Carbon−Carbon Bond Forming Reactions Mediated by Silicon Lewis Acids§

Alexander D. Dilman*,† and Sema L. Ioffe‡

Institut de Chimie Moleculaire d'Orsay, Université Paris Sud, Bât 420, Laboratoire de Synthesé Asymetriqué, 91405 Orsay Cedex, France, and N.D. Zelinsky Institute of Organic Chemistry, 119991, Moscow, Leninsky Prospekt 47, Russia

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Alexander Dilman was born in Moscow, in 1976. He started learning organic chemistry in Moscow Chemical Lyceum, where he studied from 1991 to 1993. Then he entered the Higher Chemical College and at the same time joined the group of S. Ioffe at the N. D. Zelinsky Institute of Organic Chemistry as a research assistant. He graduated summa cum laude in 1999 and continued the education at Zelinsky Institute, where received his Ph.D. in 2001 under the supervision of Professor Ioffe. Currently he is a Rhodia Company postdoctoral fellow in the group of Professor H. B. Kagan at the Université Paris Sud. His interests cover elaboration of chemo-, regio-, and stereoselective reactions and, of course, total synthesis.

Sema Ioffe was born in Moscow, in 1938. He graduated from the Moscow D. I. Mendeleev Institute of Chemical Technology in 1960. From 1960 to 1963, he was a graduate student at the N. D. Zelinsky Institute of Organic Chemistry. He then served as Junior Researcher (1963–1967), Senior Researcher (1967–1985), and, since 1985, as Principal Researcher at the Zelinsky Institute. He received his Ph.D. in 1964 and his Doctor of Science in 1980. He has been a Professor since 1993. His scientific interests include the different topics of chemistry of aliphatic nitro and high nitrogen compounds. His additional interest is connected with the advanced chemical education of gifted youth.

I. Introduction

Among various synthetic applications of organosilicon compounds,[1] the transformations utilizing derivatives containing leaving groups at the silicon atom have become especially widespread. It is al-

§ This paper is dedicated to Professor Herbert Mayr on the occasion of his 55th birthday.

* Corresponding author. Tel: +33 1 69 15 61 62. Fax: +33 1 69 15 46 80. E-mail: dilman@icmo.u-psud.fr.
† Université Paris Sud.
‡ N.D. Zelinsky Institute of Organic Chemistry.

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Table 1. Synthesis of R_3SiX

compound	method	ref	compound	method	ref
Me_3SiOTf [a]	$Me_3SiCl + TfOH$	2b	*t*-$BuMe_2SiOTf$	*t*-$BuMe_2SiCl + TfOH$	2b
	$Me_3SiCH_2CH{=}CH_2 + TfOH$	14	Me_3SiOSO_2F	$Me_3SiCH_2CH{=}CH_2 + FSO_3H$	21
	$Me_4Si + TfOH$	15	Me_3SiI [d]	$Me_3SiCl + NaI$	12
	$PhSiMe_3 + TfOH$	16		$Me_3SiSiMe_3 + I_2$	22
Me_3SiNTf_2	$Me_3SiCH_2CH{=}CH_2 + HNTf_2$	17		Me_3SiH + MeI/cat. $PdCl_2$	13
	$Me_3SiCl + AgNTf_2$	18		$Me_3SiCH_2CH{=}CH_2 + I_2$	23
$Me_3SiN(SO_2F)_2$ [b]	$Me_3SiCl + AgN(SO_2F)_2$	19a	*i*-Pr_3SiOTf	*i*-Pr_3SiH (*i*-Pr_3SiCl) + TfOH	24a (24b) [e]
Me_3SiClO_4 [c]	$Me_3SiCl + AgClO_4$	20	*t*-$BuPh_2SiOTf$	*t*-$BuPh_3Si + TfOH$	25

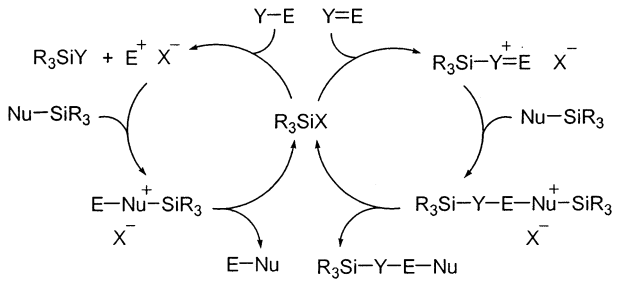
[a] Synthesis and properties of numerous silyltriflates are given in the ref 2c; synthesis and properties of triflate-substituted oligosilanes are discussed in the ref 26; [b] In the ref 19a (footnote 5) it is stated that $Me_3SiN(SO_2F)_2$ can be stored for months in a refrigerator in the atmosphere of nitrogen, whereas in ref 17a it is mentioned that this reagent is not very stable at room temperature. [c] This compound is explosive upon heating. Therefore, its isolation should be performed on a small scale (1−2 mL).[20] [d] For review on Me_3SiI, see ref 27. [e] In the ref 24b it is mentioned that *i*-Pr_3SiOTf was obtained from *i*-Pr_3SiCl and TfOH, though no procedure is given.

ready a routine to employ silylating agents for functional group manipulations.[2] The behavior of these compounds is determined primarily by the tendency of the silicon atom to expand its valence shell, giving rise to five- and six-coordinate intermediates.[3] This property allows one to consider silylating agents as Lewis acids, thereby justifying their use as mediators in carbon−carbon bond forming reactions.

Silicon Lewis acids (SLA) offer some advantages over traditional metal-centered activators. For example, SLA are compatible with many synthetically valuable C-nucleophiles, such as silyl enol ethers, allyl organometallic reagents, and cuprates. Unlike metal halides, SLA are not prone to aggregation, and this substantially simplifies the analysis of the reaction mechanisms. Furthermore, the reactivity of SLA of R_3SiX structure can be finely controlled by varying the steric volume of alkyl substituents.

However, the most advantageous circumstance is the opportunity to realize the processes in the presence of catalytic amounts of SLA if SLA and a nucleophile (e.g., silyl enol ether) have identical trialkylsilyl fragments. Thus, depending on the type of electrophile, two mechanistically different pathways may be considered (Scheme 1). In case of acetals

Scheme 1



and acetal-like compounds, SLA abstract heteroatomic substituent, followed by reaction of electrophilic species formed with a nucleophile (left circle). When the substrates possess carbon−heteroatom double bond (e.g., carbonyl compounds, imines) SLA bind to their basic function, leading after C,C-bond forming event to the products containing silyl group (right circle).

The approach generalized in Scheme 1 was first realized by Noyori in the early eighties.[4] Afterward SLA gained wide acceptance as mediators of a variety of transformations.[2b,c,4,5,6]

This review surveys the data on the behavior of SLA of the general formula R_3SiX in carbon−carbon bond forming processes. Besides transformations based on Scheme 1, the cycloaddition and conjugate addition reactions are also covered. The effects of interactions of Lewis acids with substrates on chemo-, regio-, and stereoselectivity of reactions are discussed in detail.

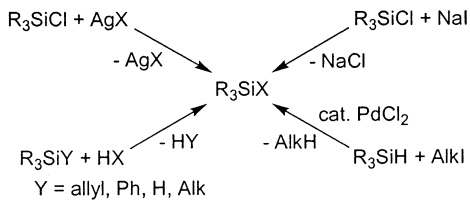
The tendency of silicon to the hypervalent state is further enhanced upon insertion of two or more electron-withdrawing substituents, with the result that silicon becomes more prone to the formation of six-coordinate intermediates. Reactions involving compounds of the R_2SiX_2 or $RSiX_3$ types are beyond the scope of the present review and will not be discussed henceforth.

In this review, no consideration is also given to processes in which the center of Lewis acidity is present in the nucleophilic molecule. These are reactions of silacyclobutyl[7] and silacyclopropyl[8] derivatives and reactions of substrates containing $Si-Hal_3$[9] or siliconate fragments.[10,11]

II. Silicon Lewis Acids: Synthesis, Storage, and Solvent Compatibility

Of all possible SLA, trialkylsilyl derivatieves of strong protic acids (e.g., TfOH) are most frequently used for forming C,C bonds. Generally, these esters are prepared by reactions of acids HX with silanes $Y-SiR_3$ or from R_3SiCl and the silver salt AgX (Scheme 2). Various trialkyliodosilanes can be syn-

Scheme 2



thesized by reactions of the corresponding chlorosilanes and sodium iodide in acetonitrile[12] or by $PdCl_2$-catalyzed reactions of trialkylsilanes R_3SiH with AlkI.[13] Table 1 gives the conditions for the

preparation of selected SLA of this type, which are in most common use.

Since all neutral SLA are very readily hydrolyzed by moisture, operations with these reagents must be carried out under an atmosphere of inert gas. The addition of a small amount of Me_4Si or poly(4-vinyl)-pyridine to Me_3SiX often makes it possible to bind HX formed upon storage of these reagents, but it does not eliminate partial hydrolysis upon their transfer to a reaction flask. It should be emphasized that traces of free acid HX formed upon hydrolysis of R_3SiX can change the outcome of the reactions promoted by SLA. Hence, the presence of the acid HX must always be taken into account. It is recommended that sterically hindered bases (for example, 2,6-di-*tert*-butylpyridine,[28] 2,6-di-*tert*-butyl-4-methylyridine,[29] 2,4,6-tri-*tert*-butylpyrimidine,[30] 2,6-bis(tri-*iso*-propylsilyl)pyridine,[31] or their polymeric analogues[32]) be added to remove HX from the reaction mixture. Alternatively, it is advisable to examine the effect of protic acid on the course of the reaction by performing a suitable experiment.[29b,33] It is believed that sterically hindered pyridines rapidly bind strong protic acids while being inert with respect to electrophilic intermediates.

Trialkyliodosilanes are rapidly oxidized by atmospheric oxygen to give elemental iodine, which can be captured upon storage over copper chips.

