Some Aspects of the Chemistry of Alkynylsilanes

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Abstract In amongst the considerable chemistry of acetylenes there lies some unique chemistry of alkynylsilanes (silylacetylenes) some of which is reviewed herein. This unique character is exemplified not only in the silyl protection of the terminal C–H of acetylenes, but also in the ability of the silyl group to be converted into other functionalities after reaction of the alkynylsilane and to its ability to dictate and improve the regioselectivity of reactions at the triple bond. This, when combined with the possible subsequent transformations of the silyl group, makes their chemistry highly versatile and useful.

1 Introduction
Alkynylsilanes (silylacetylenes) as referred to in this review are those wherein the silyl moiety is directly bonded to the sp-carbon of the C≡C bond. Alkynylsilanes such as propargylsilanes are, therefore, not included. Acetylene chemistry has been extensively reviewed over the years. Several of the more recent additions are noted here.¹

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A significant portion of the applications of silylacetylenes occurs where the silyl group, typically trimethylsilyl, serves as a group for the protection of the reactive terminal C≡C–H bond. Supporting this silyl-protection strategy is that both the introduction and removal of the silyl group can be accomplished in high yield under a variety of mild

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Key words alkenes, azides, cross-coupling, enynes, protecting groups, silicon, Stille reaction

1 Introduction

Alkynylsilanes (silylacetylenes) as referred to in this review are those wherein the silyl moiety is directly bonded

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conditions. The desilylation protocols are, in general, highly tolerant of other functional groups with the notable exception of silyl-protected alcohols. The reader will note several examples in this review where the silyl group basically provides a protective function, but has further synthetic potential. A further advantage of the terminal silylacetylenes is that the presence of the silyl group, for both steric and electronic reasons, can often influence the regio- and stereochemistry of reactions at the C≡C bond. This is most often reflected in cyclization reactions and it bears remembering that the regioselectively placed silyl group has the potential to be another group including hydrogen. Finally, the trimethylsilyl group has its own reactivity in the final product of a reaction at the C≡C bond. These often result in the generation of a vinylsilane unit, which can be further reacted under a number of conditions including protodesilylation to the parent alkene. Examples of these aspects of the chemistry are to be found throughout the review.

2 Safety

A report of an explosion using (trimethylsilyl)acetylene in an oxidative coupling under Glaser–Hay conditions was published. After a thorough investigation the cause of the explosion was attributed to static electricity between the syringe needle used to introduce the copper catalyst and a digital thermometer inside the flask and not the thermal instability of the silane. It is interesting to note that the trimethylsilyl group can impart stability to alkynyl systems. A good example of this is 1,4-bis(trimethylsilyl)buta-1,3-diyne, which shows excellent thermal stability compared to that of the parent buta-1,3-diyne.

3 Synthesis

A well-known and often used approach to silylacetylenes is via the straightforward acid-base metalation, typically with RMgX or n-BuLi (the base), of a terminal acetylene (the acid) followed by reaction with an appropriate chlorosilane or related reactive organosilane. As a specific example, 1-(triisopropylsilyl)prop-1-yne was prepared by lithiation of propyne followed by reaction with triisopropylsilyle triflate (Scheme 1).4

The direct trimethylsilylation of a terminal alkyne can be carried out in a single step with the combination of LDA and TMSCl at low temperature. This was applied to the synthesis of 1, which was used in a synthesis of complanadine A (Scheme 2).5

Marciniec and co-workers have demonstrated the direct silylation of terminal acetylenes using an iridium carbonyl catalyst and iodotrimethylsilane in the presence of Hüning’s base.6 The yields are excellent and the process works well for diynes and is tolerant of OH and NH2 groups, albeit these end up as their trimethylsilylated derivatives in the final product (Scheme 3).

A direct dehydrogenative cross-coupling of a terminal alkyne and a hydrosilane provided a convenient and simple route to silylacetylenes. Thus, reaction of a terminal acetylene and a silane with a catalytic amount of NaOH or KOH gave the desired silylacetylene in high yield with expulsion of hydrogen. The reaction of a variety of acetylenes with dimethyl(phenyl)silane showed excellent general reactivity for 25 examples (Scheme 4).7
4 Protodesilylation

Because trialkylsilyl groups are very commonly used to protect the terminal C–H of an acetylene, protodesilylation back to the parent acetylene is an important transformation. This can be accomplished under a number of mild reaction conditions. Among these is the simple reaction of (trimethylsilyl)acetylene derivatives with K₂CO₃/MeOH or, for more hindered silanes, TBAF/THF. Examples of these are to be found throughout this review. The selective protodesilylation of (trimethylsilyl)acetylene group in the presence of an (triisopropylsilyl)acetylene group with K₂CO₃/THF/MeOH illustrates the potential for selective protection/deprotection (Scheme 5).⁸

1,4-Bis(trimethylsilyl)buta-1,3-diyne was metalated with one equivalent of MeLi and reacted with acrolein and subsequently protodesilylated to yield vinyl diynyl carbinol 2. Transmetalation of 1,4-bis(trimethylsilyl)buta-1,3-diyne with five equivalents of MeLi and reaction with acrolein gave the diol 3 in excellent yield.⁹ These key intermediates were carried forth in syntheses of (+)- and (−)-falcarinol and (+)- and (−)-3-acetoxyfalcarinol (Scheme 6).⁹

5 Sonogashira Reactions

Of the many reactions at the terminal C–H of simple silylacetylenes, the Sonogashira reaction stands among the most important, where it has proved to be a very important synthetic entry into arylacetylenes and conjugated enynes.¹⁰ These approaches typically make use of the Pd-catalyzed protocols employed in most cross-coupling reactions. The Au-catalyzed use of silylacetylenes in Sonogashira cross-coupling reactions has been reviewed.¹¹

Under the standard Sonogashira reaction conditions the C–Si bond does not react thus providing excellent protection of this position along with adding more desirable physical properties. Moreover, it provides an excellent entry into a variety of substituted silylacetylenes. Though the silyl group nicely provides protection of a terminal position in the Sonogashira cross-coupling, under modified conditions wherein the silyl group is activated, a Sonogashira-type conversion at the C–Si bond is possible, thus providing an alternative to a two-step protodesilylation/Sonogashira sequence.

In an example of the use of the TMS group as a protecting group eventually leading to an unsymmetrically arylated system, 1-(trimethylsilyl)buta-1,3-diyne, prepared from 1,4-bis(trimethylsilyl)buta-1,3-diyne, was coupled with aryl iodide 4 to give the diyne 5, which was protodesilylated and further cross-coupled to give 6, a potential hepatitis C NSSA inhibitor (Scheme 7).¹²
Modest yields of symmetrical 1,4-diarylbuta-1,3-diyynes resulted from the Sonogashira reaction of an aryl bromide and (trimethylsilyl)acetylene followed by treatment with NaOH/MeCN. The reaction sequence was the combination of the Sonogashira cross-coupling and a Glaser coupling in a two-step, single-flask operation. The second step did not require the further addition of catalyst. The reaction was tolerant of HO, CO₂H, and CHO functional groups (Scheme 8).¹³

![Scheme 8 Sonogashira arylation and homocoupling without prior desilylation](image)

The Beller group developed a copper-free protocol for the Sonogashira reaction with the more available and less costly aryl chlorides. Both (trimethylsilyl)acetylene and (triethylsilyl)acetylene reacted without loss of the silyl group. The key to the success of the reaction proved to be the sterically hindered ligand 7 (Scheme 9).¹⁴

![Scheme 9 Copper-free Sonogashira cross-coupling](image)

[3-Cyanopropyl(dimethyl)silyl]acetylene (CPDMSA, 8) was prepared and utilized in the synthesis of arene-spaced diacetylenes. The purpose of this particular silylacetylene was twofold, firstly it could be selectively deprotected in the presence of the (triisopropylsilyl)acetylene group and, secondly, it provided polarity allowing for a facile chromatographic separation of the key intermediates in the syntheses of the diethylacetylenes (Scheme 10). The arene groups were introduced via Sonogashira cross-coupling.¹⁵

![Scheme 10 Sonogashira cross-coupling and selective protodesilylation](image)

