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Newly designed acylsilanes as versatile tools in organic synthesis[1]

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Abstract

Structural variations in acylsilane molecules allow a number of new selective synthetic processes to be performed which lead to sulfur-containing heterocycles, highly functionalized and unsaturated polycarbonyl derivatives, polyenes, and β- and γ-aminoalcohols. The synthesis of these compounds, most of them not easily accessible through conventional routes, takes advantage of the site-selective reactions occurring at the C–Si bonds, of the increased stability of acylsilanes with respect to that of the corresponding aldehydes and of the high diastereofacial selectivity introduced by the SiR_3 group. Herein we report the different synthetic strategies leading to the synthesis of several functionalized acylsilanes and their synthetic applications. The use of new selective polymetallic reagents for the nucleophilic silylation will be presented as well.

Keywords: Acysilanes; Polymetallic reagents; Chemioselectivity; Stereoselectivity

1. Introduction

In spite of the long tradition of acylsilane chemistry [1], these compounds are still intriguing molecules. Thus far, several questions related to acylsilane ground and excited state features are still unanswered and their reaction behavior reveals striking differences with respect to those observed for ordinary carbonyl compounds.

The two main synthetic routes to acylsilanes, outlined in Scheme 1, are based on electrophilic silylation, performed according to Corey and Seebach ([2]a) and by Brook ([2]b) through the quenching of 1,3-lithium-dithianyl derivatives with 'R_3Si^+ equivalents' such as silyl halides and on the nucleophilic silylation of carboxylic acid derivatives. In the latter approach [3], an organometallic (mono or polymetallic) reagent in which the Si is bound to a metal (M), more electropositive than silicon provides the source for the nucleophilic silicon R_3Si^-.

In addition to these two procedures, many other useful methods [4] have been proposed which, however, lack generality. This article is aimed at demonstrating how, through the design and the synthesis of new acylsilanes, unprecedented synthetic protocols can be envisioned which lead to a variety of highly functionalized and not otherwise easily accessible building blocks.

2. Results and discussion

Three different approaches directed to the exploitation of the synthetic usefulness of acylsilanes are shown in Scheme 2, based on (i) the replacement of the O of the carbonyl group with an S atom, (ii) the introduction of unsaturated chains and (iii) the introduction of chiral frameworks belonging to the class of natural products.

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[1] Dedicated to the memory of Professor Antonino Fava (deceased December 19, 1997), Professore Emerito of the University of Bologna.

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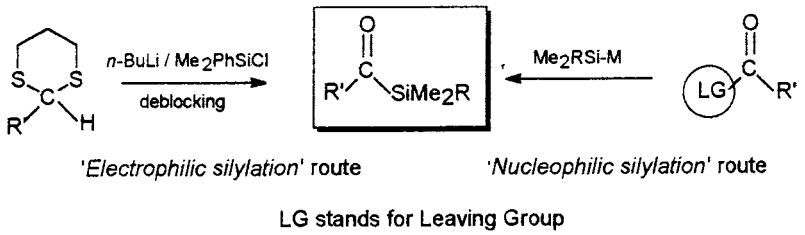
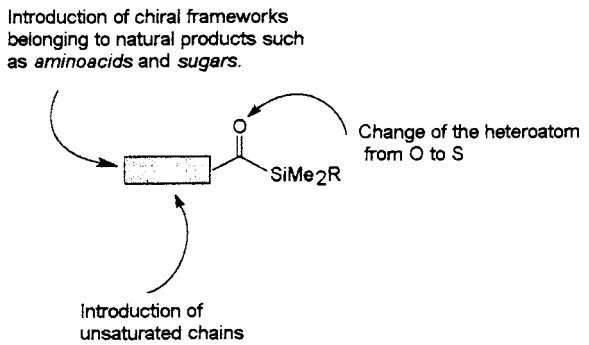


Scheme 1.



Scheme 2.

The new compounds exhibit a much wider reaction potential than that of their simpler counterparts and through them a number of new highly functionalized compounds can be synthesized.

2.1. Synthesis and synthetic applications of enethiolizable thioacylsilanes

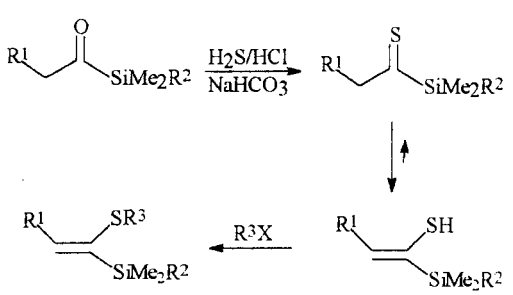
The replacement of the C=O with the C=S functionality in acylsilanes has been reported to occur (Scheme 3) in good yields by treatment [5] of the acylsilanes with H_2S/HCl or, under milder conditions, taking advantage of the use of $Me_3Si–S–SiMe_3$ as the thionating agent under $CoCl_2/6H_2O$ catalysis [6].