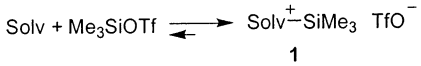
Although all compounds of the R_3SiX type can be isolated in the individual form, they are sometimes generated in situ by protodesilylation of allyltrialkylsilanes. Under these conditions, R_3SiX are generally formed in quantitative yields. However, side processes were observed in some cases. For example, it was assumed that propene eliminated in the reaction of allyltrimethylsilane with $HNTf_2$ can partially consume the acid to form *i*-$PrNTf_2$.[17b] It was also reported that the reaction of allyltrimethylsilane with FSO_3H afforded FSO_3SiMe_3 in only 50% yield along with inert polymers.[21]

Because the procedure for purification of silyl perchlorates is potentially dangerous, these derivatives are sometimes generated from trialkylsilanes and trityl perchlorate directly in a reaction flask.[34]

A polymeric analogue of silyl triflate is obtained by silylation of perfluorinated resin−sulfonic acid. This reagent exhibits satisfactory reactivity, while being less sensitive to moisture compared to Me_3SiOTf.[4,35]

The C,C cross-coupling reactions involving R_3SiX can be carried out in various solvents, such as hexane, benzene, toluene, ether, CCl_4, dichloromethane, dichloroethane, or acetonitrile. Generally, the reaction rate increases as the polarity of the solvent increases. In some cases, acetonitrile proved to be the solvent of choice. Probably, its efficiency is associated not only with high polarity ($\epsilon = 37.5$) but also with the equilibrium formation of a silylnitrilium intermediate,[12a,27] which is a better donor of the silyl group compared to the starting R_3SiX compound (for more details, see section VII.A.). A the same time, many polar solvents, such as dimethylformamide (DMF), *N*-methyl-2-pyrrolidone, *N*,*N*′-dimethylpropyleneurea (DMPU), pyridine, hexamethylphosphoramide (HMPA), and dimethyl sulfoxide (DMSO), are not recommended because they can readily form complexes **1**, which may be weaker silyl donors than the starting SLA (Scheme 3).[36] In addition, combination of the sulfoxide fragment, SLA, and a base can lead to the Pummerer rearrangement (see section XII), whereas redox processes can occur in the presence of Me_3SiI or Me_3SiBr.[37]

Scheme 3



1

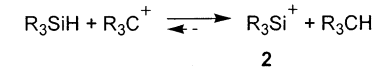
Ethyl acetate and nitroalkanes (*i*-$PrNO_2$ or $MeNO_2$) can be used in combination with Me_3SiCl or Me_3SiOTf in the absence of bases, while Me_3SiI is oxidized by nitro compounds to form hexamethyldisiloxane and elemental iodine.[38] Thus, Olah and coworkers carried out the reactions of primary, secondary, and tertiary nitroalkanes with Me_3SiI in CH_2Cl_2 or $CHCl_3$ at room temperature for 16 h.[38] At the same time, Enders used Me_3SiI, generated from Me_3SiCl/NaI in acetonitrile, to perform hydrolysis of phosphorus esters containing the primary nitro group upon refluxing for 12 h. In the latter reaction, the nitro group remained intact.[39]

Tetrahydrofuran can be used in combination with Me_3SiOTf at −78 °C, whereas the ring opening is possible at higher temperatures.[40]

III. Lewis Acidity of Silicon Derivatives

In the last two decades, the problem of observation of the trialkylsilyl cation R_3Si^+, which is apparently the strongest SLA, attracted considerable attention. According to the results of ab initio calculations[41] and experimental data,[42] the equilibrium shown in Scheme 4 is substantially shifted to the right.

Scheme 4



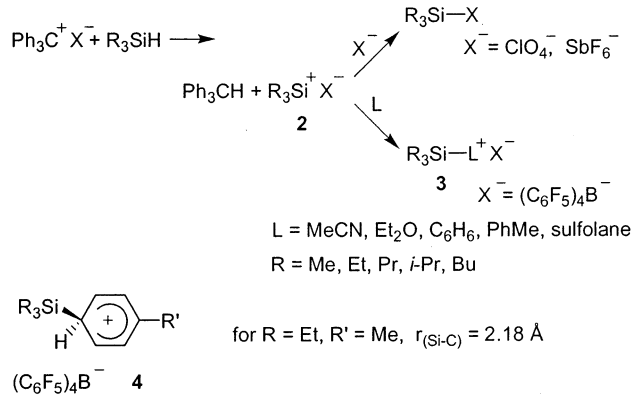
2

Correspondingly, silyl cations **2** may be readily formed in the gas phase where they can be characterized and studied.[43] However, observation of these cations in the condensed state (in solution or in the crystalline state) presents considerable difficulties.[44] Thus, trialkylsilyl cation **2**, which is readily generated in solution by the reactions of silanes with the triphenylmethyl cation, immediately reacts with counterions (for example, with SbF_6^- or ClO_4^-) or with donor solvents L to give the corresponding derivatives **3** containing the four-coordinated silicon atom (Scheme 5).[36b] The trialkylsilyl cations form covalent σ-complexes of type **4** even with benzene and toluene.[45]

In the presence of $[B(C_6F_5)_4]$ in dichloromethane, the R_3Si^+ cations, provided that coordinating additives are absent, abstract chlorine ions from the solvent to give R_3SiCl.[36b,46]

In summary, it can be concluded that the difficulties of observation of R_3Si^+ in condensed phase arise from high strength of silicon-heteroatom bonds.

Scheme 5



Nevertheless, Lambert demonstrated recently that the silyl cations containing bulky substituents, which hinder the approach of nucleophilic reagents to the silicon atom, can be observed in solutions. He succeeded in detecting $Mes_3Si^+B(C_6F_5)_4^-$ (^{29}Si NMR δ = 225.5),[47] or Dur_3Si^+ $B(C_6F_5)_4^-$ (^{29}Si NMR δ = 226.8)[48] (Mes = 2,4,6-trimethylphenyl, Dur = 2,3,5,6-tetramethylphenyl) in benzene, the chemical shifts being very close to the calculated value ($\delta_{(Mes_3Si^+,calcd.)}$ = 230.1).[49]

Hence, covalent compounds of the R_3Si-X type, where X is either the conjugated base of a strong acid (for example, $CF_3SO_3^-$ or ClO_4^-) or a solvent molecule (for example, MeCN), generally serve as Lewis acids in C,C bond forming reactions.

Several approaches were proposed for estimation of the Lewis acidity of R_3SiX. One of these approaches assumes that the positive charge on the silicon atom is proportional to the chemical shift in ^{29}Si NMR spectra. However, this scale can be used as a reliable criterion for the relative reactivity only of those compounds in which the silicon atom is bound to the same heteroatom. The ^{29}Si chemical shifts of different trimethylsilyl derivatives are given in Table 2.

Another procedure for estimating the Lewis acidity of Me_3SiX, suggested by Simchen, is based on the comparison of the silylation rate constants of cyclopentanone and diisopropyl ketone with these reagents, in the presence of triethylamine in dichloroethane (see the bottom table).[66]

Bassindale proposed to estimate the strength of SLA from their ability to form the *N*,*N*-bis(trimethylsilyl)imidazolium cation in reactions with *N*-trimethylsilylimidazole.[58,67] On the basis of the results of the studies of the kinetics and thermodynamics of this reaction, SLA were arranged in the following row of silyl donating ability:

$$Me_3SiCl < Me_3SiBr < Me_3SiI < Me_3SiOTf < Me_3SiClO_4$$

Although quantitative data on Me_3SiNTf_2 and $Me_3SiN(SO_2F)_2$ derivatives are lacking, the results of comparative experiments (see subsequent chapters) provide evidence that these reagents are much more reactive than Me_3SiOTf.

Table 2. Chemical Shifts ^{29}Si NMR of Trimethylsilyl Derivatives Me_3SiX Relative to Me_4Si

Me_3SiX	solvent	δ (^{29}Si), ppm	ref
calculated Me_3Si^+	gas phase	354—385	50
$(Me_3Si)_3O^+$ $B(C_6F_5)_4^-$ [a]	CD_2Cl_2	51.1	51
$(Me_3Si)_2OEt^+$ BAr_4^- [b]	CD_2Cl_2	59.0	46
$Me_3SiOEt_2^+$ BAr_4^- [b]	CD_2Cl_2	66.9	46
Me_3SiClO_4	CH_2Cl_2	46.6	36b
Me_3SiOSO_2F	*c*	52.0	52
Me_3SiOTf	CH_2Cl_2	43.7	36b
		(46.6[c])	(52)
Me_3SiOTf + 1 $B(OTf)_3$	CH_2Cl_2	62.0	53
$(Me_2N)_3PO-SiMe_3^+$ OTf^-	HMPA-d18	27.5	36b
DMPU$-SiMe_3^+$ OTf^-	DMPU[d]	36.6	36b
$Ph_3PO-SiMe_3^+$ OTf^- [e]	CD_2Cl_2	37.5	36a
$Ph_2C{=}O-SiMe_3^+$ BAr_4^- [b]	CD_2Cl_2	52.3	59a
$C_5H_5NO-SiMe_3^+$ OTf^- [f]	CD_2Cl_2	49.4	36a
$Me_2NCH{=}O-SiMe_3^+$ OTf^- [g]	CD_2Cl_2	44.0	36a
$(Me_3SiO)_2SO_2$	C_6F_6	33.7	54
$(Me_3SiO)_3PO$	C_6F_6	20.0	54
$Me_3SiOOMe$	C_6F_6	22.0	54
$(Me_3SiO)_3B$	C_6F_6	12.3	54
$Me_3SiOC(O)CF_3$	*c*	34.2	52
Me_3SiOAc	*c*	21.5	52
Me_3SiOMe	*c*	17.2	52
$(Me_3Si)_2O$	CD_2Cl_2	7.0	51
$Me_3Si-NCMe^+$ BAr_4^- [b]	CD_2Cl_2[i]	36.7	55
Me_3SiNTf_2	*c*	55.9	18
		(57.2[j])	(56)
$Me_3SiN(SO_2F)_2$	—[j]	44.9	19a
pyridine-$SiMe_3^+$ OTf^-	pyridine-d5	40.8	36b
$(Me_3Si)_2NH$	C_6D_6	2.2	57
N-Me_3Si-imidazole	CD_2Cl_2	13.5	58
N,N′-$(Me_3Si)_2$imidazole$^+$ OTf^-	CD_2Cl_2	26.6	36a
Me_3SiN_3	$CDCl_3$	15.7	60
Me_3SiNCO	$CDCl_3$	3.9	60
Me_3SiNCS	$CDCl_3$	5.3	60
$(Me_3Si)_2S$	CD_2Cl_2	12.9	61
$(Me_3Si)_3S^+$ $B(C_6F_5)_4^-$	CD_2Cl_2	38.8	61
Me_3SiSMe	CD_2Cl_2	15.9	61
$(Me_3Si)_2SMe^+$ $B(C_6F_5)_4^-$	CD_2Cl_2	40.8	61
Me_3SiF	*n*	30.5	57
Me_3SiF + 4 SbF_5 [k]	SO_2ClF	102	62
Me_3SiCl	CH_2Cl_2	31.1	36b
Me_3SiCl + 1 $B(OTf)_3$	toluene-d8	45.0	53
Me_3SiCl + 1.2 $AlCl_3$	CH_2Cl_2	32.4	52
Me_3SiBr	CH_2Br_2	27.3	52
		(27.6[l])	(58)
Me_3SiBr + 1.2 $AlBr_3$	CS_2	43.5	52
Me_3SiBr + 3 $AlBr_3$	CS_2	54.2 (62.7[m])	52
Me_3SiBr + 1.2 BBr_3	CH_2Br_2	46.0	52
Me_3SiI	CH_2Cl_2	9.9 (10.2)	36b
			(58)
$Me_3Si-C_6D_6^+$ $B(C_6F_5)_4^-$	C_6D_6	83.6	63
Me_3SiCN	C_6D_6	−12.1	64
Me_3SiCNO	$CDCl_3$	−9.5	65
Me_3SiPh	*n*	−4.4	57
Me_3SiH	C_6D_6	−17.5	63
$Me_3SiSiMe_3$	*n*	−19.8	57