In a good example of the use of (trimethylsilyl)acetylene as a precursor to 1,2,4,5-tetraethynylbenzene, 1,2,4,5-tetraiodobenzene was reacted with (trimethylsilyl)acetylene under Sonogashira conditions to give 1,2,4,5-tetrakis[(trimethylsilyl)ethynyl]benzene. The trimethylsilyl groups were then converted into bromides with NBS in greater than 90% over the two steps. 1,2,4,5-Tetrakis(bromoethynyl)benzene was subsequently reacted with cyclohexa-1,4-diene to give 2,3,6,7-tetrabromoanthracene (Scheme 11).¹⁶

![Scheme 11 Formation of 1,2,4,5-tetraakis(bromoethynyl)benzene](image)

In related chemistry the direct ethynylation of tautomizable heterocycles under Sonogashira conditions without the need for conversion of the heterocyclic into an aryl halide was reported. These worked well for both (trimethylsilyl)acetylene and (triethylsilyl)acetylene (Scheme 12).¹⁷

![Scheme 12 Direct ethynylation](image)
tigated as an intermediate in a route to anthra[2,3-b:6,7-b’]difuran (anti-ADT). In this reaction the Sonogashira cross-coupling occurred selectively at the triflate leaving the bromine groups available. This route did not, however, result in a synthetic approach to the desired anthracene difuran. Success was realized via the Sonogashira cross-coupling of (trimethylsilyl)acetylene with 2,6-diacetoxy-3,7-dibromoanthracene followed by desilylative cyclization. The thiofuran analogue, anti-ADT, was prepared via cross-coupling of 9 with (trimethylsilyl)acetylene, iodine cyclization, and reduction. A Suzuki–Miyaura cross-coupling and protodesilylation gave the phenyl-substituted anti-ADT 10.

In an analogous manner the anti-diselenophene 12 was prepared from 11 in 62% yield over three steps (Scheme 14). The relatively simple and economical catalyst system of FeCl₃/N,N’-dimethylethylenediamine was used in the synthesis of 1-aryl-2-(triethylsilyl)acetylenes (6 examples, 40–90% yields). The reaction conditions were not mild, requiring 135 °C and 72 hours for completion (Scheme 15).

The Sonogashira reaction of several terminal alkynes with 1-fluoro-2-nitrobenzene gave 1-(2-nitrophenyl)-2-(triethylsilyl)acetylene. The use of (triethylsilyl)acetylene gave a considerably higher yield than other terminal alkynes. The TES group was not reacted further in this study (Scheme 16).
6 Cross-Coupling with the C–Si Bond

Hatanaka and Hiyama were the first to report the cross-coupling of (trimethylsilyl)acetylenes. This they accomplished with cross-coupling with β-bromostyrene to form conjugated enynes with TASF promotion. It bears mentioning that under the same conditions (trimethylsilyl)ethenes were cross-coupled in high yield with aryl and vinyl iodides (Scheme 17).

Tertiary 3-arylpropargyl alcohols reacted with bis(trimethylsilyl)acetylene under Rh catalysis to give the hydroxymethyl-enyne regio- and stereoselectively with loss of benzophenone and one equivalent of the starting aryl-ethynyl group as its TMS-substituted derivative. Under Pd catalysis this silylated enyne could be cross-coupled with an aryl iodide, which was converted into the alkylidene-dihydrofuran. The alkylidene-dihydrofurans thus prepared exhibited fluorescent properties (Scheme 18).

Seeking a practical entry into 1,4-skipped diynes as potential precursors to polyunsaturated fatty acids, the Syngenta group investigated the cross-coupling of 1-aryl- or 1-alkyl-2-(trimethylsilyl)acetylene derivatives with propargyl chlorides. Under the best conditions the reaction of a (trimethylsilyl)acetylene with a propargyl chloride gave the 1,4-skipped diyne under promotion with fluoride ion and CuI catalysis. The method avoids the need for protodesilylation to the parent acetylene, a requirement in other copper-catalyzed coupling protocols. The reaction failed with nitrogen-containing groups on the silylacetylene. The reaction proceeded well with 1-phenyl-2-(tributylistannyl)acetylene (70%) and 4-phenyl-1-(trimethylgermyl)but-1-yn-1-ene (90%) (Scheme 19).

Denmark and Tymonko demonstrated the cross-coupling of alkynyl(dimethyl)silanols with aryl iodides under promotion with potassium trimethylsilanolate (Scheme 20). This protocol avoids the typical necessity of fluoride ion promotion and the associated disadvantages of cost and low tolerance for silicon-based protecting groups. The alkynylsilanols were prepared in a two-step reaction sequence. Interestingly, a direct comparison of the reaction rates of hept-1-yne, hept-1-ynyldimethylsilanol, and 1-((trimethylsilyl)hept-1-ynyl under the potassium trimethylsilanolate promotion conditions showed the hept-1-ynyldimethylsilanol to be considerably faster than hept-1-yne and the 1-((trimethylsilyl)hept-1-ynyl to be unreactive. This strongly suggests a role of the silanol group in the cross-coupling. A similar experiment with TBAF promotion showed all three to react with the silanol derivative being the fastest. Under the same conditions 4-bromotoluene gave a 25% conversion showing the advantages of using iodoarenes. The TBAF-promoted cross-coupling of alkynylsilanols with aryl iodides had previously been shown.

The bis(trimethylsilyl)enyne 13 was nicely prepared via a Suzuki cross-coupling with 1-bromo-2-(trimethylsilyl)acetylene. The bis(trimethylsilyl)enyne 13 cross-coupled with aryl iodides in a sila-Sonogashira reaction to provide the silylated conjugated enyne 14. Similar cross-coupling reactions of bis(trimethylsilyl)enyne 13 with vinyl iodides led to 1,5-dien-3-ynes 15. Cyclic vinyl triflates also reacted well with bis(trimethylsilyl)enyne 13 to form 1,5-dien-3-ynes 16 (Scheme 21).
7 Stille Cross-Coupling

(Trimethylsilyl)acetylene was deprotonated and reacted with tributyltin chloride to give 1-(tributylstannyl)-2-(trimethylsilyl)acetylene (17) in good yield (Scheme 22).28

1-(Tributylstannyl)-2-(trimethylsilyl)acetylene (17) was prepared directly from (trimethylsilyl)acetylene and tributyltin methoxide in 49% isolated yield (Scheme 23).29

Scheme 22 Synthesis of 1-(tributylstannyl)-2-(trimethylsilyl)acetylene

Scheme 23 Alternative synthesis of 1-(tributylstannyl)-2-(trimethylsilyl)acetylene

The bis(silyl)enyne 19 was prepared by cross-coupling 1-(tributylstannyl)-2-(trimethylsilyl)acetylene (17) with vinyl iodide 18 in 75% yield. In another approach to this end in the same paper, vinylstannane 20 reacted with 1-bromo-2-(trimethylsilyl)acetylene and 1-bromo-2-(triisopropylsilyl)acetylene to give the bis-silylated conjugated enynes 21 in good yield (Scheme 24).30

Scheme 24 Stille cross-coupling reactions

1-(Tributylstannyl)-2-(trimethylsilyl)acetylene (17) was cross-coupled with the highly substituted aryl bromide 24 in a synthesis of (±)-kibdelone A. The TMS group was re-
moved in 93% yield with AgNO₃·pyridine in aqueous acetone (Scheme 27).³³

Similarly to the Sonogashira reaction of (trimethylsilyl)acetylene, where the cross-coupling occurs at the C–H bond, the cross-coupling of 1-(tributylstannyl)-2-(trimethylsilyl)acetylene (17) occurs at the C–Sn bond rather than the C–Si bond. This was employed in the synthesis of the indole piece of sespendole (Scheme 28).³⁴

In an approach to the synthesis of lactonamycins, a model glycine was prepared wherein a critical step was the addition of an ethynyl group onto a highly substituted arene. Thus, bromoarene 25 was subjected to a Stille cross-coupling with 1-(tributylstannyl)-2-(trimethylsilyl)acetylene (17) to give the ethynylarene 26 in 91% yield. This compared favorably with a three-step sequence (Scheme 29).³⁵