Thiocarbonyl compounds do not enethiolize or give mixtures of thione and enethiol [7]. On the contrary aliphatic thioacylsilanes containing an hydrogen atom α to the carbon–sulfur double bond, undergo quantitative and stereoselective Z-enethiolization [8] (Scheme 4).

Quenching of the thiol moiety with suitable alkylating agents, gives rise to a variety of α-silyl vinyl sulfides. In a similar way, ω-haloacylsilanes synthesized, as illustrated in Scheme 5, and transformed via thioacylsilanes into Z-d-silylenethiols [9], undergo, in the presence of bases, intramolecular cyclization leading to formation of 2-silylthiacycloalk-2-enes of different sizes (Scheme 6).

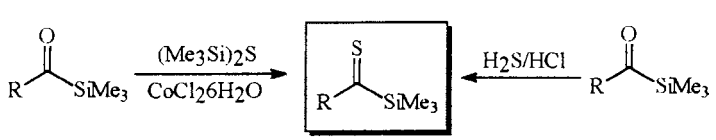
The Z-α-silyl vinyl sulfides are interesting species as they combine both vinylsilane and vinyl sulfide functional groups with their opposing polarization on the olefinic bond. They can be used as starting materials for useful synthetic transformations according to their synthetic equivalence to vinyl-anion and cation synthons. Vinylsulfides and substituted vinyl silanes can be synthesized in high yields [8] and with good stereochemical control by F^- induced protodesilylation and Ni-promoted desulfurative alkylation with Grignard reagents, respectively. On the other hand, open chain and cyclic α-silyl vinyl sulfides, obtained from thioacylsilanes, react with acid chlorides in the presence of a Lewis acid to give open chain and thioannulated enones, respectively [10], with byclic or tricyclic structures depending upon the nature of the acyl chloride (Scheme 7).

In all cases, acylation is controlled by sulfur and occurs at the β-position probably following the mechanism outlined in Scheme 8. The cyclic compounds are generated via a Nazarov-type cyclization.

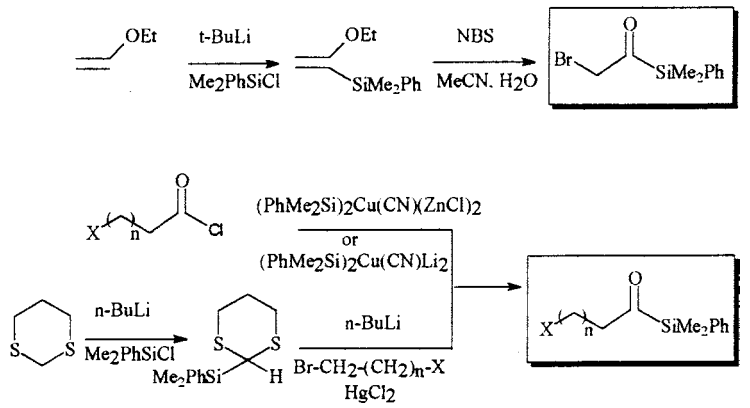


R^1 = Ph, Et. R^2 = Me, Ph. R^3 = Me, CH_2COOEt, $(CH_2)_2COOEt$, CH_2Ph, $CH_2CH{=}CH_2$. Yields = 80-98%

Scheme 4.



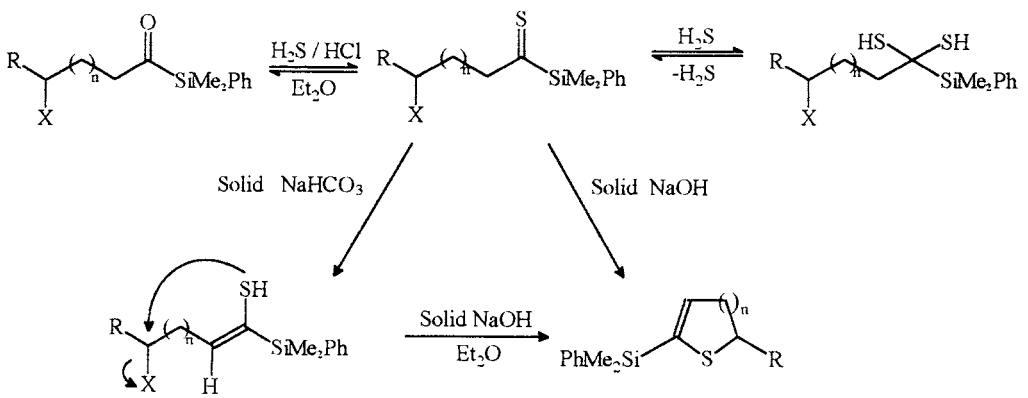
Scheme 3.