[a] Stable at -70 °C in CH_2Cl_2, upon raising the temperature decomposes with formation of Me_3SiCl. [b] Ar = 3,5-bis(trifluromethyl)phenyl. [c] Solvent not specified. [d] DMPU = (*N*,*N*′-dimethylpropyleneurea). [e] 1:1 mixture of Ph_3PO:Me_3SiOTf. [f] 1:1 mixture of pyridine *N*-oxide:Me_3SiOTf. [g] 1:1 mixture of DMF:Me_3SiOTf. [i] At −10 °C. [j] Without solvent. [k] At −100 °C. [l] CD_2Cl_2. [m] In CH_2Br_2. [n] Neat liquide containing up to either 25 vol % of CD_2Cl_2 or 12 vol % of C_6D_6.

Relative Rates for the Silylation of Ketones with Me_3SiX

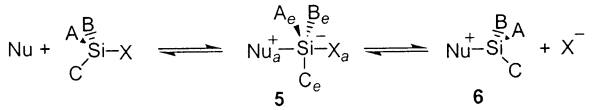
X	Cl	$MeSO_3$	TsO	$PhSO_3$	Me_3SiOSO_3	*p*-$BrC_6H_4SO_3$	Br	$F_3CCH_2SO_3$	F_3CSO_3	I
k_{rel}	1	40	100	160	270	570	10^4	1.4×10^4	6.7×10^8	$\sim 7 \times 10^9$

On the whole, the results obtained by different research groups makes it possible to arrange the most commonly used neutral SLA in the following qualitative activity series: $Me_3SiCl < Me_3SiOMs < Me_3SiOTs < Me_3SiBr \ll Me_3SiOTf \approx Me_3SiOSO_2F \leq Me_3SiI \leq Me_3SiClO_4 < Me_3SiN(SO_2F)_2 < Me_3SiNTf_2$. Positively charged species such as $MeCN{-}SiMe_3^+$ or complexes generated from neutral SLA and metal-centered Lewis acids might be even more reactive than Me_3SiNTf_2.

IV. Principles of Action of SLA

As mentioned above, the chemical behavior of organosilicon compounds is determined primarily by the tendency of the silicon atom to expand its valence shell.[3b,c] Thus, nucleophilic substitution at the silicon atom always proceeds by the associative mechanism through five-coordinate intermediate **5** (Scheme 6).[3]

Scheme 6. Subscripts *a* and *e* Denote Apical and Equatorial Positions of Trigonal Bipyramid 5: ∠*a* Si *a* = 180″°, ∠*a* Si *e* = 90′°, ∠*e* Si *e* = 120″°



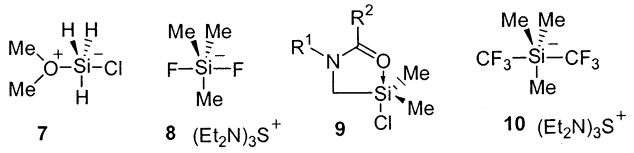
In contrast to the S_N2 substitution at the carbon atom where the structure analogous to **5** is usually considered as the transition state, silicon intermediate **5** can exist for some time before the leaving group X is eliminated. Moreover, in some cases intermediate **5** was isolated and characterized.[3b,c,68]

In the general case, the position of the equilibrium presented in Scheme 6 depends on the nature of the entering and leaving groups and on the properties of the substituents A, B, and C. These substituents may have a pronounced effect on the kinetics and thermodynamics of the substitution reaction, although they are not directly involved in the process.

Reactive SLA (for example, silyl triflates) can form the corresponding salts when interact with strong nucleophiles such as amines, amides, imines, imidazoles, and pyridines.[2c] On the contrary, ethers, aldehydes, and nitriles cannot, as a rule, displace even good leaving groups.

Generation of a five-coordinate species is favored by the presence of hydrogen atoms at the silicon atom. An example is offered by the complex of chlorosilane with dimethyl ether **7**, which was characterized by X-ray diffraction analysis at −173 °C (Scheme 7).[68a] The presence of alkyl groups at the

Scheme 7

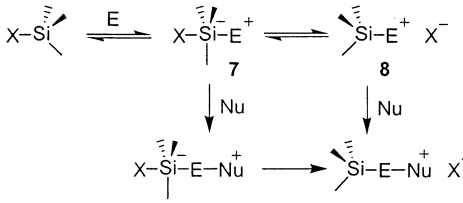


silicon atom makes the five-coordinate intermediate much less stable for both electronic and steric reasons. Stable five-coordinate trialkylsilyl derivatives are generated in the presence of fluoride anions (for example, **8**[68d,69]) or, as in the case of **9**,[68c,70] when they are favored by intramolecular coordination (Scheme 7). Anion **10** containing five carbon substituents at the silicon atom was also studied by X-ray diffraction analysis. However, this salt is stable only at temperatures below 0 °C.[68e]

Trialkyl-substituted SLA, in particular, Me_3SiOTf and *t*-$BuMe_2SiOTf$, are the most frequently used silicon reagents. No visible changes (NMR spectroscopy) generally occur upon mixing these reagents with weak Lewis bases (aldehydes, ethers, or nitriles), indicating that the equilibrium shown in Scheme 6 is shifted toward the starting compounds. Nevertheless, both five-coordinate intermediate **5** and cationic complex **6** can be present in the reaction mixture in very low equilibrium concentrations. At the same time, it is not inconceivable that a strong Si-X bond does not dissociate and, hence, cationic complex **6** cannot be generated.

In reactions of C,C bond formation between electrophiles (E) and nucleophiles (Nu), the function of SLA is to activate the electrophilic component serving as a Lewis base (e.g., aldehyde). The subsequent nucleophilic attack can proceed both at intermediate **7** and cation **8** (Scheme 8). It is evident that neutral

Scheme 8



adduct **7** is much less electrophilic than cation **8**. If cation **8** is not generated in the equilibrium mixture, the reaction of adduct **7** with a nucleophile becomes the rate-determining step.

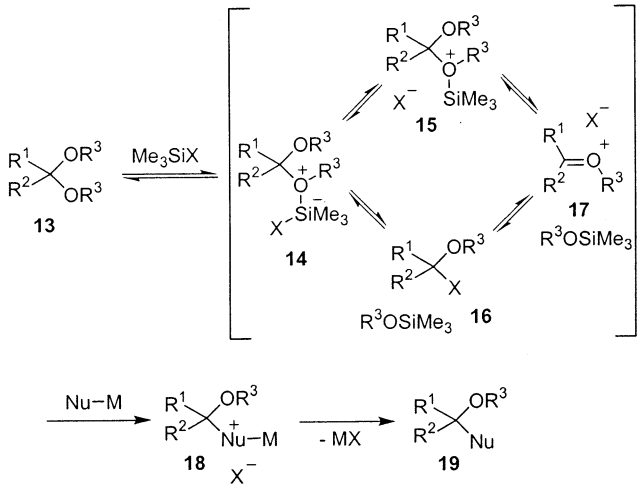
Hence, the possibility of the process to occur depends on the nature of the electrophile, the reactivity of the nucleophile, the strength of the silicon-heteroatom bond, and some other factors. In addition, the contribution of each factor depends on the type of the reaction. The reactions of C,C bond formation promoted by SLA will be detailed in the following sections. The review is classified according to the type of electrofile employed. Within some chapters further classification is made taking into account the types of nucleophiles, as well as other peculiarities of the processes under consideration.

V. Reactions of Acetals with Nucleophiles

Various C-nucleophiles react with acetals **13** in the presence of Me_3SiX with the replacement of the alkoxy group. The general reaction mechanism is shown in Scheme 9.

Initially, the acetal reacts with Me_3SiX to form complexes **14** or **15**. The related cation, viz., trimethylsilyldiethyloxonium $Me_3SiOEt_2^+$, is very reactive and can be generated only with the use of the nonnucleophilic tetraarylborate counterion (see Table 2).[46] Hence, complexes **14** and **15** are likely to be short-lived intermediates, which either very rapidly

Scheme 9



revert to the starting compounds or react further with C-nucleophiles present in the system. In the latter case, two extreme mechanisms of C,C bond formation should be considered: the dissociative mechanism (S_N1) through oxocarbenium cation **17** and the classical S_N2 mechanism. Depending on the nature of the counterion X, cation **17** could also produce the covalent intermediate **16**, which also could react with a nucleophile by the S_N2 mechanism. In the final step, elimination of MX from the charged intermediate **18** gives the final product **19**.

