, which presumably is due to the bulkiness of the silyl group α to the aldehyde. The β -elimination step of the β -hydroxysi-



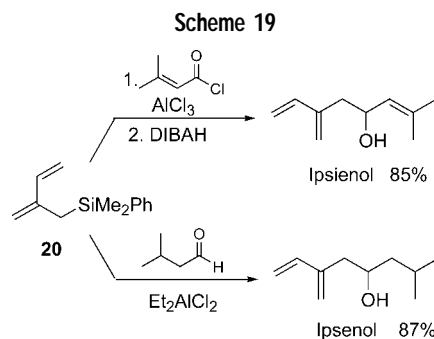
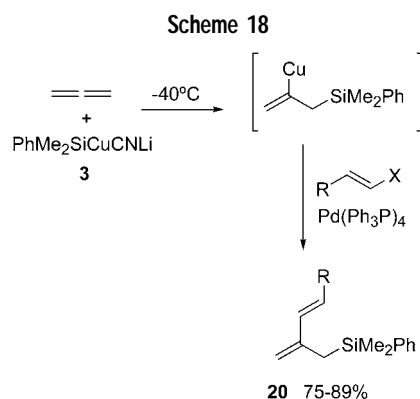
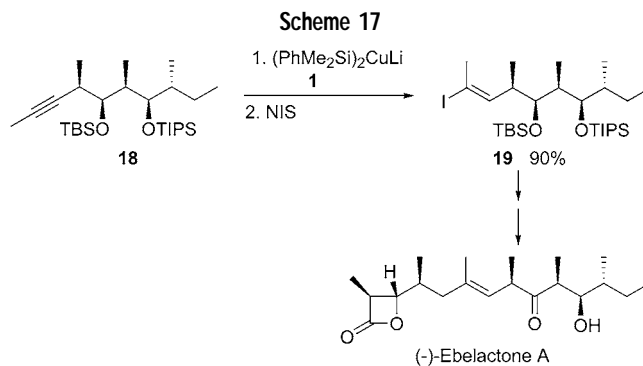
lanes under acidic or basic conditions, cleanly leads to *Z* or *E* disubstituted alkenes (Scheme 14).

The possibility of obtaining trisubstituted alkenes via reaction of β -*tert*-butyldiphenyl ketones **14** with organometallics has also been explored.¹⁸ This time, the isolation of the intermediate β -hydroxysilane is not possible because it undergoes “in situ” a syn β -elimination process. The stereoselectivity of the reaction with ketones **14** is lower than the corresponding reaction with aldehydes **13** but still favors the expected trisubstituted alkenes according to the Felkin–Anh model (Scheme 15).

Fleming et al. have used the silylcupration of alkynes to control the geometry of the double bond of an intermediate in the synthesis of (–)tetrahydrolipstatin.²⁴ A completely regioselective syn stereospecific silylcupration of the terminal alkyne **15** gave only the *trans* vinylsilane **16**, which was converted to the *cis* cuprate **17** by bromodesilylation and subsequent halogen–lithium exchange (Scheme 16).

Mandal has used the silylcupration of acetylene **18** to obtain the corresponding vinylsilane, which was converted²⁵ with retention of configuration into the vinyl iodide derivative **19**, which is an intermediate in the total synthesis of (–)-ebelactone A (Scheme 17).