Scheme 5.

2.2. Synthetic applications of α,β-ethylenic and -acetylenic silyl ketones

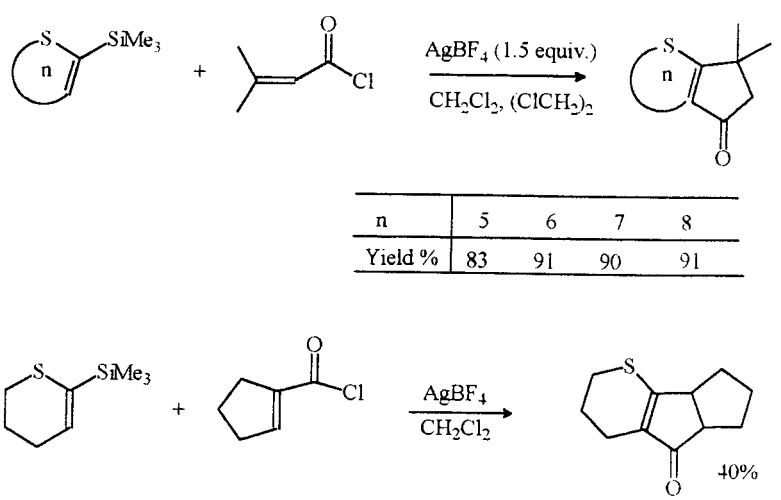
The α,β-ethylenic and -acetylenic silyl ketones, made available by the synthesis devised by Reich in 1982 [11], are very versatile building blocks. However, since the beginning they have been involved only in a limited number of synthetic applications mainly as acetylenic



X = Cl, Br

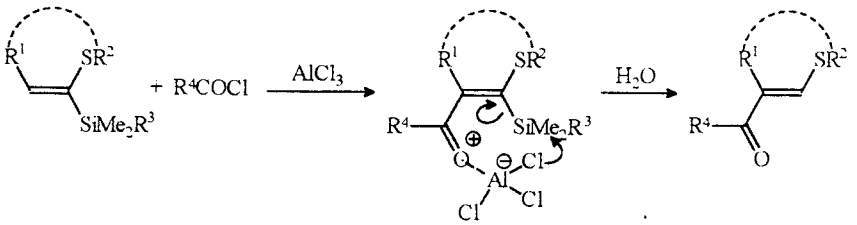
n	2	3	4	5	9	11
Yield %	100	100	100	65	71	63

Scheme 6.

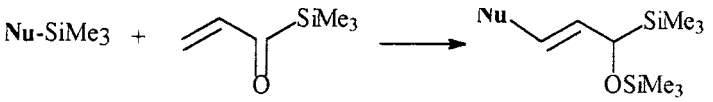


n	5	6	7	8
Yield %	83	91	90	91

Scheme 7.



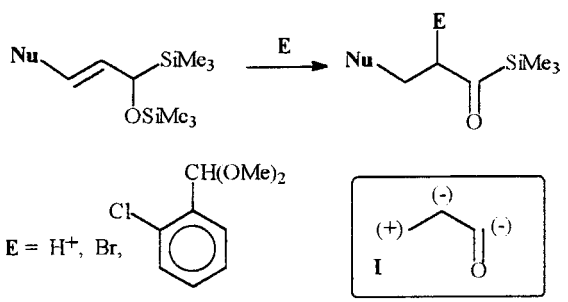
Scheme 8.



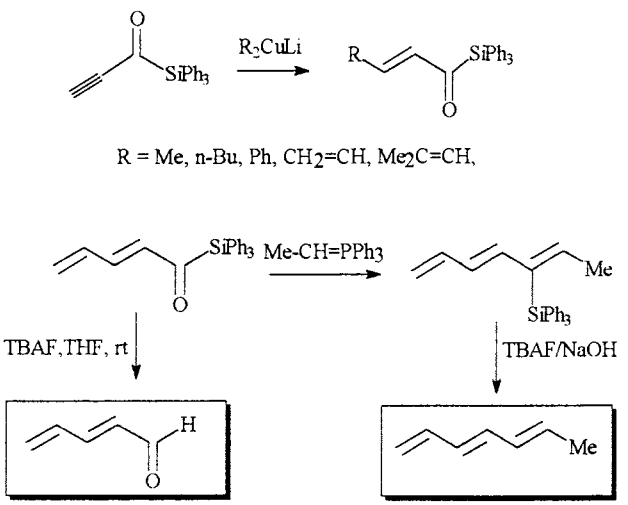
Nu = Et_2N, Me_3SiNH, Im, PhS, MeS, Me_3SiS, Br, N_3.