The synthetic significance of this reaction gave impetus to detailed studies about its mechanism.[71] Among a large body of research in this field, which are based primarily on stereochemical data, studies carried out by Sammakia provide the most convincing results.[72]

For example, the reactions of acetal **20**, which is deuterium-labeled at only one methoxy group, was examined (Scheme 10).[72a] The S_N2 nucleophilic attack must be accompanied by inversion of the configuration at the reaction center, whereas the S_N1 attack must lead to epimerization. Hence, reactions of acetal **20** with nucleophiles can give rise to two isomers **21a**,**b** in the case of S_N2 substitution, or four isomers **21a**−**d** in the case of S_N1 substitution. Actually, the reaction of **20** with Me_3SiCN, trimethylsilyl enol ether of pinacolone, and allyltributylstannane in the presence of Me_3SiOTf affords four products **21a**−**d** in approximately equal amounts, isomerization of unconsumed acetal **20** being at most 10%. However, in the case of allyltrimethylsilane, isomerization of acetal **20** proceeds more rapidly than substitution. Therefore, all the above results provide evidence in favor of the S_N1 mechanism.

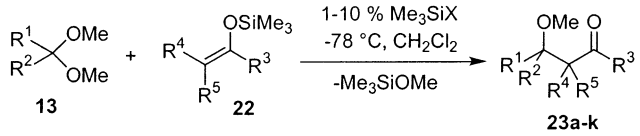
Acetals of aromatic and α,β-unsaturated aldehydes, leading to more stable carbocations, react with nucleophiles more rapidly than acetals derived from aliphatic aldehydes.

If the reaction shown in Scheme 9 involves a silylated nucleophile (M = SiR_3), the formation of the C,C bond is followed by regeneration of the starting silylating agent (MX = R_3SiX). Therefore, it is possible to carry out the process in the presence of a catalytic amount of the silyl activator R_3SiX. It should be emphasized that the step **18** → **19**, which is very rapid in the case of trimethylsilyl derivatives, proceeds via nucleophilic substitution at the silicon atom rather than through elimination of the silyl cation.

A. Reactions with Enol Ethers

The reactions of acetals **13** with silyl enol ethers **22**, catalyzed by Me_3SiOTf,[4,5,73,74] Me_3SiI,[75] or $Me_3SiN(SO_2F)_2$[19a] (1−10 mol %), proceed smoothly at −78 °C to give the corresponding products **23** in high yields (Scheme 11, Table 3).

Scheme 11



In the presence of Me_3SiOTf, the reactions are complete within 4−12 h, whereas the reactions catalyzed by Me_3SiI or $Me_3SiN(SO_2F)_2$ take 0.5−1 and 0.5 h, respectively, according to the relative activity of SLA.

The versatility of this transformation, which is an equivalent of the aldol condensation, is demonstrated by the great structural diversity of the reacting components. Mono-, di-, and trisubstituted silyl enol ethers **22** give C,C cross-coupling products with acetal derivatives of aldehydes, ketones, and thioesters. These reactions can also afford sterically hindered products containing the adjacent quaternary carbon atoms (Table 3, entry 3). In the reactions of acetals of α,β-unsaturated aldehydes, the nucleophilic attack proceeds in a 1,2-fashion (Table 3, entry 9).

Trimethyl orthoformate smoothly reacts with silyl enol ethers (Table 3, entries 6 and 10), whereas trimethyl orthoacetate proved to be completely unreactive. Thus, the reaction of trimethyl orthoacetate

Scheme 10

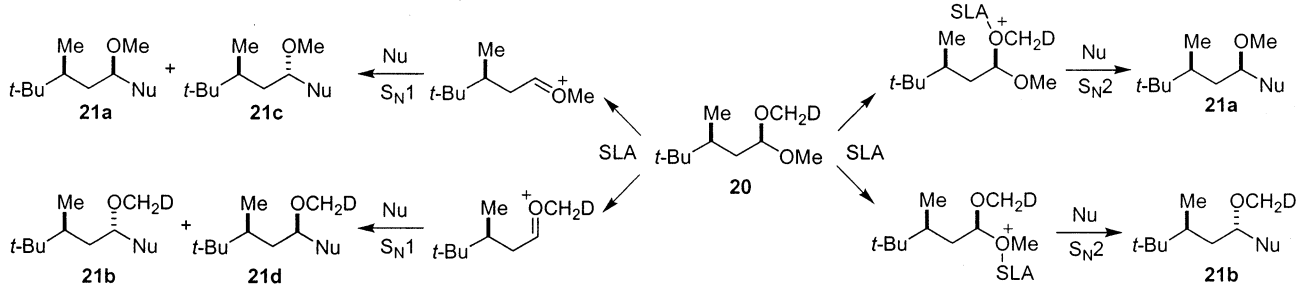
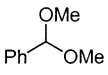
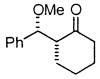
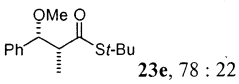
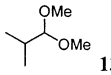
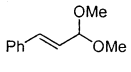
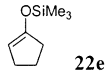
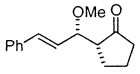
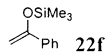
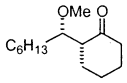
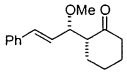


Table 3. Coupling of Acetals 13 with Silyl Enol Ethers 22[a]

№	Acetal **13**	Nu	X	Cat. Mol %,	Time, h	Product, Syn/anti	Yield %
1	 **13a**	 **22a**	OTf	1	10	 **23a**, 93 : 7	89[b]
2	 **13b**	**22a**	OTf	5	10	 **23b**	87
3	**13b**	 **22b**	OTf	5	4	 **23c**	85
4	**13a**	 **22c**	OTf	5	4–5	 **23d**	from *E*-**22c**: 71 : 29 from *Z*-**22c**: 84 : 16	83 97
5	**13a**	 **22d**	OTf	5	4–10	 **23e**, 78 : 22	92
6	$(MeO)_3CH$ **13c**	**22a**	OTf	5	12	 **23f**	89
7	**13a**	**22a**	I	10	1	**23a**, 95 : 5	89
8	 **13d**	**22a**	I	10	0.4	 **23g**, 79 : 21	70
9	 **13e**	 **22e**	I	10	0.5	 **23h**, 80 : 20	82
10	**13c**	 **22f**	I	10	1	 **23i**	88
11	$(MeO)_2CHC_6H_{13}$, **13f**	**22a**	$N(SO_2F)_2$	5	0.5	 **23j**, 86 : 14	82
12	**13e**	**22a**	$N(SO_2F)_2$	5	0.5	 **23k**, 84 : 16	87

[a] The selected data are given from refs 4, 5, 73 (X = OTf), 75 (X = I), and 19 (X = $N(SO_2F)_2$). [b] In the presence of 5% Me_3SiOTf and 5% 2,6-di-*tert*-butylpyridine, the product **23a** is obtained in 76% yield with syn/anti = 75:25.

with silyl enol ether **22a** and Me_3SiOTf, in the molar ratio 1:1:1 in CH_2Cl_2 at 25 °C, gives rise to methyl acetate, $MeOSiMe_3$, and MeOTf in quantitative yields, whereas the starting compound **22a** remaines unconsumed.[5,76] However, it was reported that the reaction of trimethyl orthoacetate with 1,1,2-tris(trimethylsilyloxy)ethylene in the presence of Me_3SiOTf (1 mol %) at −78 °C afforded the corresponding C,C cross-coupling product in 80−90% yield.[74b]

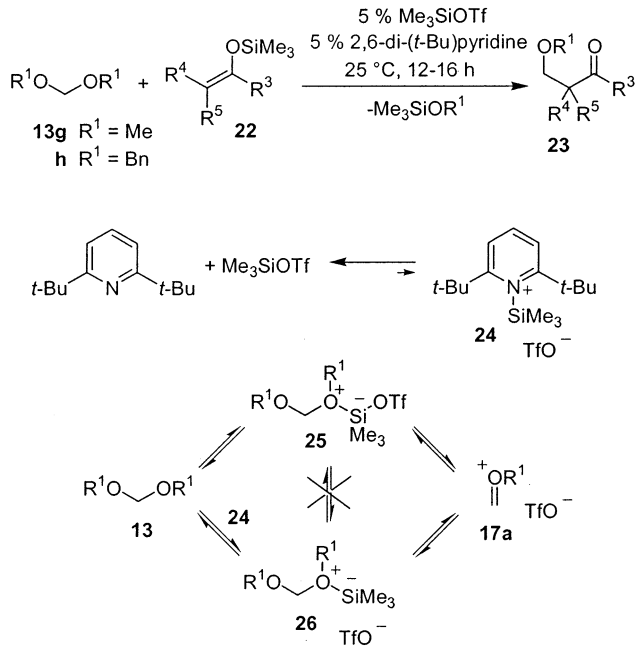
Formaldehyde acetals **13g**,**h** are inert with respect to silyl enol ethers in the presence of Me_3SiOTf at −78 °C. However, this reaction can be carried out at 25 °C by adding 2,6-di-*tert*-butylpyridine (Scheme 12).[5,77]

The reaction does not take place in the absence of a sterically hindered base. It was assumed that combination of 2,6-di-*tert*-butylpyridine with Me_3SiOTf leads, at the equilibrium, to the formation of a small amount of complex **24**, which is a much stronger silyl donor than Me_3SiOTf (Scheme 12).[5] It may be tentatively proposed that in the reaction with acetal, complex **24** can generate active silyloxonium cation **26**, whereas the triflate anion is not necessarily eliminated from five-coordinate intermediate **25** due to the strength of the Si−O bond. For the reaction with a nucleophile to proceed via S_N1 pathway, an oxocarbenium cation of type **17** must be formed. Apparently, the latter is more readily generated from **26** than from **25**.[78]

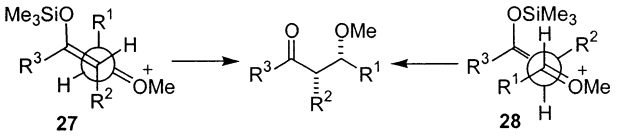
The reactions leading to β-alkoxyketones **23** containing two adjacent asymmetric centers affords predominantly syn isomers (see Table 3), the syn/anti ratio ranging from 57:43 to 95:5 independently of the geometry of the double bond of the starting silyl enol ether (see Table 3, entry 4). The preferential syn selectivity was explained by assuming the involvement of open transition states **27** (for *E* enolates) and **28** (for *Z* enolates) (Scheme 13).[5]

In the reactions of α-alkoxy-substituted tetrahydropyrans, nucleophiles add predominantly at the equatorial position. This fact can be explained on the basis of the geometry of the ion pair of the oxocar-