In keeping with the common use of silylacetylenes as surrogates for the simple ethynyl organometallics, an ‘in situ’ process for the ethnylation of aldehydes was developed. In this chemistry a combination of ZnBr₂, TMSOTf, and Hüning’s base was used to generate the ethynylzinc reagent in situ and, along with a silylating agent, it was reacted with the aldehyde to generate the doubly silylated propargyl alcohol, which was O-deprotected with dilute hydrochloric acid (Scheme 33).³⁹

8 Reactions at the Terminal Carbon

Under a co-catalysis approach, (triisopropylsilyl)acetylene reacted with enones to form β-ethynyl ketones in high yields (Scheme 30). The reaction worked well with (tert-butyldimethylsilyl)acetylene and (tert-butyldiphenylsilyl)acetylene as well, although (triethylsilyl)acetylene gave only 40% yield. Under the same reaction conditions the non-silylated terminal acetylenes phenylacetylene and oct-1-yne gave alkyn oligomerization. An asymmetric version of the reaction, which gave good yields (5 examples, 53–93%) and acceptable ee (81–90%), was also presented.³⁶

Carreira and co-workers reacted terminal acetylenes including (trimethylsilyl)acetylene with aldehydes in the presence of (+)-N-methylephedrine to give the propargyl alcohol in high yield and high ee (Scheme 31).³⁷

The aldehyde 27 was reacted with (trimethylsilyl)acetylene under Carreira conditions to give a single diastereomer of 28, which was O-silylated followed by protodiisatation of the TMS group. This material was carried forth in a synthesis of hyptolide and 6-epi-hyptolide (Scheme 32).³⁸

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The aminomethylation of terminal alkynes was applied to a variety of acetylene derivatives including a single example with (triethylsilyl)acetylene, which provided the triethylsilylated propargyl amine in good yield. This was subsequently protodesilylated and the resulting propargyl amine converted into a mixed bis(aminomethyl)alkyne in a 49% yield over three steps (Scheme 34).40

(Triisopropylsilyl)acetylene was employed in a Ni-catalyzed, three-component reaction of the ethynylsilane, an alkyne, and norbornene. A variety of norbornene derivatives were reacted with good success. When (triisopropylsilyl)acetylene was used as the sole acetylene reactant, the bis(triisopropylsilyl)-1,5-enyne was produced. One example with a bicyclo[2.2.2]octene gave the corresponding product in only 12% yield when reacted with (triisopropylsilyl)acetylene (Scheme 35).41

(Trimethylsilyl)acetylene could be directly alkylated to give 1-(trimethylsilyl)dodec-1-yne in modest yield. The yield of this sole silicon example was comparable to the direct alkylation of other terminal alkynes (Scheme 36).42

9 Cross-Coupling with SilylethynylMagnesium Bromides

In a useful synthetic approach to alkynylsilanes (triisopropylsilyl)ethynylmagnesium bromide was cross-coupled with anisoles (23 examples 42–94% yield). In the cross-coupling of either 4-fluoroanisole or 4-cyanoanisole, the coupling of the F or CN substituent was favored over that of the methoxy group. The trimethylsilyl enol ether of cyclohexanone cross-coupled, as did 4,5-dihydrofuran. In one exam-
The TIPS group was removed with TBAF/H₂O and the resulting acetylene cross-coupled in a Sonogashira reaction to the diarylacetylene (Scheme 37).43

The bromomagnesium reagents of (triisopropylsilyl)acetylene (32) and (tert-dimethylsilyl)acetylene were cross-coupled with primary and secondary alkyl iodides and bromides in a Sonogashira-type reaction employing the iron complex 33. The reaction was tolerant of ester, amide, and aryl bromide groups (6 examples, 69–92% yield, 2 examples with TBS, both 83% yield). The free radical nature of the reaction was shown by the cross-coupling/cyclization of 34 (Scheme 38).44

The synthesis of 2-alkylated ethynylsilanes was accomplished via a FeBr₂-catalyzed coupling reaction between a silylethynylmagnesium bromide reagent and a primary or secondary alkyl halide. This nicely broadens the scope of entries into 2-alkylated ethynylsilanes (Scheme 38).45

The Pd-catalyzed phenylation of 1-iodo-2-(trimethylsilyl)acetylene in a Kumada-type coupling reaction illustrated the potential of this route to 1-aryl-2-silylacetylenes. Numerous non-silicon terminated iodoalkynes were similarly arylated (Scheme 40).46

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1-Iodo-3-(trimethylsilyl)acetylene was converted into (trimethylsilyl)ynamide 40, which was subsequently prodesilylated and the parent ynamide then converted into the iodoynamide. In a more practical approach, (trimethylsilyl)acetylene and (triisopropylsilyl)acetylene were reacted in a two-step, single-flask protocol with NBS
and a secondary amine to prepare the corresponding silylated ynamide. The silylated ynamides were subsequently reported to be excellent precursors to highly substituted indolines (Scheme 41).

Danheiser and Dunetz were able to prepare ynamides from bromo- and iodoacetylenes, including 1-bromo-2-(trimethylsilyl)acetylene and 1-bromo-2-(triisopropylsilyl)acetylene. This work complements other approaches to substituted acetylenes. The protocol was extended to include cyclic carbamates, ureas, and sulfonamides, but not with silyl-substituted acetylenes. The key to the success of the reaction was the pre-formation of the amidocopper intermediate. The resulting functionalized silylacetylenes could be readily protodesilylated to the parent alkyne (Scheme 41).

The zinc reagent from 41 was reacted with either 1-iodo-2-(trimethylsilyl)acetylene or better with 1-bromo-2-(trimethylsilyl)acetylene to form 2-amino-5-(trimethylsilyl)pent-4-ynoate 42, which was subsequently protodesilylated and the parent acetylene cross-coupled to the 4-position of 43 in a total synthesis of the COPD (chronic obstructive pulmonary disease) biomarker, (+)-desmosine (44) (Scheme 42).

Under indium catalysis 1-iodo-2-(trimethylsilyl)acetylene was reacted onto the anomeric carbon of glycals to furnish the α-ethynyl-2,3-unsaturated-C-glycoside. Only a single example employing 1-iodo-2-(trimethylsilyl)acetylene was reported. The trimethylsilyl group was converted into the iodide in 90% yield; this was in turn used in the preparation of a C-disaccharide bridged by an ethynyl group (Scheme 43).

The advantages of the selective chemistry of different silyl groups was applied to the synthesis of tris(biphenyl-4-y)silyl (TBPS) terminated polyynes. Based on the findings that bulky groups on the termini of polyynes provide stability and calculations showing the TBPS group to have over twice the radius of the TIPS group, this group was investigated in the synthesis and stability of TBPS-terminated polyynes. The synthesis of the polyynes started with the reaction of lithium (trimethylsilyl)acetylide with tris(biphenyl-4-y)chlorosilane. Selective protodesilylation gave the...
TBPS-substituted acetylene, and NBS bromination gave 1-bromo-2-[(tris(biphenyl-4-yl)silyl)acetylene. This bromo derivative was cross-coupled with (trimethylsilyl)acetylene to give the mixed silylbuta-1,3-diyne, which was subjected to selective protodesilylation and homocoupling to give 1,8-bis[(tris(biphenyl-4-yl)silyl]octa-1,3,5,7-tetrayne in 77% over two steps. Iterations of these reactions were used to prepare the triyne 45 and hexayne 46 (Scheme 44).53

Scheme 44 Synthesis of polyynes

11 Cycloaddition Reactions

Silylacetylenes, like many alkynes, undergo an extensive variety of cycloaddition reactions. In many cases based on electronic and steric factors the silyl group can impart useful regio- and stereoselectivities in addition to the ability to chemically transform the silyl group to other useful functionalities.