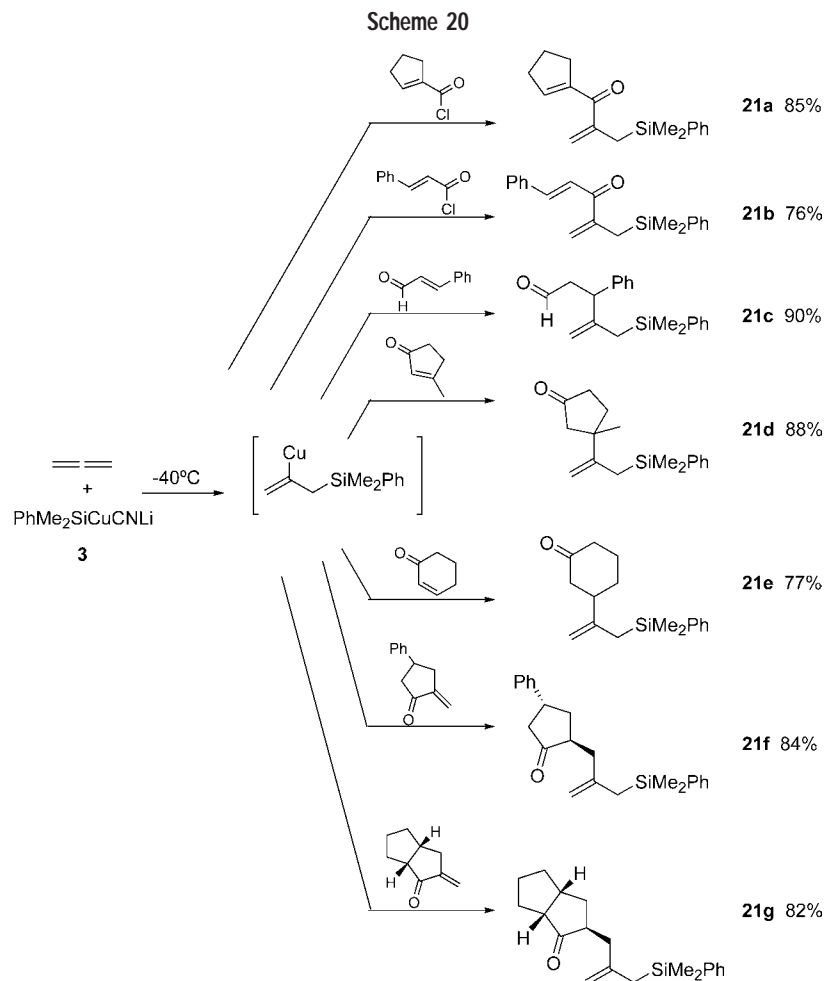
Reactivity of Allylsilanes. The construction of conjugated dienes in a single chemical step represents a particularly efficient approach to the synthesis of complex



molecular structures, since such systems are present in many natural pheromones. Although the coupling of two vinylic fragments has been well established using palladium-catalyzed reactions,²⁶ the direct coupling between an alkenylcopper and a vinylhalide has received little attention. In fact, Normant and co-workers²⁷ reported that lithium alkenylcuprates as well as alkenylcopper reagents showed little reactivity toward vinyl halides. Recently, we reported²⁸ the palladium-mediated coupling reaction of an allylsilane–vinylcopper reagent and alkenylhalides. This organocopper reagent, obtained by silylcupration of allenes, reacts in the presence of Pd(0) catalysts with vinylic halides, leading to silylated 1,2-dienes **20** with retention of configuration (Scheme 18).

Due to the known nucleophilicity of allylsilanes, the synthons thus obtained can be formally considered as synthetic equivalents of an isoprenyl anion²⁸ and thus used in the construction of terpenoid structures such as ipsenol and ipsdienol (Scheme 19).

The importance of five-, six-, and seven-membered rings in organic synthesis is exemplified by their being the structural core of a large number of biologically important



natural products and serving as target molecules for numerous synthetic studies. Thus, we have used allylsilanes as synthetically useful tools for the synthesis of methylenecyclopentanols and other related bi- or tricycles.

Silylcupration of allene followed by trapping of the allylsilane–vinylcopper intermediate with α,β -unsaturated acid chlorides and ketones provides an easy method of obtention of oxoallylsilanes **21c–g** or silylated divinyl ketones^{29,30} **21a,b** (Scheme 20). Oxoallylsilanes **21c–g** containing a nucleophilic allylsilane unit and an electrophilic carbonyl moiety undergo intramolecular allylsilane-terminated cyclization when treated with a Lewis acid,^{29,30} leading to methylenecyclopentanols **22c–g** (Scheme 21). Divinyl ketones **21a,b** undergo silicon-directed Nazarov cyclization when treated with TFA, leading to conjugate methylenecyclopentenones **22a,b**. Both methods are simple and efficient approaches to cyclopentane annulations. The cyclization reaction shows a high level of stereoselectivity in the formation of fused bi- and tricyclopentanols. This route allowed the preparation of derivatives of β -capnellene.³⁰