80-98% yields

Scheme 9.



Scheme 10.



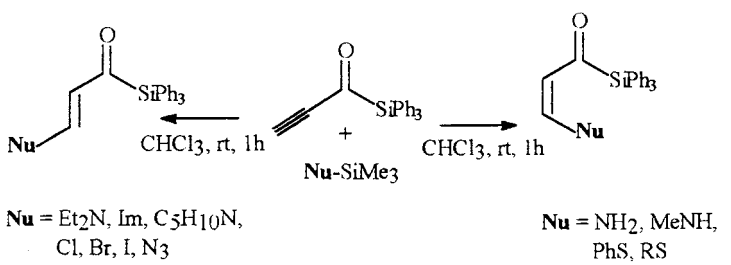
Scheme 12.

dienophiles or in the application of the Brook rearrangement to the synthesis of not otherwise accessible silyl enol ethers [12].

Their synthetic potential can be greatly expanded taking into account the ability of these unsaturated acylsilanes to act as Michael acceptors even more effectively [13] than the organic counterparts and the beneficial effect exerted by the R_3Si group on the chemio- and regioselectivity of the addition reactions.

Thus, propenoyltrimethylsilane reacts [14] with silylated nucleophiles to yield the β-functionalized silyl enol ethers of acylsilanes (Scheme 9). The reactions, which proceed in the absence of solvent and without any catalyst, lead to 95% configurationally pure *E*-silyl enol ethers which have important applications in the stereoselective synthesis of alicyclic molecules bearing multiple asymmetric centers.

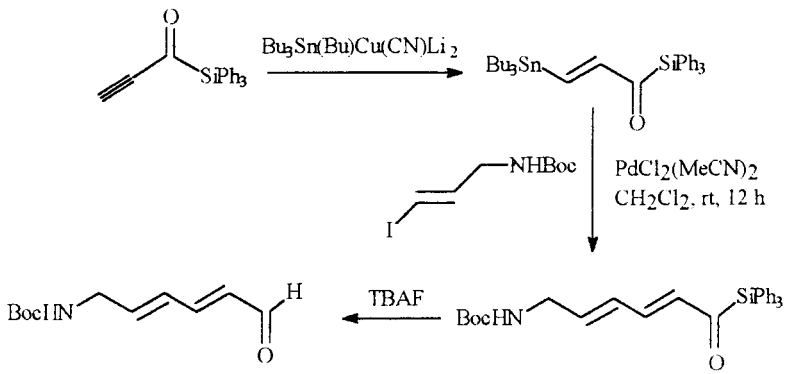
By acidic hydrolysis of these new silylated enol ethers, saturated acylsilanes variously functionalized at the β-position and readily convertible into the corre-



Nu = Et_2N, Im, $C_5H_{10}N$, Cl, Br, I, N_3

Nu = NH_2, MeNH, PhS, RS

Scheme 11.



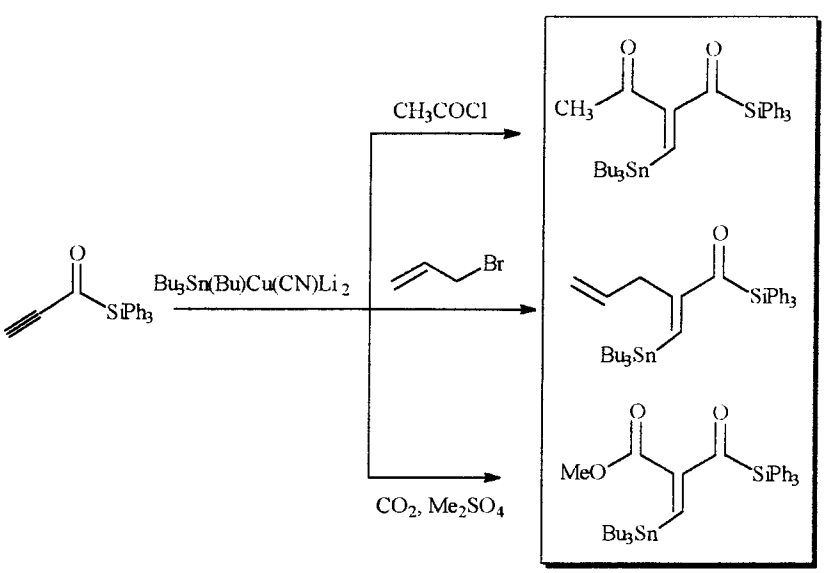
Scheme 13.

sponding aldehydes by desilylation can be obtained in good yields. Furthermore, these species undergo the typical reactions of silyl enol ethers with electrophiles leading to acylsilanes with different functional groups at the α- and β-positions, thus exploiting the synthetic equivalence of this class of compounds to the polysynthon **I** (Scheme 10).