11.1 Formation of Aromatic Rings

The tricyclization of alkynes to aromatic rings has long been recognized, as has the use of silylacetylenes in this practice. Silyl-protected arylacetylenes reacted with 2-(phenylethynyl)benzaldehyde under acid catalysis to produce the 2-aryl-3-silylnaphthalene in good yield. The TMS-protected arylalkynes resulted in the formation of 2-aryl-naphthalene with protodesilylation taking place under the reaction conditions. However, the more hindered TES-, TBS-, and TIPS-protected derivatives gave the corresponding 3-silylnaphthalenes allowing for the ICl ipso iodination of the silyl group to provide the iodonaphthalene for further elaboration via cross-coupling chemistry. The chemistry was applied to the synthesis of several highly encumbered polyaromatic systems (Scheme 45).54

Scheme 45 Cyclization to aromatic rings from arylacetylenes

The Rh-catalyzed reaction of (trimethylsilyl)acetylenes with cyclobutenols gave 1,2,3,5-tetrasubstituted benzenes with the trimethylsilyl group regioselectively positioned in the 2-position. No conversions of the trimethylsilyl group were carried out in this work (Scheme 46).55

Scheme 46 Cyclobutenol to a TMS-substituted arene

Methyl 3-(trimethylsilyl)propynoate was successfully employed in the synthesis of 2H-quinolizin-2-ones. In this approach the trimethylsilyl group conveniently served the purpose of protecting the acidic hydrogen of the parent terminal acetylene (Scheme 47).56

Scheme 47 Quinolizin-2-ones from methyl 3-(trimethylsilyl)propynoate

The cationic rhodium catalyst [Rh(cod)2]BF4/BIPHEP brought about the cyclotrimerization of (trimethylsilyl)acetylene and unsymmetrical electron-deficient acetylenes. Unfortunately, neither the stoichiometry nor the regioselectivity of the cyclization was optimal. Larger silyl groups tended to favor the addition of one of the silylacetylene moieties and two of the electron-deficient alkynes, whereas increasing the steric bulk of the electron-deficient...
alkyne resulted in the reaction of two equivalents of the silylacetylene. (Triisopropylsilyl)acetylene failed to react. Protodesilylation of a mixture of regioisomers was able to simplify the reaction mixture, but reaction with ICl gave a synthetically challenging mixture of isomers in modest yield (Scheme 48).57

The cyclotrimerization of ethyl 3-(trimethylsilyl)propynoate gave 47 as a single regioisomer in 92% yield (Scheme 49).58

Complete regioselection in the formation of 2-aryl-1,3,5-tris(silyl)benzene was realized in the Pd-catalyzed reaction of two equivalents of a terminal alkyne, including (trimethylsilyl)acetylene, and an equivalent of a β-iodo-β-silylstyrene. The nature of the silylstyrene proved crucial as trialkylsilyl (TMS, TES, TBS, Me2BnSi) groups gave poor yields and the phenylated silyl groups gave better yields, with the β-PhMeSi-substituted styrene proving optimal. Selective electrophilic substitution of the 5-(trimethylsilyl) group, para relative to the aromatic substituent, proved possible. In a demonstration of the potential synthetic utility of the highly silylated systems, a number of conversions of the silyl groups were carried out including protodesilylation, acylation, iodination, and Denmark cross-coupling. It is noteworthy that the iododesilylation of 48 was selective for the formation of 49 and that iododesilylation of a phenyl group from the Ph2MeSi group did not occur. Comparable selectivity was noted in the acetylation of 48 to 4-phenylacetophenone (Scheme 50).59

11.2 Diels–Alder Cyclizations

Silylacetylenes were shown to provide excellent regiochemical control in the cobalt-catalyzed Diels–Alder reaction with 1,3-dienes. In the unsubstituted case various (trialkylsilyl)- and (triphenylsilyl)acetylenes were reacted with 2-methylbuta-1,3-diene under cobalt catalysis. The regioselectivity was highly dependent on the accompanying ligand employed with CoBr2(py-imin) [py-imin = N-mesityl-1-(pyridin-2-yl)methanimine, 56] favoring the meta regiosomer 50 after DDQ oxidation to the aromatic derivative. On the other hand, the use of CoBr2(dppe) [dppe = 1,2-bis(diphenylphosphino)ethane] favored the para isomer 51. In addition a number of 1-(trimethylsilyl)alk-1-ynes were reacted with 2-methylbuta-1,3-diene. Here the yields were
very high, but the regioselectivity was less than that observed with the simple silylacetylenes. Of particular interest was the result from the reaction of 3-(trimethylsilyl)propargyl acetate with Danishefsky’s diene, 2-(trimethylsiloxy)buta-1,3-diene (Scheme 51).60

Scheme 51  Diels–Alder cyclization of silylacetylenes with 1,3-dienes

ICl/CH2Cl2 gave only 5% of the iodide 54, NIS/MeCN gave modest yields of the iodide in 5 cases, but the reaction was very slow and product decomposition led to purification difficulties. The combination of H2O2/ZnI2 gave modest yields, but again in a slow reaction that required further oxidation with DDQ for completion. Finally, the use of tert-butyl hydroperoxide with ZnI2 and K2CO3 was found to give high yields of the desired iodides (Scheme 52).61

Scheme 52  Diels–Alder cyclization to cyclic 1,4-dienes

The synthesis of aryl and vinyl iodides has taken on increased importance due to their facility as electrophilic partners in various cross-coupling reactions. Building on the Diels–Alder chemistry of butadienes with (trimethylsilyl)acetylenes, the Hilt group devised an efficient route to highly substituted aryl iodides wherein the TMS group served nicely to define the regiochemistry and provide the iodide functionality. The complete reaction sequence could be carried out in a single flask although considerable effort was placed on the oxidation/iiodination step. For example, 11.3 Formation of Heterocycles

The diynes 57 were subjected to cyclotrimerization with hex-1-yne; the TMS-substituted derivative (R = TMS) gave considerably better yields and regioselectivities than the protonated analogues (R = H). Interestingly, the application of this cyclotrimerization towards the synthesis cannabinoids employed the use of 3-(trimethylsilyl)prop-1-yne (instead of hex-1-yne), which showed clean regioselectivity to give 61 from 60. The bis(trimethylsilyl)arene 61 was protodesilylated to 62, which was carried through to cannabinol (63) (Scheme 53).62

Scheme 53  Cyclizations leading to cannabinoids

\[ R_{3}Si^{+} + \text{CoBr}_{2} (\text{py-imin}) (10 \text{ mol\%}) + \text{Fe powder} (20 \text{ mol\%}) + \text{Zn dust} (20 \text{ mol\%}) + \text{ZnI}_{2} (20 \text{ mol\%}) \]
\[ \rightarrow \text{TMS} + \text{TBS}, \text{TIPS}, \text{TBS}, \text{Ph}_{3} \text{Si} \]
\[ 80–92\%; 50\%: 51 = 92:8–96:4 \]

\[ R_{3}Si^{+} + \text{CoBr}_{2} (\text{dppe}) (10 \text{ mol\%}) + \text{Zn dust} (20 \text{ mol\%}) + \text{ZnI}_{2} (20 \text{ mol\%}) \]
\[ \rightarrow \text{TMS} + \text{TIPS}, \text{TBS}, \text{Ph}_{3} \text{Si} \]
\[ 72–93\%; 50\%: 51 = 4:93–8:92 \]

\[ R_{3}Si^{+} + \text{CoBr}_{2} (\text{py-imin}) (10 \text{ mol\%}) + \text{Fe powder} (20 \text{ mol\%}) + \text{Zn dust} (20 \text{ mol\%}) \]
\[ \rightarrow \text{TMS} + \text{TBS}, \text{Ph}_{3} \text{Si} \]
\[ 9\text{ examples: } 72–96\%; 52: 53 = 98:2–18:82 \]

\[ R_{3}Si^{+} + \text{TMS} \]
\[ \rightarrow \text{TMS} + \text{TBS}, \text{Ph}_{3} \text{Si} \]
\[ 72–96\%; 52: 53 = 98:2–18:82 \]

\[ R_{3}Si^{+} + \text{TMS} \]
\[ \rightarrow \text{TMS} + \text{TBS}, \text{Ph}_{3} \text{Si} \]
\[ 72–96\%; 52: 53 = 98:2–18:82 \]
Under strong base catalysis, 1-aryl-2-silylacetylenes were converted into oxasilacyclopentenes upon reaction with aldehydes or ketones. The reaction required that the silyl moiety contain a Si–H bond [SiHMe2, SiH(i-Pr)2, SiHPh2]. Among the catalysts investigated KOt-Bu was clearly superior, with fluoride ion sources tending to give more of the product of direct alkynylation of the carbonyl. Silylalkynylation of the carbonyl followed by base-catalyzed intramolecular hydrosilylation of the C≡C bond is proposed.