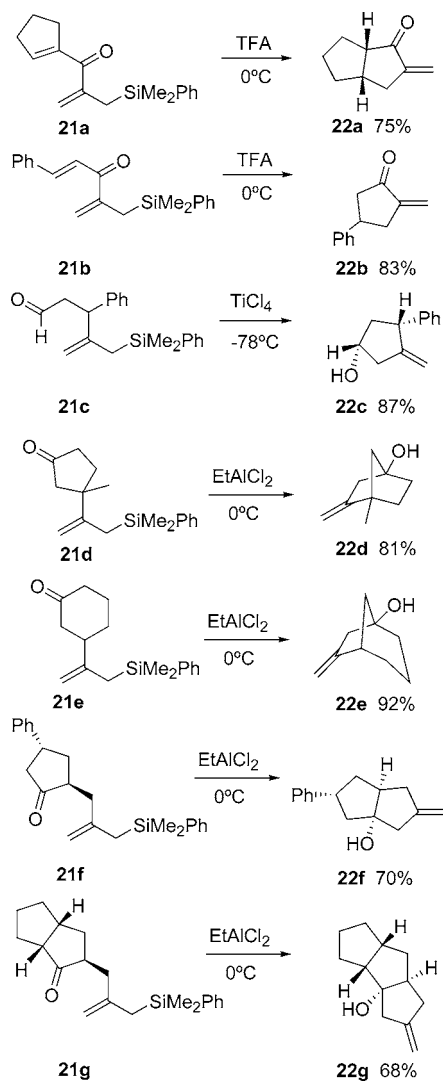
Moreover the synthesis of seven-membered hydroxycycloalkenes and seven-membered oxacycloalkenes has been achieved through intramolecular cyclization of allylsilanes³¹ **23a,b**, which were obtained by palladium-catalyzed intramolecular bis-silylation of optically active allylic alcohols (Scheme 22).

Ketones containing both an allylsilane group and a vinylsilane moiety **24** have been prepared in our laboratory through an interesting tandem diaddition process by silylcupration of allene and capture of the intermediate species with α,β -unsaturated nitriles.³² The silyldifunctionalized ketone results from consecutive diaddition (1,2 and 1,4) of the intermediate allyl- and vinylcopper species formed in the silylcupration of allene. The diadducts undergo selective intramolecular allylsilane-terminated cyclization, while the vinylsilane unit remains unchanged (Scheme 23).

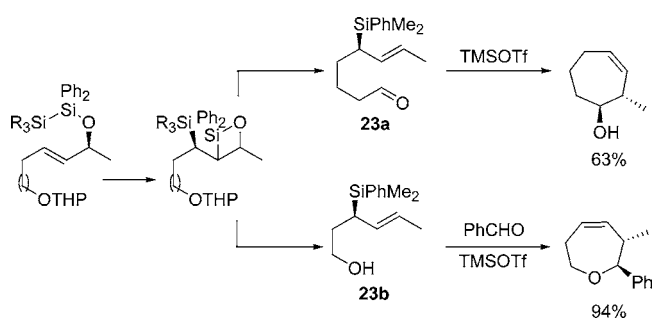
Traditionally strong Lewis acids, such as TiCl_4 , $\text{BF}_3\cdot\text{OEt}_2$, and SnCl_4 , have been used in the addition of allylsilanes to carbonyl compounds.³³ The use of metal triflates as catalyst in these reactions has also been described.³⁴ The development of new reagents with greater efficiency has attracted great interest. Thus, recently the use of iodine has been described as an efficient catalyst³⁵ for the allylation of aldehydes (Scheme 24).

Moreover, the chiral Lewis base-catalyzed allylation provides an excellent transfer of stereochemical information because the reaction proceeds through a closed assembly of the allylsilane, the aldehyde, and the chiral Lewis base.³⁶ The method has been applied³⁷ to the enantioselective synthesis of the serotonin antagonist (Scheme 25).

Scheme 21

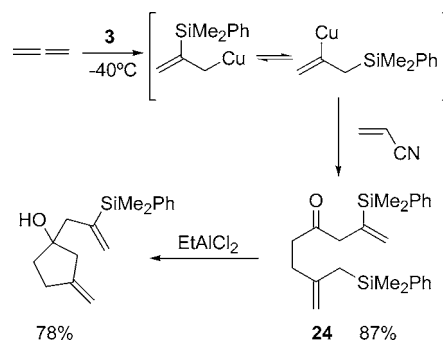


Scheme 22

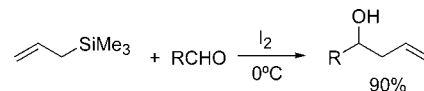


Oxoallylsilanes **25** are readily prepared by silylcupration of allene followed by addition of an α,β -unsaturated ketone. We have recently reported that oxoallylsilanes **25** containing the bulky *tert*-butyldiphenylsilyl group show two different reactivity patterns when subjected to intramolecular acid-catalyzed reaction.³⁸ The cyclization of oxoallylsilanes having a hydrogen β to the carbonyl group, **25a,b**, gives cyclopentenols **26**, which maintain the silyl group, probably through an intramolecular ene reaction involving the carbonyl unit and the allylic moiety. However the cyclization of β,β -disubstituted oxoallylsilanes,