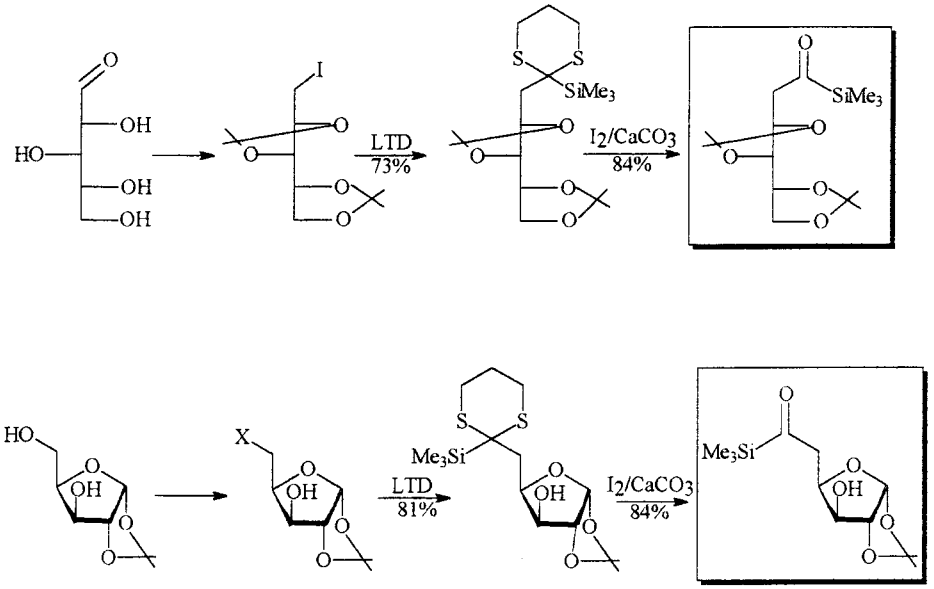
Ethynyl triphenylsilyl ketone, a synthetic equivalent of propargylaldehyde, reacts readily with nucleophiles to afford β-functionalized propenoylsilanes [15]. When reacted with silylated nucleophiles, a spontaneous and clean reaction occurs, similar to that of the ethylenic series, yielding the corresponding Michael adducts in a regiospecific fashion and in almost quantitative yields (Scheme 11).

It is worth noting that in the same reactions performed on propargyl aldehyde itself, only the 1,2-adducts were formed in quantitative yields. When using unsaturated carbocuprates dienoylsilanes are obtained [16]. These synthetic equivalents of dienals can further react under Wittig conditions to afford a new and stereodefined class of silylated polyenes in which the newly formed double bond has, because of the presence of the R_3Si moiety, *Z* stereochemistry. Successive desilylation leads to the polyene with the *E* configuration which is the contrary to classic *Z* stereoselectivity of the Wittig reaction (Scheme 12). The use of unsaturated acylsilanes for the stereoselective synthesis of conjugated polyenes, a class of compounds of high interest since it includes natural products such as arachidonic acid metabolites and insect pheromones, has great advantages with respect to the previously reported carbocupration of acetylenic esters, aldehydes and ketones which suffers from extended isomerization.

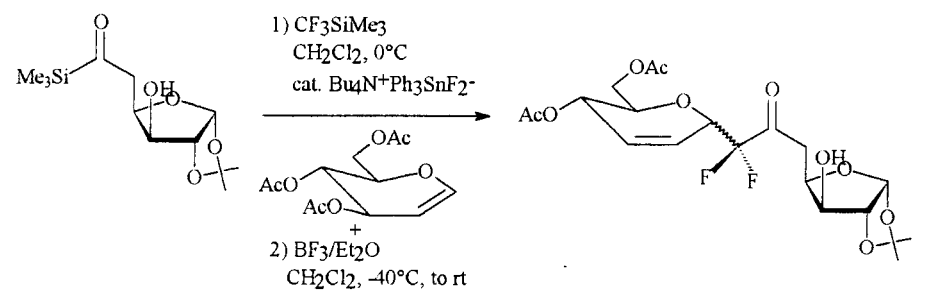
With tributylstannylcuprate as the Michael donor, the silylated acetylenic ketone affords the corresponding bismetallated compounds in good yields [17]. The presence of the stannyl moiety at position 3 of the enonic framework, inverts the polarity at the C-3 carbon with respect to that observed in carbocupration.