4-Methoxyphenyl- and 2-tolyl-substituted (dimethylsilyl)acetylenes on reaction with cyclohexanone gave only alkynylation of the ketone, but 4-fluorophenyl- and 4-(trifluoromethyl)phenyl-substituted (dimethylsilyl)acetylenes gave good yields of their respective oxasilacyclopentenes (8 examples, 48–87% yields). The oxasilacyclopentene 64 was shown to have synthetic utility as it could be oxidized, epoxidized, and cross-coupled all in good yield (Scheme 54).63

The reaction of 1-(methoxymethylsilyl)-2-phenylacetylene with propanenitrile oxide, generated in situ from 1-nitropropane and phenyl isocyanate, gave a mixture of 4- and 5-silylated isoxazoles favoring formation of the 4-silyl isomer. Acid hydrolysis of this mixture allowed isolation of the pure 4-dimethylsilanol derivative in 49% overall yield. In a similar manner the ‘in situ’ generated benzonitrile oxide reacted to give, after hydrolysis, the corresponding 4-silanol products. These silanols were subjected to Denmark cross-coupling protocols to take advantage of the position of the silyl group to introduce aryl substituents at the 4-position of the isoxazole. Unfortunately, in addition to the

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**Scheme 54** Oxasilacyclopentenes via cyclization with ketones

Cyclotrimerization of 65 (R = TMS) with 4-hydroxypentanenitrile gave the desired product regioselectivity, albeit in only 42% yield, this compared to 83% yield from the parent diyne 66 (R = H) (Scheme 55).64

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**Scheme 55** Cyclization of a silylated skipped diyne with a nitrile

 Whereas the Ru-catalyzed reaction of an internal alkyne, carbon monoxide, and an enone produced hydroquinones in a [2+2+1+1]-cycloaddition reaction, (trimethylsilyl)acetylenes reacted in a [3+2+1] fashion to form an α-pyrone, wherein the carbonyl and α-carbon of the enone provided three atoms. The resulting 3-(trimethylsilyl)-2H-pyran-2-ones were not elaborated further (Scheme 56).65,66

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**Scheme 56** Carbonylative cyclization with an enone

The reaction of 1-(methoxymethylsilyl)-2-phenylacetylene with propanenitrile oxide, generated in situ from 1-nitropropane and phenyl isocyanate, gave a mixture of 4- and 5-silylated isoxazoles favoring formation of the 4-silyl isomer. Acid hydrolysis of this mixture allowed isolation of the pure 4-dimethylsilanol derivative in 49% overall yield. In a similar manner the ‘in situ’ generated benzonitrile oxide reacted to give, after hydrolysis, the corresponding 4-silanol products. These silanols were subjected to Denmark cross-coupling protocols to take advantage of the position of the silyl group to introduce aryl substituents at the 4-position of the isoxazole. Unfortunately, in addition to the

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**Scheme 57** Cyclization to isoxazoles
cross-coupling reaction product, a considerable amount of protodesilylated isoxazole was also generated (Scheme 57).67

In a study involving the addition of 2-substituted pyridines with 3-substituted propargyl alcohols to give indolizines, 1-phenyl-3-(trimethylsilyl)prop-2-yne-1-ol was reacted with ethyl 2-pyridylacetate to give the TMS-substituted indolizine 69 (Scheme 58). The TMS group was not reacted further in this work.68

The acid-catalyzed reaction of 1-phenyl-3-(trimethylsilyl)prop-2-yn-1-ol with a series of primary amides gave 2,4-disubstituted 5-[((trimethylsilyl)methyl]oxazoles in excellent yields. The preferred Brønsted acid for this useful conversion was PTSA (Scheme 58).69

1-Alkyl- or 1-aryl-substituted 2-(trimethylsilyl)acetylenes were used as alternatives to terminal acetylenes in the synthesis of tetrahydropyridines (18 examples, 54–96% yield; dr 20:1). In this approach the presence of the trimethylsilyl group also facilitated the generation of an azomethine ylide, which could be further converted. Thus, reaction of an α,β-unsaturated imine with the 1-alkyl- or 1-aryl-substituted 2-(trimethylsilyl)acetylenes gave the dieynyl imine, which underwent an intramolecular aza-cyclization reaction. The resulting 2-silyl-1,2-dihydropyridine was reductively desilylated to the tetrahydropyridine, reacted with an alkyne to give a tropane derivative (7 examples, 48–83% yield, dr 15:1 to 20:1, or reacted via a desilylative electrocyclization to give a 2-azabicyclo[3.1.0] system (Scheme 59).70

The reaction of thioisotin with 1-(trimethylsilyl)prop-1-yne gave a single regioisomeric -3-(trimethylsilyl)-4H-benzo[b]thiophen-4-one in a decarbonylative cyclization process. The reaction with (trimethylsilyl)acetylene, however, provided a 6:1 mixture of regioisomers (Scheme 60).71

In an interesting cyclization N-(2-cyanophenyl)-N-phenylbenzamides were reacted with internal acetylenes to give quinolones. When 1-(trimethylsilyl)prop-1-yne was employed the trimethylsilyl group was placed on the 4-position with high regioselectivity as compared to that of the tert-butyl analogue (Scheme 61).72

The Ni-catalyzed [4+2] cycloaddition of an internal alkyne with an azetidin-3-one resulted in the formation of various piperidines. Interestingly, the (trimethylsilyl)acetylene derivatives employed showed reversed regioselectivity to those of the tert-butyl and trimethylstannyl analogues. Although the carbonyl and Boc groups were reduced with LiAlH₄, reactions of the trimethylsilyl group were not at-
tempted on these systems. When phenylacetylene derivatives were reacted, 1-phenyl-2-(trimethylsilyl)acetylene gave the same regioselectivity as 1-(trimethylsilyl)prop-1-yne, but 1-phenyl-2-(trimethylstannyl)acetylene and 1-(trimethylstannyl)prop-1-yne reversed their regioselectivity. A total of four different (trimethylsilyl)acetylene derivatives was investigated (Scheme 62).  

In an approach to complanadine A and various lycodine derivatives the Siegel group, 1,4-bis(trialkylsilyl)buta-1,3-diynes were used in a [2+2+2] cycloaddition strategy. Thus, the key intermediate cyanoalkyne 75 was prepared on a gram scale and reacted with three different 1,4-bis(trialkylsilyl)buta-1,3-diynes; 1,4-bis(trimethylsilyl)buta-1,3-diyne gave the best yield of the 2-alkynylated pyridine 76 when the reaction was carried out with CpCo(CO)₂ as catalyst. A small amount of the (trimethylsilyl)ethynyl group was protodesilylated upon silica gel chromatography and 76 was cleanly protodesilylated upon treatment with TBAF/THF to 77. Trimethylsilylation of the terminal alkyne 77 then provided alkynylsilane 78, which was subjected to the CpCo(CO)₂-catalyzed [2+2+2] cycloaddition with 75. This provided the undesired 2,2′-bipyriridine derivative in a modest 43% yield. After considerable study and effort it was found that modification of the cyanoalkyne 75 to the N-formyl-cyanoalkyne 79 and reaction with 78 with added triphenylphosphine and under very dilute 5 mM conditions gave an acceptable yield of the desired 2,3-bipyriridyl structure 80, which was protodesilylated and deprotected to complanadine A (Scheme 63). In model studies several 1-aryl-2-(trimethylsilyl)acetylenes were reacted with 75 to give the 2-aryl-3-(trimethylsilyl) cycloaddition products in low to modest yields. In none of these cases was the trimethylsilyl group reacted further. A facile conversion of 75 into lycodine was presented wherein the cycloadditions was carried out with bis(trimethylsilyl)acetylene followed by protodesilylation and deprotection in a 24% overall yield (Scheme 63).  