Scheme 12



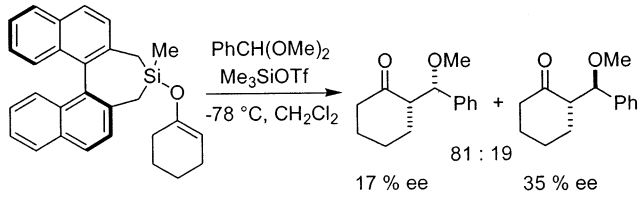
Scheme 13



benium cation in which the counterion occupies the more favorable anomeric (axial) position, thus shielding the approach of the nucleophile.[5] Electron-withdrawing groups which destabilize oxocarbenium cation through the inductive effect, usually slow the reaction. Nevertheless, coupling of acetals of 2-bromo and 2-chloroacetaldehdye with strongly nucleophilic bis(silyl) enol ether derived from acetoacetic ester proceeds in the presence of 0.3−1 equiv of Me_3SiOTf furnishing corresponding products in 38−72% yield.[79]

The reaction of cyclohexanone silyl enol ether containing the chiral binaphthalene fragment at the silicon atom with benzaldehyde dimethylacetal affords the expected product in a 81:19 syn/anti ratio, but with low enantiomeric excess (Scheme 14).[80]

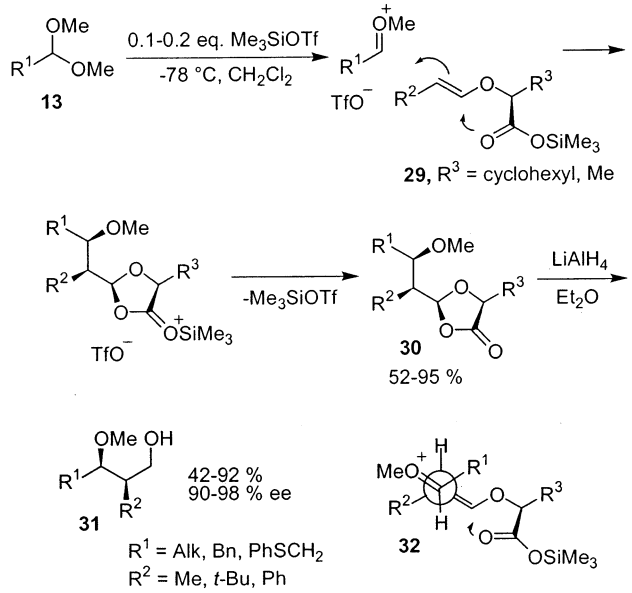
Scheme 14



The attack of electrophilic reagents at the double bond of alkyl vinyl ethers gives rise to active oxocarbenium cation, which can react with the next molecule of vinyl ether resulting in its polymerization.[81] This undesirable process can be suppressed by rapid capture of the cation formed by any other nucleophile. Generally, this scheme takes place upon intramolecular quenching of the carbocation. The following two examples demonstrate the possibilities of the use of acetals in combination with alkyl vinyl ethers under the action of Me_3SiOTf.

The reactions of silyl *O*-alkenylhexahydromandelate and *O*-alkenyl lactate **29** with acetals **13** in the presence of catalytic amounts of Me_3SiOTf (10−20 mol %) affords dioxolanones **30** with high diastereoselectivity. After removal of the chiral auxiliary with lithium aluminum hydride, optically active alcohols **31** are obtained (Scheme 15).[82]

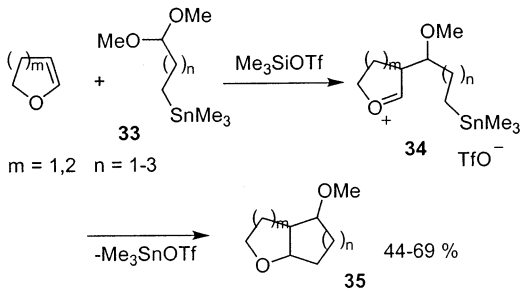
Scheme 15



The structure of **30** reflects a *syn*-addition mechanism via open-chain transition state **32**. The nature of substituents at the double bond in **29** has virtually no effect on the selectivity of the reaction; however, the reaction rate substantially depends on both electronic and steric factors. The insertion of electron-withdrawing substituents into the hydrocarbon skeleton of acetals significantly reduces their reactivity. Thus, the reactions of 3-bromopropanal dimethylacetal with enol ethers **29** proceed very slowly, whereas 2-chloroacetaldehdye dimethylacetal does not react at all.[82]

The reactions of cyclic vinyl ethers with acetals **33** containing the trimethylstannyl fragment generate oxocarbenium cations **34**, which undergo subsequent cyclization to bicyclic compounds **35** (Scheme 16).[83]

Scheme 16



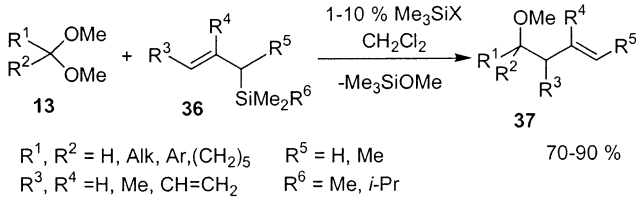
B. Reactions with Allylic Reagents

Allylic organometallic compounds represent another class of C-nucleophiles, which react with acetals

under the action of SLA. The reactions proceed as allylic electrophilic substitution by the S_E2' mechanism.

In particular, the reactions of allyltrimethylsilanes **36** with acetals catalyzed by Me_3SiOTf,[4,84] Me_3SiI,[85] $Me_3SiN(SO_2F)_2$,[19a] or Me_3SiNTf_2[56] (1−10 mol %) produce ethers of homoallylic alcohols **37** (Scheme 17).

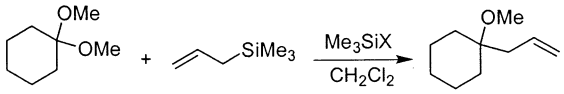
Scheme 17



However, the reactions of acetals with allylsilanes are slower than those with silyl enol ethers. Indeed, the reactions involving Me_3SiOTf[84] or Me_3SiI[85] sometimes require the rise of the temperature to −40 °C. Some reactions of acetals containing electronwithdrawing groups also require more drastic conditions. For example, the reactions of methyl-α-D-gluco- and mannopyranosides with allyltrimethylsilane are carried out at room temperature in acetonitrile using 0.5 equiv Me_3SiI as the catalyst.[86]

It appears that for this kind of processes $Me_3SiN(SO_2F)_2$[19a] and Me_3SiNTf_2[56] are the most active catalysts, which enable to perform the reactions at −78 °C for 0.5−1 h. The relative reactivities of different SLA are determined by the allylation reaction of cyclohexanone dimethylketal with allyltrimethylsilane (Scheme 18).[56]

Scheme 18

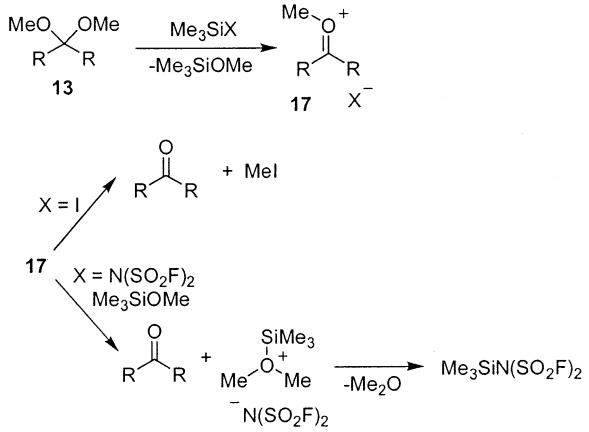


X	Equiv. of SLA	T, °C	Time, h	Yield, %
OTf	0.01	–60 - –45	18	81
$N(SO_2F)_2$	0.05	–78	0.75	91
NTf_2	0.05	–78	0.25	91

Sakurai demonstrated that the rates of the reactions of allylsilanes with acetals substantially decrease as the steric volumes of the substituents both at the silicon atom and at the α- or γ-carbon atoms of allylsilane increase.[85] Allyltriethylsilane, (α,α-dimethyl)allylsilane, and (γ,γ-dimethyl)allylsilane proved to be completely unreactive with respect to benzaldehyde dimethylacetal in the presence of Me_3SiI.

Catalysis by Me_3SiI or $Me_3SiN(SO_2F)_2$ deserves detailed consideration because acetals in the presence of these catalysts are smoothly transformed into the corresponding carbonyl compounds (Scheme 19). Deacetalization proceeds at 25 °C with the use of a stoichiometric amount of Me_3SiI.[87] The most probable mechanism of this transformation involves the initial

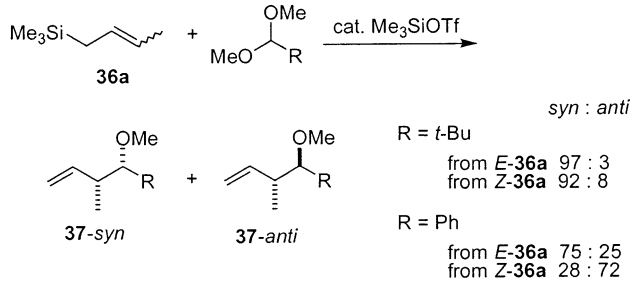
Scheme 19



formation of oxocarbenium cation **17**, followed by dealkylation through nucleophilic attack by iodide ion. In the case of $Me_3SiN(SO_2F)_2$, the reaction proceeds at −78 °C in the presence of only 5 mol % of the catalyst.[88] The mechanism proposed in the last example involves the nucleophilic attack of the oxygen atom of methoxysilane on the methyl group of cation **17** to give a carbonyl compound, dimethyl ether, and $Me_3SiN(SO_2F)_2$. If the acetal/Me_3SiX system contains a π-nucleophile (silyl enol ether **22** or allylsilane **36**), the interaction of oxocarbenium cation **17** with **22** (or **36**) proceeds faster than decomposition of cation **17** to aldehyde or ketone.