Scheme 14.



Scheme 15.

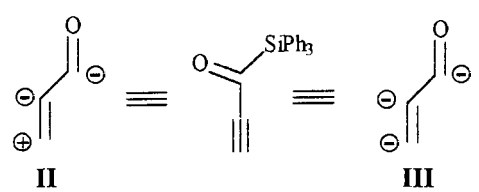


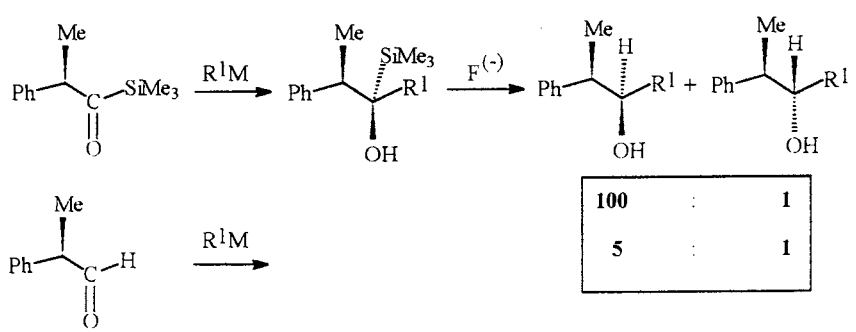
Scheme 16.

Coupling with electrophiles at the C–Sn bond of the Michael adduct therefore occurs under mild conditions (Scheme 13) according to the typical behavior of vinyltin derivatives.

The intermediate cuprate can be further reacted in situ with electrophiles to afford an easy entry into the class of polyfunctionalized compounds such as exomethylene 1,3-diketones, useful building blocks in natural product synthesis (Scheme 14).

The acetylenic silyl ketone can thus be considered as a real synthetic equivalent of polysynthons **II** and **III** in which the polarity at position 3 can be tuned according to synthetic needs, through the use of the suitable Michael donors.





Scheme 17.

Table 1
Polymetallyc reagents Me_2RSi-M as sources of 'nucleophilic silicon'

Complex	Reference
Me_2RSiLi or $Me_2RSiCu(CN)Li$ or $(Me_2RSi)_2Cu(CN)Li_2$	[21]
$Me_3Si-SiMe_3/[(\eta^3\text{-}C_3H_5)PdCl]_2/P(OEt)_3$	[22]
$LiAl(SiMe_3)_4$ or $LiMeAl(SiMe_3)_3$	[23]
$Al(SiMe_3)_3$/CuCN: an *ate* complex?	[24]

2.3. Synthesis and synthetic applications of chiral acylsilanes derived from naturally occurring compounds

Among the limited number of chiral acylsilanes reported in the literature, only recently [18] have natural products like sugars been used as starting materials for the preparation of these compounds (Scheme 15).

A good illustration of the usefulness of acylsilanes in sugar chemistry is provided by the synthesis of C-difluoro disaccharides with a difluoromethylene group in place of the anomeric oxygen shown in Scheme 16.

To date, however, acylsilanes derived from homochiral natural aminoacids are completely unknown. The potential interest in these species stems from their synthetic equivalence to amino aldehydes which are useful precursors of homochiral aminoalcohols, structural units found in a number of important bioactive compounds.

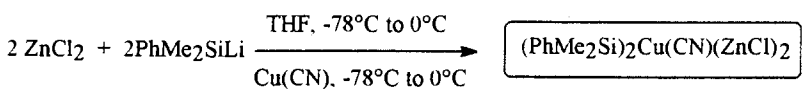
The replacement of a hydrogen with a Me_2PhSi group conveys a generally [19] remarkable stability to elusive molecules such as α- and β-amino aldehydes. On the other hand, as previously demonstrated [20], nucleophilic addition to the carbonyl functionality occurs (Scheme 17) with much higher diastereoselectivity in the case of chiral acylsilanes with respect to the corresponding aldehydes, due to the high diastereofacial selectivity exerted by the R_3Si moiety.

With these two major advantages in mind, the synthesis of aminoacylsilanes was performed by means of the nucleophilic silylation of the activated forms of the protected aminoacids.