1,4-Bis(trimethylsilyl)buta-1,3-diyne is thermally stable and, therefore, serves as an excellent substitute for the thermally sensitive buta-1,3-diyne. It was employed in a [2+2+2] cyclization with the alkyne nitrile 75. The reaction was extended to 1-aryl-2-(trimethylsilyl)acetylenes, wherein the trimethylsilyl group dictated the regioselectivity to place the trimethylsilyl group on the 3-position of the
pyridine ring formed. The yields were modest, ranging from <5% to 62% over 9 examples (Scheme 63).5

11.4 Formation of 1,2,3-Triazines

A series of 1,4-disubstituted 1,2,3-triazines 84 was prepared in a one-pot, three-step sequence involving first a Sonogashira preparation of a 1-aryl-2-(trimethylsilyl)acetylene (Scheme 64).75

1-Aryl-2-(trimethylsilyl)acetylenes, readily formed via a Sonogashira reaction from (trimethylsilyl)acetylene, reacted with sodium azide and an alkyl bromide in a three-step, one-pot sequence to yield a desilylated 1-alkyl-4-aryl-1,2,3-triazole 85 or 86. The reaction took place via initial deprotection of the trimethylsilyl group followed by the [3+2] click cycloaddition. This represents a safe and scalable process for the formation of 1,4-disubstituted 1,2,3-triazoles (Scheme 64).76

The reaction of 1-(trimethylsilyl)alk-1-ynes with CuBr/Et3N served to directly prepare the alkynyl/copper reagent without prior desilylation. The resulting copper reagent underwent reaction with various azides to form the 1,2,3-triazines 87 in excellent yields. When the reaction was carried out with (trimethylsilyl)acetylene or (triisopropylsilyl)acetylene, the reaction occurred at the C–H terminus. TIPS- and TBS-terminated acetylenes failed to react (Scheme 64).77

The dichloropyridazine 88 was converted into the 1,2,3-triazole-fused pyrazinopyridazinedione 89 in a three-step sequence with ethyl 3-(trimethylsilyl)propynoate. The TMS group was lost in the last step of the sequence, but provides the desired regioselectivity in the azide click step of the sequence (Scheme 64).78

11.5 [2+3] Cycloadditions

The reaction of ethyl and methyl 3-(trimethylsilyl)propynoate with 2-formylphenylboronic acid under [Rh(OH)(cod)], catalysis gave 3-(trimethylsilyl)-1H-inden-1-ols 90 in high yield and with high regioselectivity. Similar results were realized with 2-acyclopentenylboronic acid. 1,4-Bis(trimethylsilyl)buta-1,3-diyne reacted with 2-formylphenylboronic acid to give the enyne 92 in high yield (Scheme 65).79

In a related approach 2-bromo- and 2-chlorophenylboronic acids underwent a carboxylative cycloaddition with various alkenes including (trimethylsilyl)acetylenes to give 1H-inden-1-ones; the reaction was catalyzed by RhCl(cod).80

With the exception of ethyl 3-(trimethylsilyl)propynoate, the regioselectivity was very high. 1H-Inden-1-ones were also formed via the reaction of 2-bromophenylboronic acid, a (trimethylsilyl)acetylene, and paraformaldehyde, although the reaction took longer and required a higher temperature (Scheme 65).80

Benzoyltrimethylsilanes reacted with (trimethylsilyl)acetylenes under Au catalysis to form indan-1-ones. Mechanistic studies showed that a migration of the acylsilyl group to the C=C bond occurred to form the 2-(trimethylsilyl)indan-1-one; the trimethylsilyl group was lost upon workup. On the other hand the more sterically hindered and stable benzoyl(tetrt-butyl)dimethylsilane gave the 2-(tetrt-butyldimethylsilyl)-substituted indanone. The reaction proceeds through the formation of the interesting 2-(trimethylsilyl)-substituted silyl enol ether (Scheme 66).81
11.6 Other Cycloadditions

A three-component co-cyclization involving ethyl cyclopropyldieneacetate, a 1,3-diene, and a heteroatom-substituted acetylene gave highly functionalized cyclohepta-1,3-dienes. The 1,3-dienes reacted at only one of the C=C bonds. When 1-(trimethylsilyl)deca-1,3-diene was reacted, the hexyl-substituted C=C bond was the one that reacted to give the cycloheptadiene ring. Protodesilylation provided the terminal acetylene with concomitant formation of the enone moiety. A competition experiment using equimolar amounts of ethyl cyclopropyldiene acetate, 1-ethyl-2-(trimethylsilyl)-1H-pyrole, and 1,4-bis(trimethylsilyl)buta-1,3-diene and hexadeca-7,9-diyne resulted in the reaction of the hexadecadiyne to the exclusion of the bis(trimethylsilyl)butadiyne (Scheme 67).

![Scheme 65](image1)

**Scheme 65** [2+3] Cycloadditions of silylacetylenes with 2-functionalized phenylboronic acids

![Scheme 66](image2)

**Scheme 66** [2+3] Cycloadditions of silylacetylenes with benzylicsilanes

![Scheme 67](image3)

**Scheme 67** Mixed diyne cyclization with ethyl cyclopropyldieneacetate

![Scheme 68](image4)

**Scheme 68** Formation of silylated fulvenes
ethynylation of the C≡C bond as the predominant pathway. The silylfurone was reductively complexed with Rh(III) to give the rhodium dimer 93 (Scheme 68). The reaction of a tertiary amine with methyl 3-(trimethylsilyl)propynoate gave addition of the amine to the C≡C bond and the formation of an allenato ion. This, in the presence of an arylaldehyde, gave predominantly bis-addition of the aldehyde with 1-(trimethylsilyl)prop-1-yne giving addition at the C–H terminus of the C≡C bond giving the rhodium dimer 93 (Scheme 68).83

12 Additions to the C≡C Bond

The Ru-catalyzed hydroacylation of 4-methoxybenzaldehyde with 1-(trimethylsilyl)prop-1-yne gave a mixture of isomeric trimethylsilyl dienol ethers 94 and 95.84 The reaction of a tertiary amine with methyl 3-(trimethylsilyl)propynoate gave addition of the amine to the C≡C bond and the formation of an allenato ion. This, in the presence of an arylaldehyde, gave predominantly bis-addition of the aldehyde resulting in two products 96 and 97: aliphatic aldehydes gave addition at the C–H terminus of the C≡C bond to give 98. No reaction occurred with ethyl but-2-ynoate indicating that the trimethylsilyl group was essential (Scheme 69).85

(Trimethylsilyl)acetylenes were reacted under Ni catalysis with phthalimides to give decarboxylation and alkylation of one of the carbonyl groups. Although the reaction appears to be potentially general, all but two of 11 examples were with N-(pyrroolidino)phthalimide. The use of a catalytic amount of the strong and sterically demanding methylaluminum bis-(2,6-di-tert-butyl-4-methylphenoxoide) (MAD) was crucial in the success of the reaction. In the absence of MAD the major products were isoquinolones. Various 1-alkyl and 1-aryl-substituted (trimethylsilyl)acetylenes were utilized and gave the E-isomer as the product, but only 1-phenyl-2-(trimethylsilyl)acetylene and 1-(4-methoxyphenyl)-2-(trimethylsilyl)acetylene gave mixtures of Z- and E-isomers. Two additional examples of reactions where the silyl groups were PhMe2Si and TBS were successful, albeit in lower yield. Two internal alkynes failed to react indicating that the presence of the TMS group is necessary for the reaction (Scheme 70).86,87

The olefination of ynolates was accomplished with 3-silylpropynoates giving excellent selectivity for the E-eneyne. Ag-catalyzed cyclization of the resulting enynes was carried out to give either the 5-exo-tetronic acid derivatives or the 6-endo-pyrones. The triethylsilyl-tetronic acid 99 was stereoselectively converted into the corresponding iodide 100, which was in turn subjected to phenylation via a Suzuki cross-coupling and to ethynylation via Sonogashira cross-coupling (Scheme 71).88

A series of silylated propargylic alcohols was prepared via the straightforward reaction of a lithiated silylacetylene and a variety of aromatic and aliphatic aldehydes and ketones. These silylated propargylic alcohols were then subjected to the Meyer–Schuster rearrangement to give acylsilanes; propargyl alcohols derived from aromatic aldehydes underwent the rearrangement in good yield under catalysis with either PTSA·H2O/n-Bu4N·ReO4 or Ph3SiOReO3. The PTSA·H2O/n-Bu4N·ReO4 system did not work for electron-donating aryl systems, though the Ph3SiOReO3 catalyst worked well for these. Propargyl alcohols derived from alip-
phatic aldehydes failed to give acylsilanes with the exception of pivaldehyde. Propargylic alcohols derived from diaryl ketones gave either indanones or acylsilanes (Scheme 72).\textsuperscript{89}