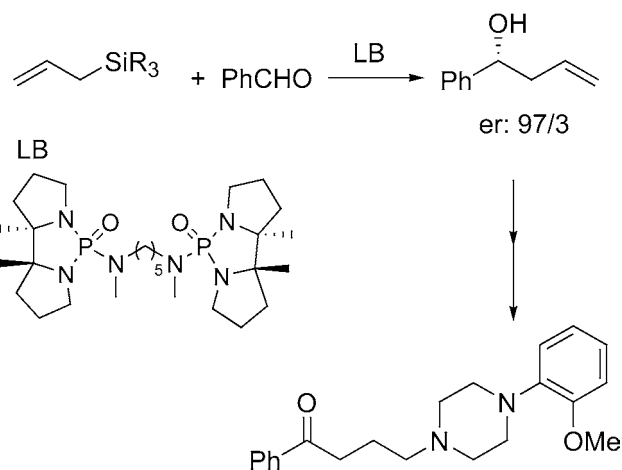
Scheme 23



Scheme 24



Scheme 25



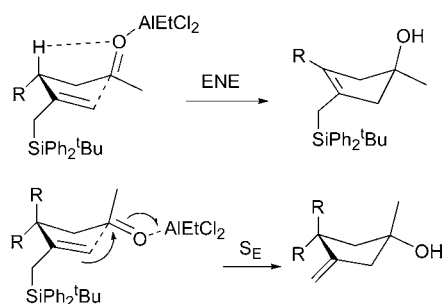
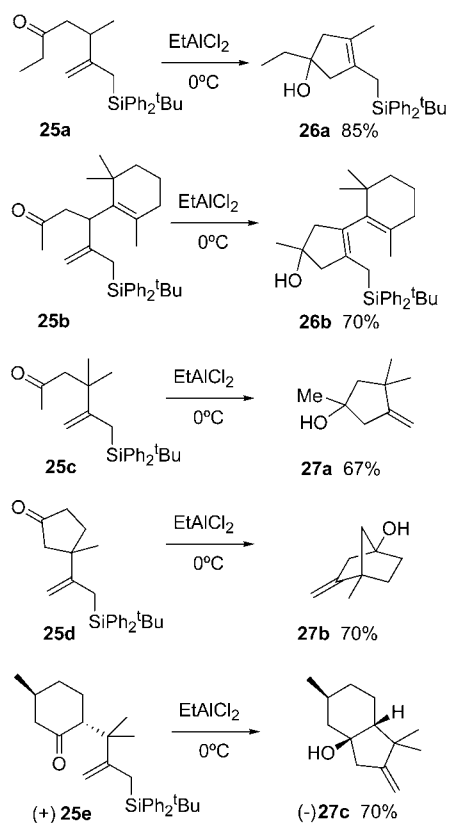
25c–e, proceeds through the normal S_{E} mechanism, losing the silyl group and leading to methylenecyclopentanols **27** (Scheme 26).

Angle et al. described³⁹ the synthesis of tetrahydropyrans via a formal 4 + 2 cycloaddition reaction of β -triethylsilyloxy aldehydes and allylsilanes. Under Lewis acid conditions, the activation of the carbonyl group is followed by addition of the allylsilane to form the β -silyl cation. Closure of the triethylsilyl ether on the cation via a six-membered transition state is more favorable than the attack of the Lewis acid-complexed alkoxide via a four- or five-membered transition state (Scheme 27).

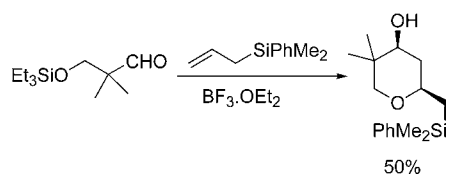
The same methodology has been applied to the synthesis of tetrahydrofurans using allylsilanes and aldehydes that contain one less carbon.⁴⁰ This stereoselective reaction (Felkin–Anh selectivity) has been used in the synthesis of the muscarine alkaloids (–)-allomuscarine and (+)-epimuscarine (Scheme 28).