E-Crotylsilanes produce predominantly syn diastereomers of ethers **37**, whereas *Z* isomers can give either syn or anti derivatives as the major products depending on the structure of the acetal (Scheme 20).[89]

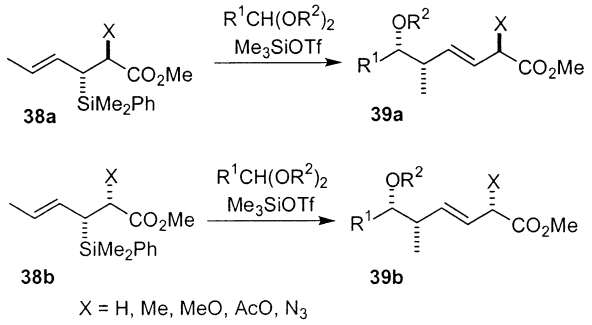
Scheme 20



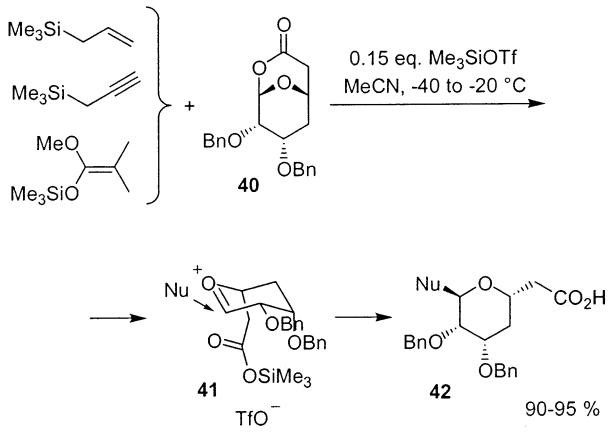
Chiral *E*-allylsilanes **38a**,**b**, which are accessible in any absolute and relative configurations, are coupled with various acetals of aromatic, aliphatic, and α- and β-alkoxy-substituted aldehydes in the presence of a stoichiometric amount of Me_3SiOTf to give products **39a**,**b** with predominant (up to 40:1) syn arrangement of the formed stereocenters. The absolute configuration of the 5-methyl group is controlled by the configuration of the carbon atom bound to the silicon atom in silanes **38a**,**b** (Scheme 21).[90]

The reactions of bicyclic acetal **40** with allyltrimethylsilane, propargyltrimethylsilane, or silyl ketene acetal in acetonitrile catalyzed by Me_3SiOTf (15%) proceed stereoselectively to form 2,6-trans isomers **42**. This is attributable to the anomeric effect and

Scheme 21



Scheme 22

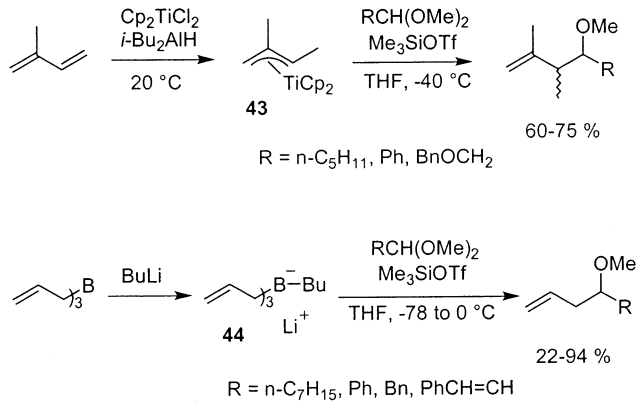


shielding of the axial position by the carboxylate group in intermediate **41**.[91]

Allyltributylstannanes react very rapidly with acetals at −78 °C; however, these reactions require a stoichiometric amount of Me_3SiOTf because the resulting Bu_3SnOTf is much less active than SLA with respect to acetals.[92]

In addition to allylsilanes and allylstannanes, other allylating reagents can be also coupled with acetals. An example is offered by 1,2-dimethyl-η^3-allyltitanocene **43**, which is readily generated in situ from isoprene, titanocene dichloride, and diisobutylaluminum hydride,[93] and by lithium butyltriallyl borate **44**, which is prepared from triallylborane and butyllithium.[94] The complexes **43** and **44** react with acetals in tetrahydrofuran in the presence of a stoichiometric amount of Me_3SiOTf (Scheme 23). In the latter case, the possibility of transmetalation of ate-complex **44** with Me_3SiOTf to form allyltrimethylsilane was

Scheme 23



demonstrated by special experiments. Nevertheless, it was suggested that transmetalation proceeds more slowly than the reaction of **44** with the acetal.

α-Heterosubstituted acetals containing an alkoxy group,[95] an alkylthio group,[95,96] or a halogen atom,[97] also react with silyl nucleophiles in the presence of Me_3SiOTf (Scheme 24). The predominant formation of the anti isomers in the reactions of α-alkythio and α-halogeno derivatives **45** and **46** counts in favor of oxocarbenium cation **47** because syn isomers would be formed in the case of cyclic intermediate **48**.

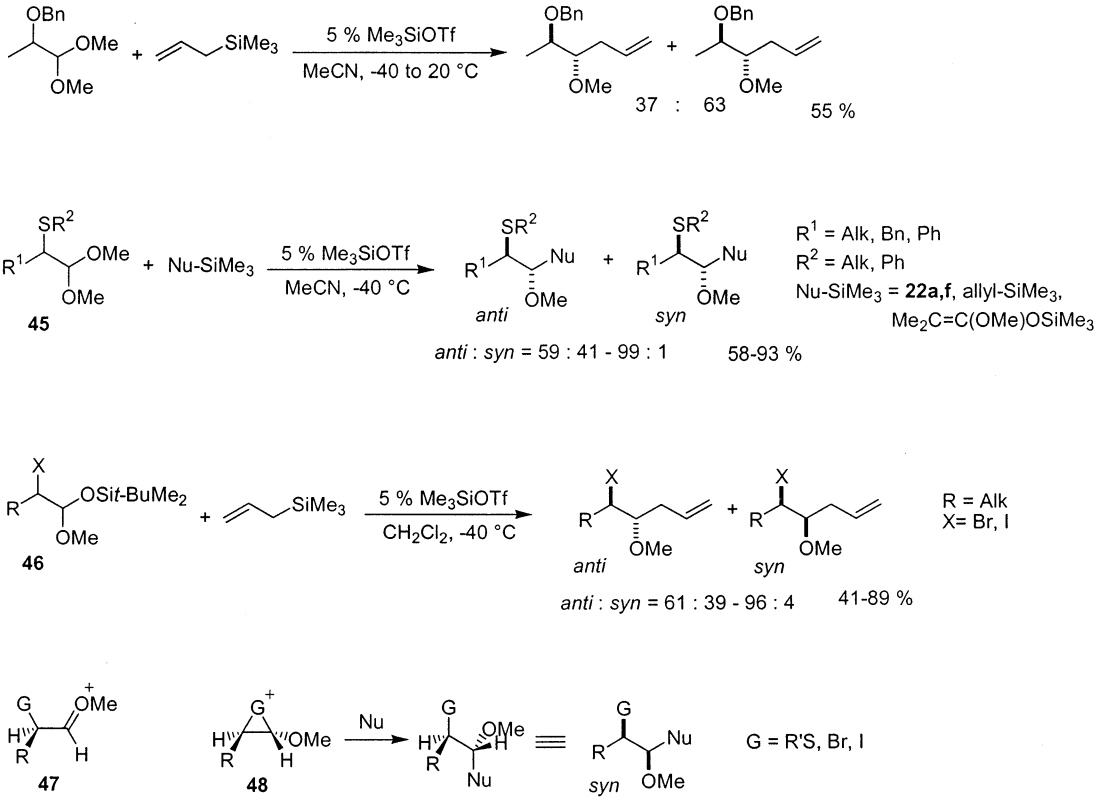
C. Reactions with Other Nucleophiles

Products of double silylation of aliphatic nitro compounds, viz., *N*,*N*-bis(silyloxy)enamines **49**, couple with acetals in the presence of a stoichiometric amount of Me_3SiOTf (Scheme 25).[98] The attack to the oxocarbenium cation gives rise to *N*,*N*-bis(silyloxy)-iminium cation **50**, which exists in equilibrium with silyl nitronate **51**. After workup, γ-alkoxy nitro compounds are obtained in 26−77% yields. In these reactions, Me_3SiOTf is the activator of choice because enamines **49** are not compatible with standard Lewis acids, such as $BF_3{\cdot}OMe_2$ or $TiCl_4$, as well as with protic acids, due to their propensity to rearrange to α-silyloxy oximes.[99] Enamines **49** are similar in activity to silyl enol ethers and are approximately 9 orders of magnitude less nucleophilic than standard *N*,*N*-dialkylenamines.[100,108] The reason for this is that compounds **49** contain two electron-withdrawing silyloxy groups favoring pyrimidalization of the nitrogen atom.[101]

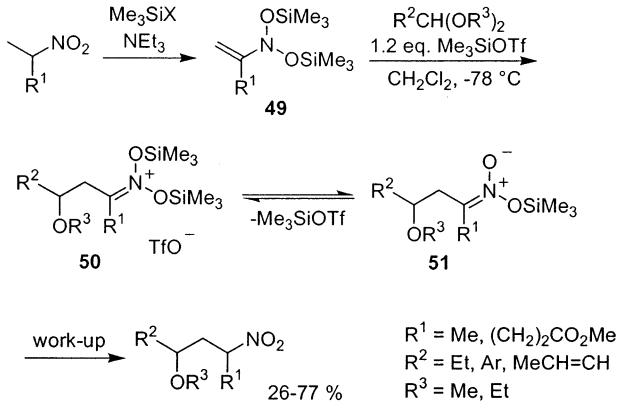
The oxocarbenium cations generated in the acetal/SLA system can smoothly react with simlpe alkenes if the intermediate carbocation may be stabilized, for example, through a sigmatropic rearrangement (Scheme 26). Thus, the electrophilic attack of the oxocarbenium cation on alkenylcyclopropanes **52a**,**b** is accompanied by ring expansion to form cyclobutyl cations **53a**,**b**. Subsequent elimination of the silyl (in the case of **53a**) or acetyl (in the case of **53b**) group affords cyclobutanone **54**. It should be noted that acetyl derivative **52b** reacts much more slowly than its silyl counterpart.[102] Coupling of vinylcyclopropane **55** with acetals yields 1,4-dienes with trans configured internal double bond regardless of the relative stereochemistry in the substrate. This is attributed to the intermidiacy of cation **56**, which undergoes ring opening from the most favorable conformation having anti orientation around incipient double bond.[103] The reaction represented by eq c in Scheme 26 proceeds analogously, involving an intermediate ring contraction leading to a spiro-ketone.[104] The intramolecular attack of the oxocarbenium cation at the double bond of homoallylic ether can be accompanied by the transfer of the allyl group followed by a hetero-Cope rearrangement (Scheme 26d).[105] It is assumed that the equilibrium between intermediates **57** and **58** shifted to phenyl-stabilized cation **58** is established more rapidly than their intermolecular reduction with tributylstannane. A high degree of chirality transfer is likely associated with intramolecular character of the allyl group transfer.