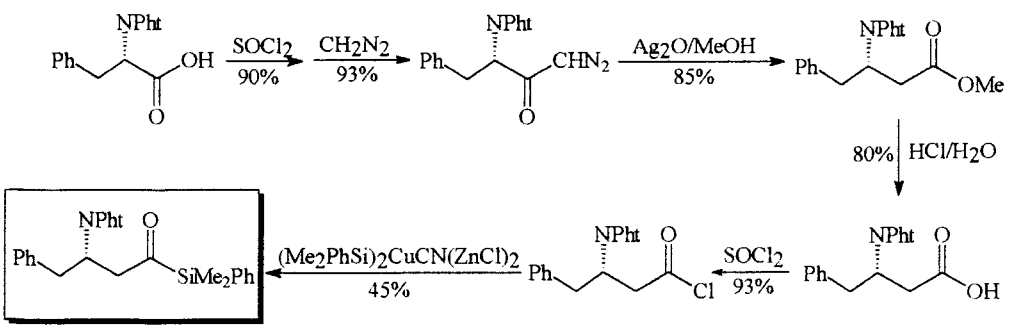
The most common sources of nucleophilic silicon already reported in the literature, based on R_3SiLi or polymetallic reagents available through the transmetallation procedure, are shown in Table 1.

The high degree of functionalization of the starting materials required, however, a careful choice of the nucleophilic silylation reagent and prompted us to avoid reagents which are highly basic and unselective or based on hard-to-handle starting materials. The excellent transmetallation ability of zinc due to its low-lying empty orbitals, as well as its use in a large number of recent synthetic applications involving highly functionalized compounds [25], suggested the design of a new low-basicity and highly stable and selective polymetallic reagent for the delivery of nucleophilic silicon [26]. The new reagent was prepared (Scheme 18) according to the procedure previously used by Yamamoto [27] for the 'higher order' (HO) zinc carbocuprate reagents.

As summarized in Chart 1, very clean cross-coupling reactions took place with a variety of carboxylic acid chlorides containing reactive functionalities leading to the corresponding acylsilanes in high yields. It is important to note that starting from *N*-protected aminoacids, such as *N*-tosylproline and *N*-phtaloylphenylalanine, the new α-aminoacylsilanes were obtained without any loss of optical purity.



Scheme 18.



Scheme 19.