A one-step hydroiodination of 1-aryl-2-silylacetylenes to the vinyl iodide, highly useful substrates for cross-coupling applications, was found to occur upon treatment of the 1-aryl-2-silylacetylenes with iodotrimethylsilane. The reaction sequence of a Sonogashira cross-coupling of (trimethylsilyl)acetylene and an aryl halide followed by the hydroiodination resulted in a facile synthesis of α-iodostyrene derivatives; the reaction resulted in the Markovnikov addition of HI to the C≡C bond. It was further found that the terminal acetylene itself would undergo the reaction as well. More hindered silyl groups gave a lower yield of the vinyl iodide (Scheme 73).\textsuperscript{90}

A three-component with methyl 3-(trimethylsilyl)propynoate, an amine, and an imine is directed by both the ester and the trimethylsilyl moieties. The reaction involves a 1,4-silyl shift. When salicyl imines were used as substrates the products were chromenes. This reaction was shown to proceed through the aminal 101, which could be trapped with allyltrimethylsilane or the TMS enol ether of aceto-phenone (Scheme 74).\textsuperscript{91}

A variety of 3-silylpropynals and silylethynyl ketones, prepared via a silylation, deprotection, oxidation sequence, were converted into 2-silyl-1,3-dithianes, which are useful synthons via their potential for anion relay chemistry (ARC).\textsuperscript{92} Although 8 different silyl groups showed good results, the dithiation did not occur when the silyl was sterically hindered, as with TBDPS, TIPS, t-Bu2HSi, or i-Pr2HSi (Scheme 75).\textsuperscript{93}
The lithium aluminum hydride reduction of 4-silylbut-3-yn-2-ones provided the 4-silylbut-3-en-2-ol in good yields and high $E/Z$ ratios (Scheme 76). The $\beta$-silyl effect to stabilize $\beta$-cationic intermediates was employed in the regioselective addition of ICl to silylacetylenes. The diastereoselectivity of the addition is the opposite of that found for the reaction of ICl with the simple terminal alkyne. The $Z/E$ selectivity is higher with aryl-substituted silylacetylenes, though the $Z$ selectivity of alkyl-substituted silylacetylenes increases with an increase in the size of the silyl group (Scheme 77).

The addition of the halogens to (trimethylsilyl)acetylene in the absence of light produced the $E$ isomer, which could be equilibrated to a mixture of both stereoisomers. In the cases of the $E$-dichloride or $E$-dibromide the equilibration was brought about by exposure to light in the presence of a trace of bromine. In the case of the $E$-diiodide, prolonged refluxing in cyclooctane produced an $E/Z$ mixture of 9:1 (Scheme 78).

The reaction of Weinreb amides with internal acetylenes promoted by a Kulinkovich-type titanium intermediate gave $\alpha,\beta$-unsaturated ketones in modest yield. The reaction conditions were mild with activation of the titanium promoter as the last step at room temperature. With TMS-terminated acetylenes, the yields were comparable to those of other alkynes investigated, though with slightly lower regioselectivity (Scheme 79).

The syn addition of two aryl groups from an arylboronic acid to an internal alkyne resulted in the formation of 1,2-disubstituted 1,2-diarylethenes. In the single example using a silylacetylene, the reaction of ethyl 3-(trimethylsilyl)propynoate with $p$-tolylboronic acid under Pd catalysis gave the highly substituted ethyl 2,3-di($p$-tolyl)-3-(trimethylsilyl)propenoate via the addition of two equivalents of the $p$-tolyl group (Scheme 80).

The highly regio- and stereoselective addition of a boronic acid to silylacetylenes occurred under mild conditions and in high yields. Interesting points were that 1-(trimethylsilyl)hex-1-yne was more regioselective than (trimethylsilyl)hex-1-yne, which gave a mixture of isomeric vinylsilanes indicating that the steric effect of the silyl group plays a role, and extended reaction times gave reduced stereoselectivity. The resulting arylated vinylsilanes could be converted into their corresponding iodide or bromide. In the case of the iodide this was performed in a two-step, one-pot reaction sequence, whereas the bromide required two independent steps. In a further extrapolation of

\[ \text{Scheme 76 Lithium aluminum hydride reduction of silylpropargyl alcohols} \]

\[ \text{Scheme 77 Iodochlorination of silylacetylenes} \]

\[ \text{Scheme 78 Halogenation of (trimethylsilyl)acetylene} \]

\[ \text{Scheme 79 Reaction of Weinreb amide with silylacetylenes} \]
the chemistry the regio- and stereoselective synthesis of (Z)-α-(4-tolyl)-β-(4-methoxyphenyl)styrene (102) was accomplished in three steps from 1-phenyl-2-(trimethylsilyl)acetylene. The E-isomer was prepared starting from 1-(4-tolyl)-2-(trimethylsilyl)acetylene (Scheme 80). The reaction was also possible with the addition of a vinylboronic acid giving a dienylsilane.100

The Oshima group reported the syn-hydrophosphination of terminal and internal alkynes. With arylacetylenes the regioselectivity was approximately 9:1 and with (triethylsilyl)acetylene, the sole silicon example, it was 94:6, slightly less than that with alkylacetylene substrates, which showed a 100:0 regioselectivity all placing the phosphine on the terminal position. The products were isolated as their phosphine sulfides (Scheme 81).101

A chiral NHC catalyst was employed in the enantioselective conjugate addition of 1-(trimethylsilyl)alk-1-ynes to 3-substituted cyclopenentones and 3-substituted cyclohexenones. Thus, the 1-(trimethylsilyl)alk-1-yne was reacted with diisobutylaluminum hydride to form the 1-(trimethylsilyl)vinylaluminum reagent, which was then reacted with the enone, catalyzed by the chiral NHC complex 103. In reactions with the cyclopenentones, up to 10% of addition of the isobutyl group from aluminum was observed; this increased to up to 33% for cyclohexenones. The er values were excellent, ranging from 92.5:7.5 to 98.5:1.5. Of considerable

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importance, the resulting vinylsilanes were further reacted. Oxidation with m-chloroperoxybenzoic acid gave the ketone. NCI converted it into the vinyl iodide and protodesilylation to the parent alkene. This chemistry was applied to a short synthesis of riccardiphenol B (104) (Scheme 82).102

The reaction of indoles with 1-(halophenyl)-2-(trimethylsilyl)acetylenes under Cu(I) catalysis gave addition of the indole to the C≡C bond and, under the basic conditions, protodesilylation to form the corresponding alkene as a mixture of stereoisomers. Very little amination of the aryl halogen bond occurred. In fact, a control experiment wherein indole was reacted with a mixture of 1-(4-bromophenyl)-2-(trimethylsilyl)acetylene and 4-iodoanisole a 50% yield of addition to the C≡C bond and only 6% reaction of the iodophenyl bond was observed (Scheme 83).103

The hydrosilylation of various propynoate esters was carried out and served to prepare α-silyl-α,β-unsaturated esters in good yields. When this reaction was performed with 3-(trimethylsilyl)propynoate esters, the product formed was the (E)-2,3-bis(silyl)propenoate. Other similar systems such as the ynone 105 and sulfone 106 gave good yields of addition products (Scheme 84).104

1,4-Bis(trimethylsilyl)buta-1,3-diyne underwent carbo-magnesiation of one of the C≡C bonds with arylmagnesium bromide reagents. The resulting vinylmagnesium bromide intermediate could be further reacted, including cross-coupling to form various substituted silylated enynes. 1-Phenyl-4-(trimethylsilyl)buta-1,3-diyne underwent carboxamidation at the phenyl-substituted C≡C bond (Scheme 85).105

Kimura and co-workers reported on the Ni-catalyzed, four-component coupling of internal alkynes, buta-1,3-diene, dimethylzinc, and carbon dioxide. The reactions of 1-substituted 2-(trimethylsilyl)acetylenes gave lower yields and poorer regioselectivity than those of alkyl- or aryl-substituted alkynes (Scheme 86).106