Epoxyallylsilanes are easily obtained by silylcupration of allene followed by reaction of the intermediate cuprate with conjugated enones and further epoxidation (via sulfur-ylide) of the resulting oxoallylsilane. Despite its synthetic significance, the cyclization of epoxyallylsilanes has not been widely explored. It has been reported that the stabilization of the incipient charge in the Lewis acid-

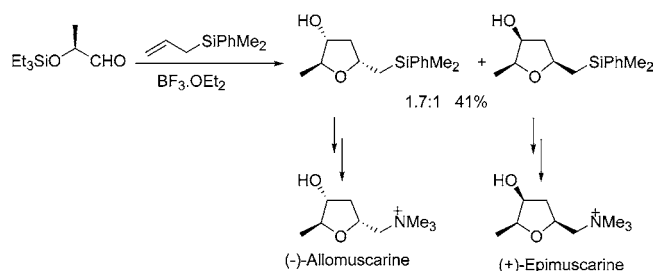
Scheme 26



Scheme 27

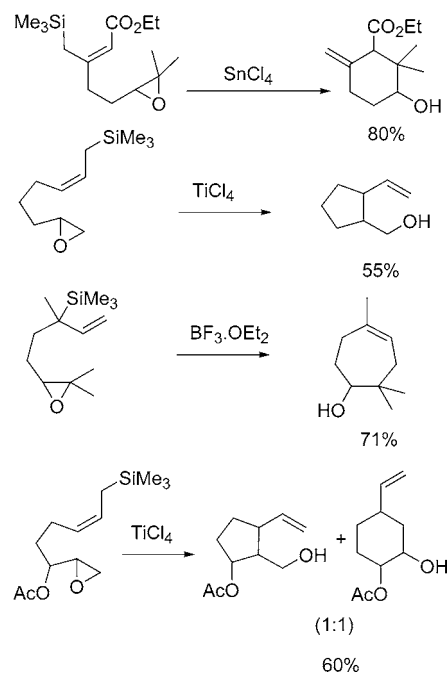


Scheme 28



mediated intramolecular process overrides entropic and stereoelectronic factors. Under Lewis acid conditions,

Scheme 29

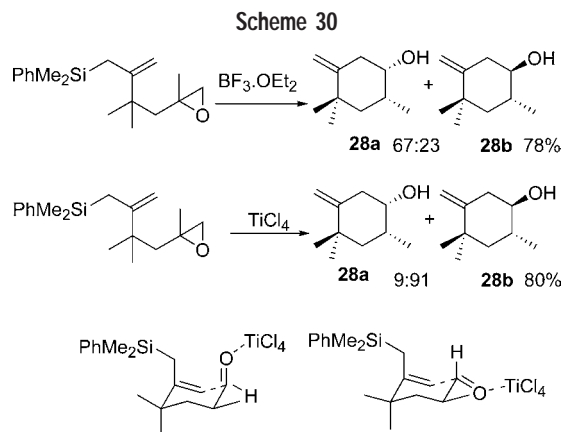


nucleophilic substitution usually takes place at the most substituted carbon center of the epoxide⁴¹ unless the presence of electron-withdrawing groups next to the epoxide destabilizes the developing carbocation⁴² (Scheme 29).

Recently, we showed that the nature of the substituents in the silyl group causes important modifications in the mechanism of these cyclization processes.⁴³ Thus, when the epoxyallylsilane contains the phenyldimethylsilyl group, the acid-catalyzed intramolecular reaction results in a rearrangement–cyclization process, which leads to methylenecyclohexanols **28a, b**, instead of the normal products of 5-exo or 6-endo attack.⁴⁴ The diastereoselectivity of the process depends on the Lewis acid used.⁴³ The preference for the cis isomer **28a** when boron trifluoride was used is due to the countercurrent flow of electrons in the Csp²-C(Si) and C=O bonds, which is favored when these structural elements are aligned parallel.⁴⁵ However the use of a bulkier Lewis acid such as titanium tetrachloride leads to the trans isomer **28b** as the major one, this result suggesting the intervention of a transition state with both the R and the carbonyl-LA groups in equatorial for minimal steric repulsions (Scheme 30). Work in progress on epoxyallylsilanes carrying the bulky *tert*-butyldiphenylsilyl group shows that Lewis acid-assisted cyclization occurs without losing the silyl group to give silylated cyclohexenols.

Conclusions

This report deals with the synthesis of functionalized allylsilanes and vinylsilanes by way of silylcupration of multiple bonds and capture of the intermediate cuprate with electrophiles. The vinylsilanes thus obtained have been used in multiple applications such as the synthesis of natural products (salicylihalamide, tetrahydrolipstatin,



and ebelactone A) and the stereoselective synthesis of disubstituted and trisubstituted alkenes. Allylsilanes prepared by silylcupration of allenes are useful intermediates in the synthesis of cycles with a potential synthetic interest (methylenecyclopentanols, methylenecyclohexanols, seven-membered cycloalkenes, tetrahydropyrans, and tetrahydrofurans). The reactions proceed under mild conditions and are highly diastereoselective.

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