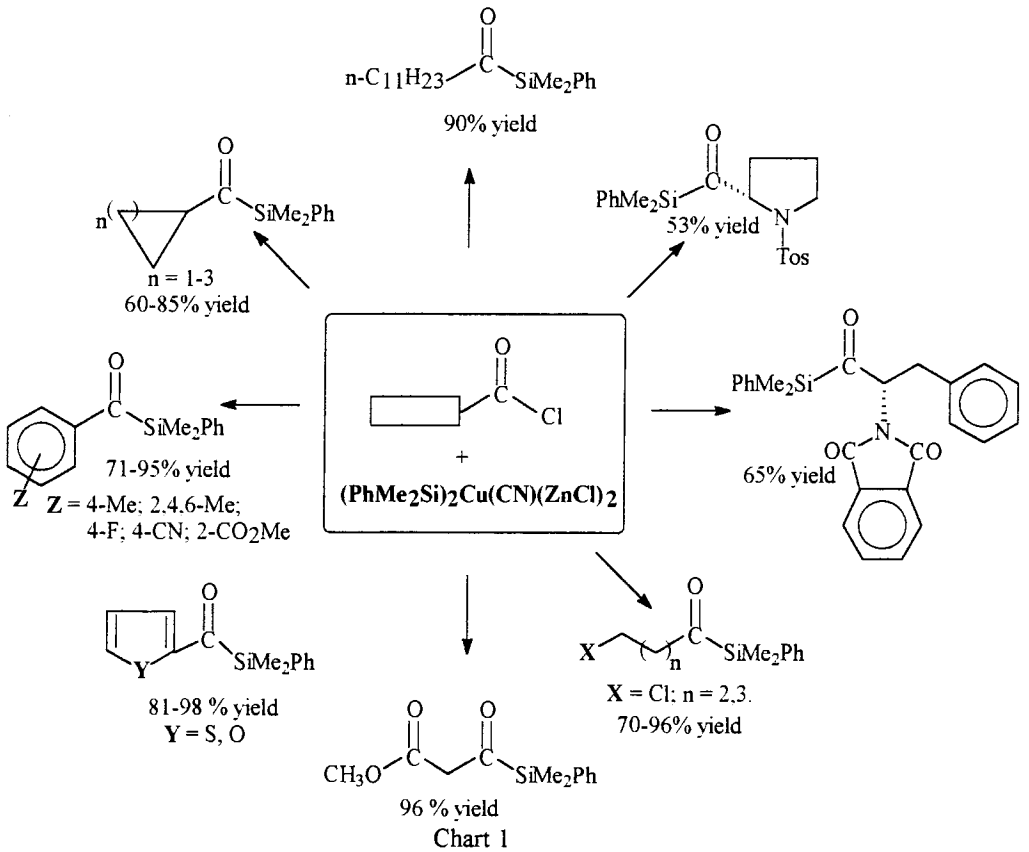


Chart 1

Although the precise structure of this new, less reactive but more stable polymetallic Si–Cu–Zn reagent remains ambiguous, this compound appears superior to the standard HO silylcyanocuprates. Its application is preferable to the $Me_3Si–SiMe_3$/Pd procedure which leads through complex reaction mixtures, to the expected products in much lower yields.

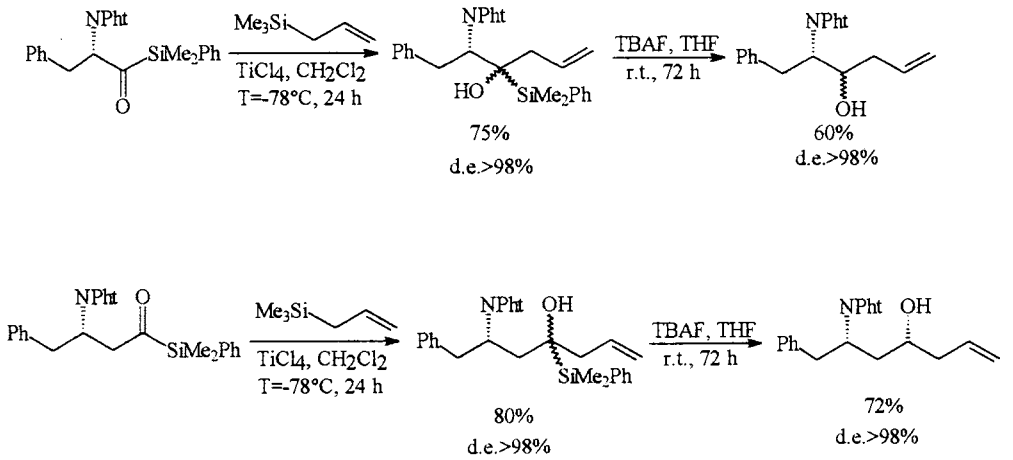
For the synthesis of β-aminoacylsilanes, synthetic equivalents of highly unstable β-aminoaldehydes, *N*-Pht-L-phenylalanine was homologated (Scheme 19) via the Arndt–Eistert reaction, which is known to give enantiopure β-aminoacids from their α-analogues, and by using the Si–Cu–Zn reagent in the silylation step.

The first application of both α- and β-aminoacylsilanes [28] was directed toward the synthesis of 1,2- and 1,3-amino hydroxyl systems and was accomplished through a $TiCl_4$-mediated addition of allyltrimethylsilane (Scheme 20). Protodesilylation with TBAF of the resulting hydroxysilanes led to the formation of 6-Ph-5(*S*)-phthalimido-1-hexen-4-ol (60%) and of (4*R*,6*R*)-7-Ph-6-phthalimido-1-epten-4-ol (80%) as single diastereoisomers, thus suggesting d.e. values $>98\%$.

The effectiveness of the new homochiral aminoacylsilanes in the highly stereoselective synthesis of β- and γ-aminoalcohols reveals the high potential of these compounds as powerful building blocks. As such, the chemistry of homochiral aminoacylsilanes derived from a wider range of natural aminoacids is likely to be influential in achieving asymmetric synthesis.

3. Conclusions

The aim of this article is to demonstrate that, even though acylsilanes are not new compounds, their synthetic potential can be further exploited toward the synthesis of a variety of new highly functionalized compounds, conditionally to the introduction of suitable structural modifications. The new synthetic strategies, if on one side are based on the well known reaction features resulting from the introduction of a R_3Si moiety into an organic molecule, on the other hand take advantage of the use, among others, of new highly selective Cu-based polymetallic reagents. This combination between Group-14 and transition metal chemistry, appears very promising for developing new methodologies useful for regio-, chemio- and stereoselective organic synthesis. There remains a need to continue to develop a range of new acysilanes and to optimize the procedures for their synthesis through the 'invention' of more reliable and selective nucleophilic silylation reagents.



Scheme 20.

Acknowledgements

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