The three-component coupling of acetylenes, vinyloxiranes, and dimethylzinc was reported to give alka-2,5-dien-1-ols. Bis(trimethylsilyl)acetylene and (trimethylsilyl)acetylene gave lower yields than 1-(trimethylsilyl)prop-1-yn-1-ene and alkyl- or arylalkynes. In a similar manner vinyl-cyclopropanes gave 1-silyl-1,4-dienes (Scheme 87).107
The addition of DIBAL-H to 1-(trimethylsilyl)prop-1yne followed by conversion into the lithium alinate and reaction with formaldehyde resulted in vinylsilane 110. This was in turn used to generated vinylsilane 111 and, from that, vinyl iodide 112, which was then converted in two steps into norfluorocurarine (113) (Scheme 90).¹¹⁰

A study on the iododesilylation of a series of vinylsilanes wherein the silyl group included TIPS, TBS, and TBDPS was carried out.¹¹¹ This was the first report of the iododesilylation of a vinylsilane with sterically hindered silyl moieties. Interestingly, it was found that the rate of the reaction with TIPS or TBS groups was about the same, but that of TIPS was faster than that of TBDPS. Four different sources of I⁺, N-iodosuccinimide (NIS), N-iodosaccharin (NISac), 1,3-diodo-5,5-dimethylhydantoin (DIH), and bis(pyridine)iodonium tetrafluoroborate (Ipy₂BF₄) were investigated with comparable results for each. The success of the reaction depended on the solvent system with 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) showing good results. The reaction was tolerant of epoxides, alkenes, esters, TIPS ethers, and a TIPS acetylene (12 examples, 86–96% yield) (Scheme 91).¹¹¹

**13 Reactions at the C–Si Bond**

An iron-catalyzed imine-directed 2-vinylation of indole with internal alkynes produced the 2-vinylated derivative in good yield and regioselectivity. Terminal acetylenes did not react under the conditions employed. This deficiency was circumvented by the use of a (trimethylsilyl)acetylene, which reacted with high regioselectivity forming the C₂–C₃ bond β to the TMS group. These conditions also proved useful for the formation of C₂–C₃ bonds when the reaction was carried out with alkenes (Scheme 89); again the reaction did not occur with terminal alkenes.¹⁰⁹

**Scheme 87** Alkylative three-component coupling of silylacetylenes with vinyloxiranes and a vinylcyclopropane

**Scheme 88** Hydroacetation of a silylacetylene

**Scheme 89** Coupling of a (trimethylsilyl)acetylene with an α,β-unsaturated imine

**Scheme 90** DIBAL-H addition to 1-(trimethylsilyl)prop-1-yn

**Scheme 91** Iodination of vinylsilanes, readily available from silylacetylenes

1,4-Bis(trimethylsilyl)buta-1,3-diyne was treated with Meli-LiBr to prepare the monolithiated diyne, which was
reacted in a Sonogashira cross-coupling with 2-iodoaniline. The coupling product was reacted with trichloroacetyl isocyanate and this converted into desilylated urea 115 in a single step. The resulting diyne was subjected to a double cyclization to give the pyrimido[1,6-a]indol-1(2H)-one 116 (Scheme 92).112

Pan and co-workers reported the conjugate addition of alkynyl groups to acrylate derivatives via the reaction of a (trimethylsilyl)acetylene derivative under InCl₃ catalysis. Silyl moieties other than that of the TMS group were not investigated. The reaction worked best for 1-phenyl-2-(trimethylsilyl)acetylene wherein the phenyl group is a strongly electron-donating aryl group. Thus, 4-CN-, 4-CO₂Me-, and 4-CF₃-substituted 1-phenyl-2-(trimethylsilyl)acetyl- 

ly)acetylenes failed to react. A direct comparison of 1-buty- 

yl- and 1-phenyl-2-(trimethylsilyl)acetylene with hex-1-
yn e and phenylacetylene, that is, the H-terminated acety-
lenes, showed that TMS-terminated acetylenes gave better 

yields. Chlorobenzene was found to be the best solvent and 

Et₃N the best base. 1,4-Bis[(trimethylsilyl)ethynyl]benzene 117 reacted with ethyl acrylate to give the mono- or 

disubstituted γ,δ-ethynyl esters. The reaction was also oc-

curred with methyl vinyl ketone as the acceptor (Scheme 93).113

This protocol compares well with the conjugate addition 

of terminal alkynes to acrylates catalyzed by 

Ru₃(CO)₁₂/bis(triphenylphosphine)iminium chloride and 

with Pd(OAc)₂.114,115

14 Miscellaneous Reactions

β-Amino enone 118 was converted in a two-step, single-

pot sequence into enol ether 119 via reaction with 3-

(trimethylsilyl)propargyllithium in 51% overall yield; using 

propargylmagnesium bromide gave the corresponding H-

terminated product in 40% yield. Enol ether 119 was uti-

lized in a synthesis of 7-hydroxycopodine (Scheme 94).116

1-[Trialkylsilyl]ethynyl)cyclopropan-1-ols were ring 

expanded to 2-alkylidenecyclobutanones in a reaction cata-

lyzed by the Ru catalyst 120. Interestingly, the favored 

stereoisomer was the Z-isomer. Similar results were ob-

Scheme 92 Lithiation of 1,4-bis(trimethylsilyl)buta-1,3-diyne

Scheme 93 Ethynylation of α,β-unsaturated esters with (trimethylsilyl)acetyl-

lyenes

Scheme 94 Reaction of 3-(trimethylsilyl)propargyllithium with an 
iminium salt

Scheme 95 Rearrangement of 1-(silyl)ethynyl)cyclopropan-1-ols
tained with electron-deficient alkylnl cyclopropanols. On the other hand, under the same conditions 1-alk-1-ynyl-cyclopropan-1-ols underwent ring expansion to cyclopentenones. Stabilization of a β-carbocation in the silyl-substituted examples and a favored Michael addition in the electron-deficient examples helps to explain the formation of the four-membered ring (Scheme 95).117

3-(Trimethylsilyl)propynal was nicely used in a convenient synthesis of ethynyl-β-lactone 121; propynal did not undergo a corresponding reaction to give 122. The silylated enantiomerically enriched β-lactone 121 was utilized in synthetic approaches to leustroducsin B and the protiodesi-lylated ethynyl lactone 122 was converted to derivatives of similar structure to the natural products (−)-muricaticin, (−)-japonilure, and (+)-eldanolide.118–120

Corey and Kirst were the first to report the synthesis and utility of 3-(trimethylsilyl)propargyllithium (123). The direct lithiation of 1-(trimethylsilyl)prop-1-yne occurred using n-BuLi/TMEDA in 15 minutes. The reagent 123 reacted with primary alkyl halides in diethyl ether to form the desired alkynes with only small amounts of the isomeric alene, a common side product found with propargylmagnesium chloride reagent.121

Corey and Rucker then utilized 1-(triisopropylsilyl)prop-1-yne (124), which was readily lithiated to give the more sterically encumbered 3-(triisopropylsilyl)propargyllithium (125). Lithium reagent 125 was reacted with cyclohexenones in a 1,2- and 1,4-manner. In addition it was converted into the 1,3-bis(triisopropylsilyl)prop-1-yne (126) in quantitative yield on treatment with triisopropylsilyl triflate. Reaction of 125 with cyclohexenone gave 1,4-addition in THF/HMPA and 1,2-addition in THF. Bis-TIPS reagent 126 reacted with BuLi/THF to give lithiated 126, which reacted with aldehydes in a Peterson reaction to form an enynes (Scheme 97).4

3-(Trimethylsilyl)propargyllithium (123) was used to introduce the propargyl group into epoxygeranyl chloride in 85% yield over three steps from geraniol. The TMS group was removed with TBAF and the resulting enyne was used in a synthesis of the triterpene limonin (Scheme 97).122

3-(Trimethylsilyl)propargyllithium (123) reacted with lactone 127 and this was followed by mesylation/elimination to give enynes 128 and 129 in good yield. The TMS group was removed with AgNO3/aq EtOH en route to stereoisomers of bis(acetylenic) enol ether spiroacetals of artemisia and chrysanthemum (Scheme 97).123

Fu and Smith demonstrated the enantioselective Ni-catalyzed, Negishi cross-coupling arylation of racemic 3-(trimethylsilyl)propargyl bromides; the yields and the ee values were excellent. The protocol was applied to the synthesis of 131, a precursor to pyrimidine 132, an inhibitor of dihydrofolate reductase (Scheme 98).124
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