The incipient carbocation can also be stabilized through homoconjugation of the unoccupied orbital

Scheme 24



Scheme 25



with the C−Sn σ-bond, as in the reaction of the acetal with stannane **59**, to give the corresponding cyclopropane after elimination of the stannyl group (Scheme 27).[106] However, this effect is much weaker than stabilization in allylic system. Consequently, the reactivity of π-nucleophiles increases in the series homoallylstannane < allylsilane < allylstannane.[106a,107,108]

If the carbocation, formed upon attack of an electrophile at the multiple C,C bond, does not have opportunity for stabilization, the rapid addition of the nucleophilic species present in the solution should occur. Such an approach is applied to the cyclization of acetals **60** promoted by Me_3SiI (Scheme 28).[109] In this case, Me_3SiI acts not only as a Lewis acid activating acetal but also as a source of strongly nucleophilic iodide anion.

Along with usual π-nucleophiles, organometallic reagents containing the C−M σ-bond as the nucleophilic center can be also involved in reactions with acetals. For example, cations **61**, generated from 4-acetoxy-1,3-dioxanes under the action of Me_3SiOTf, reacted with diorganozinc compounds to form 1,3-dioxanes **62** (Scheme 29a). It should be emphasized that both alkyl substituents of R_2Zn can be used for the formation of the C,C bond. Moreover, the process is characterized by high diastereoselectivity. It is assumed that the bulky *tert*-butyl substituent in **61** tends to be located in the pseudoequatorial position thereby providing prerequisites for diastereotopic face differentiation.[110]

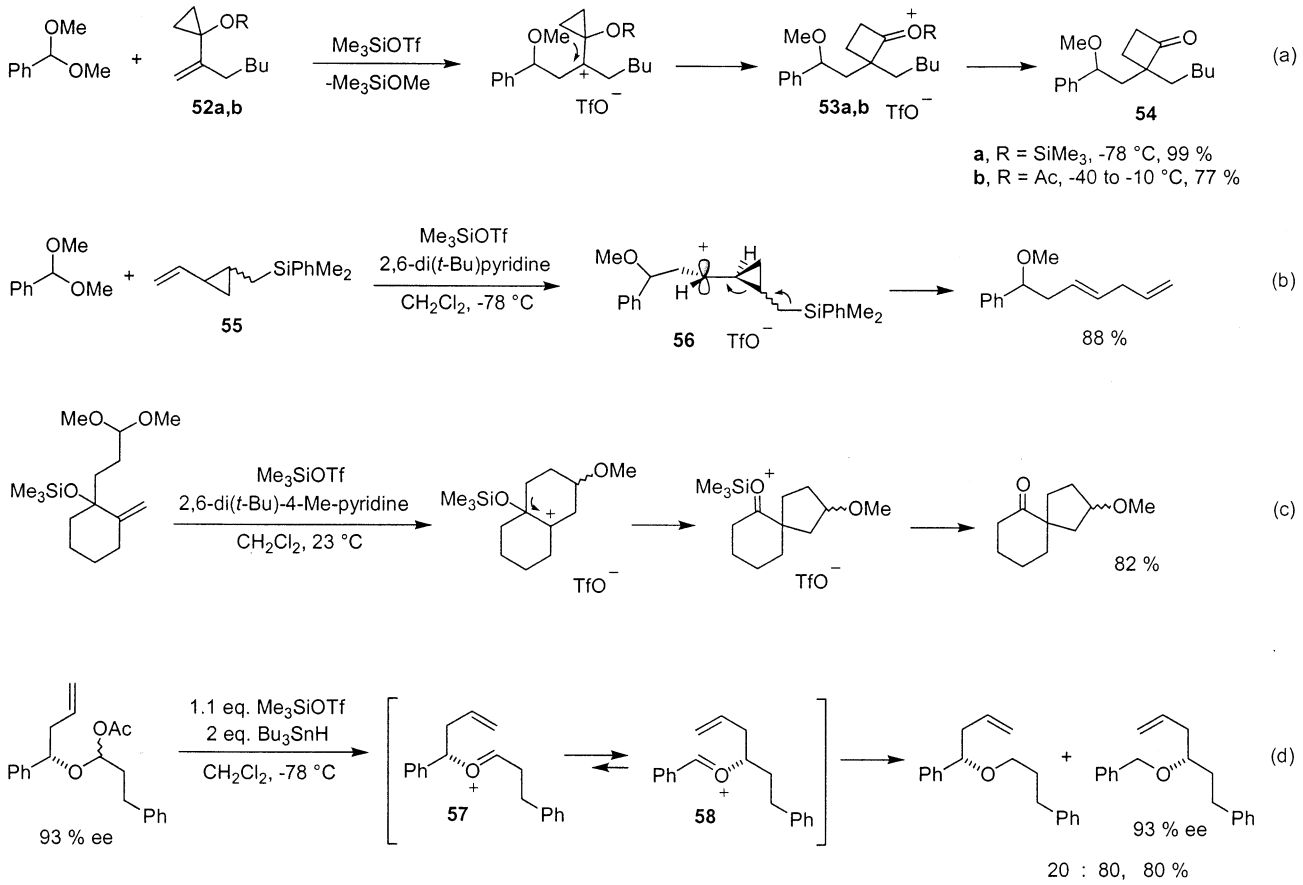
β-Dialkylaminoacetals also react with diethylzinc in the presence of Me_3SiOTf leading preferentially to anti substituted products (Scheme 29b). High selectivity of the reaction is attributed to the coordination of organozinc species with nitrogen lone pair, structure **63**. The intramolecular delivery of the ethyl group occurs from the side opposite to substutent R.

VI. Reactions of Acetal-Like Compounds with Nucleophiles

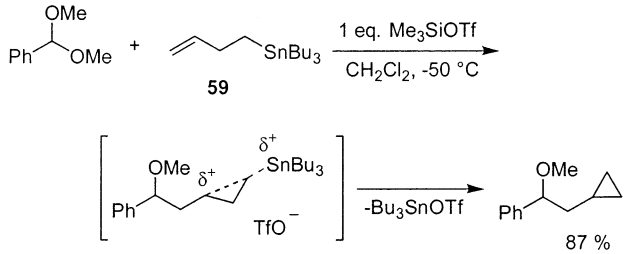
Under the action of SLA, several compounds of general formula A−CH_2−B, where A and B are heteroatoms, can generate stabilized CH_2=A^+ (or CH_2=B^+) cations accompanied by silyl derivatives R_3-SiB (or R_3SiA). The direction of the reaction is generally determined by stability of the carbocation, whereas the strength of the silicon−heteroatom bond is of minor importance.

For example, α-chloroethers **64a** react with silyl enol ethers[111] or allylsilanes[112] in the presence of catalytic amounts of SLA (Me_3SiOTf or Me_3SiI,

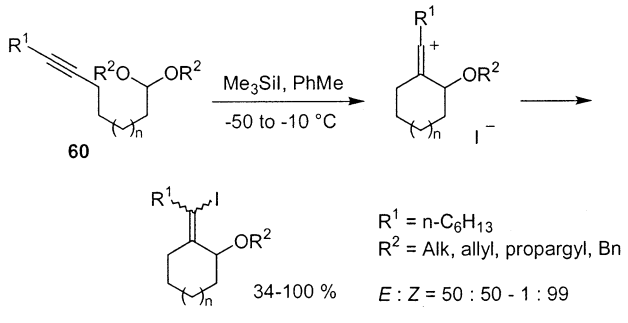
Scheme 26



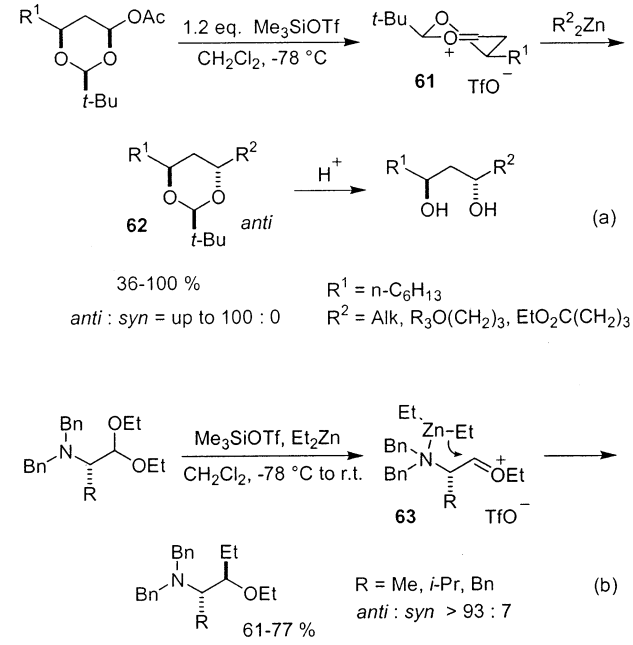
Scheme 27



Scheme 28



Scheme 29

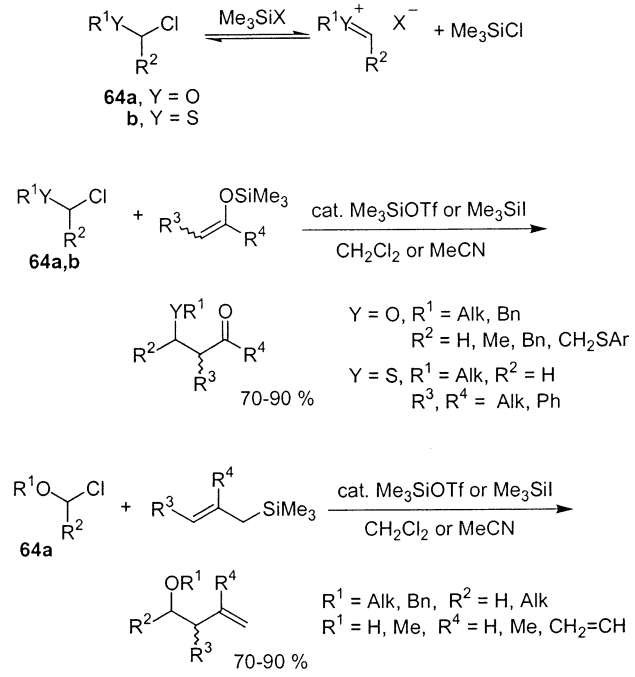


Scheme 30). The reaction rate depends primarily on the structure of α-chloroether. Thus, formaldehyde derivatives (**64a**, $R^2 = H$) react with nucleophiles at 0−20 °C, whereas derivatives of other aldehydes (**64a**, $R^2 \neq H$) rapidly react even at −78 °C. Apparently, the rate-limiting step involves the formation of an electrophilic species from compounds **64**.

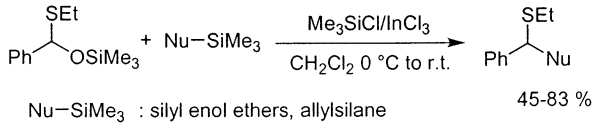
α-Chlorosulfides (**64b**) behave analogously.[111a] However, the sulfur atom less efficiently stabilizes the α-cationic center, and, as a consequence, the reactions of α-chlorosulfides require more drastic conditions (refluxing in CH_2Cl_2).

Monothioacetals react with silyl enol ethers and allyltrimethylsilane upon catalysis by $Me_3SiCl/InCl_3$ to give products resulting from the replacement of the silyloxy group (Scheme 31)[113] (for more detailed data on the combined action of SLA and other Lewis acids, see section VII.C.). Apparently, the reactions

Scheme 30



Scheme 31

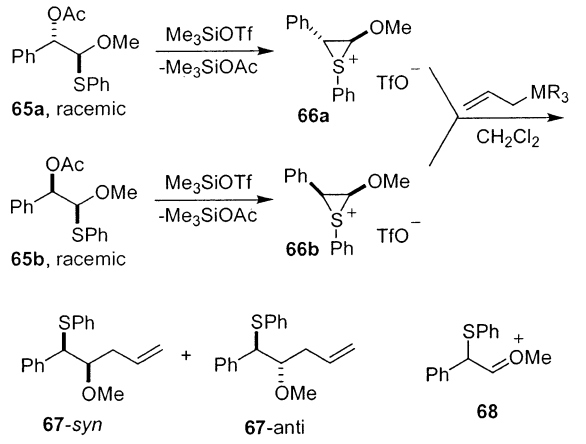


proceed through a less favorable thio-stabilized carbocation, the direction of this process being determined by the formation of a very strong Si−O bond upon the generation of the electrophilic intermediate.[113b]

Treatment of compounds **65a**,**b** with SLA causes the elimination not of the acetal alkoxy group, but that of the adjacent acetoxy function, followed by the reaction of episulfonium ions **66a**,**b** with allylic nucleophiles (Scheme 32).[114] On the basis of the dependence of selectivity (**67**, syn/anti) on the nature of the nucleophile, the following scheme was originally proposed. The reactions of **66a**,**b** with weak nucleophiles, viz., allylsilane and allylgermane, proceed by the S_N1 mechanism, i.e., through oxocarbenium cation **68** resulting in the predominant formation of the syn isomer, independently of the configuration of the starting substrate. The reactions with stronger nucleophiles, viz., allyltrialkylstannanes, were assumed to follow the S_N2 mechanism with inversion of configuration at the C-2 of **66**. However, taking into account that the reactions of **65a** and **65b** involving allyltriphenylstannane proceed with equal selectivity, it can be suggested that the dissociative S_N1 mechanism is more probable in the case of allylstannanes as well.[72]

Iminium cations **69** can be readily prepared from various derivatives of aminals or hemiaminals under the action of SLA (Scheme 33)[115] In the case of X = Cl, iminium derivatives **69** exist as ionic pairs in which the chloride anion forms a hydrogen bond with the protons of the CH_2 group, whereas iminium triflates (X = OTf) produce purely ionic salts.[116] The

Scheme 32



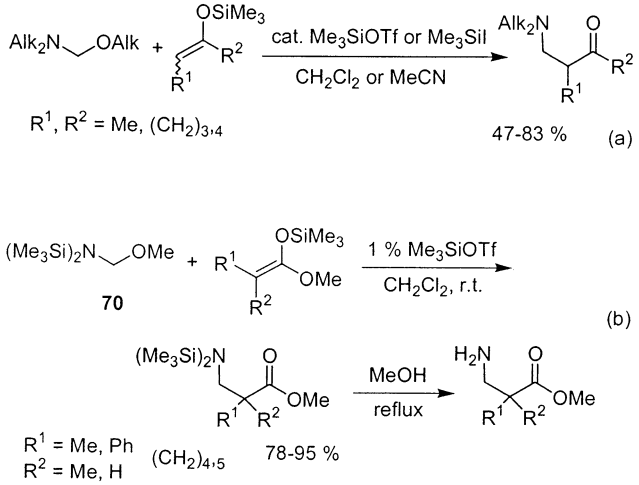
starting	MR_3	**67** *syn* : *anti*	starting	MR_3	**67** *syn* : *anti*
65a	$SiMe_3$	80 : 20	**65a**	$SnMe_3$	96 : 4
65b	$SiMe_3$	79 : 21	**65b**	$SnMe_3$	14 : 86
65a	$GeMe_3$	84 : 16	**65a**	$SnBu_3$	89 : 11
65b	$GeMe_3$	73 : 27	**65b**	$SnBu_3$	12 : 88
			65a	$SnPh_3$	78 : 22
			65b	$SnPh_3$	76 : 24

Scheme 33

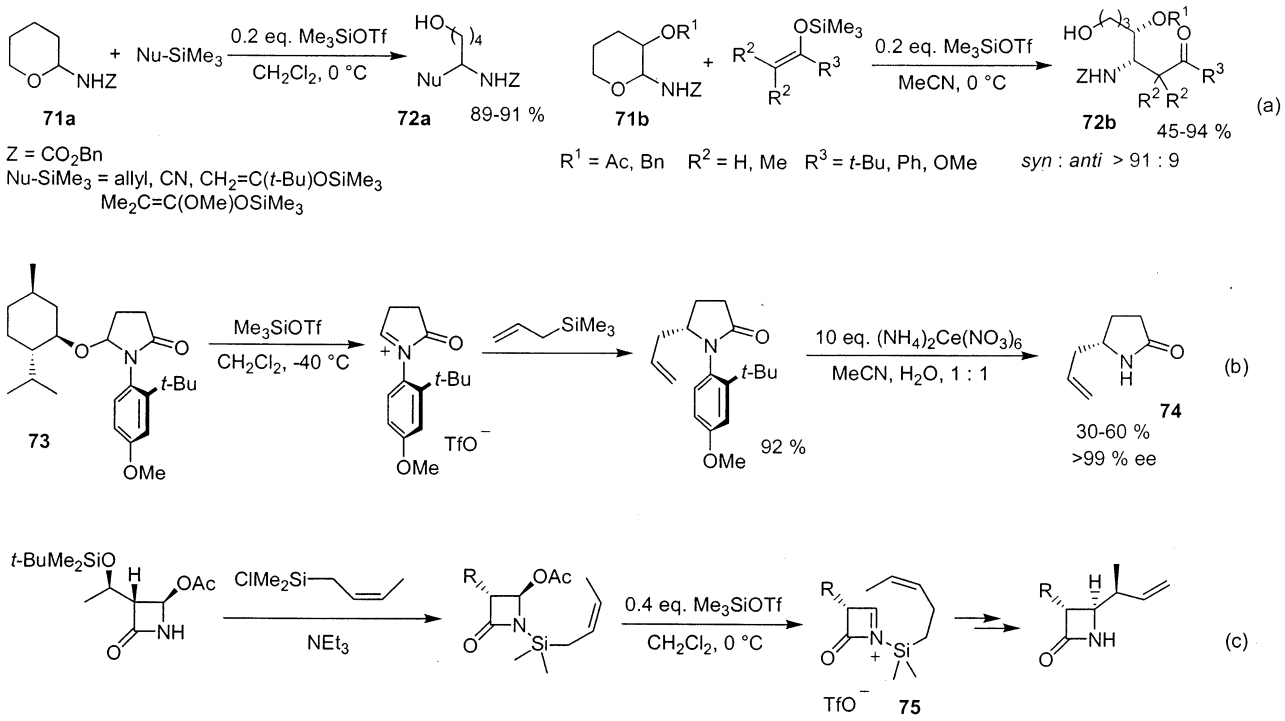
chloride ion can be replaced by the triflate ion under the action of Me_3SiOTf.[117]

Although salts **69** can be isolated in the individual form, C,C cross-coupling reactions are often performed with the use of these salts generated in situ in the presence of a nucleophile. If the nucleophile contains the leaving R_3Si group (for example, silyl enol ether), a catalytic amount of SLA is sufficient for the reaction to proceed (Scheme 34a).[118] Of special note is reagent **70** because it enables one to directly

Scheme 34



Scheme 35



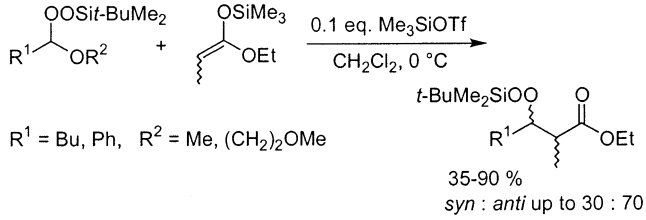
introduce the unsubstituted amino group (Scheme 34b).[119]

The *N*-acyliminium cations are more electrophilic than usual iminium salts due to the presence of the electron-withdrawing acyl group.[120] As a rule, these cations are generated using strong SLA, such as Me_3SiOTf. For example, the reactions of *N*-benzyloxycarbonyl-protected 2-aminotetrahydropyrans **71a** with a wide range of nucleophiles in dichloromethane in the presence of Me_3SiOTf furnishes acyclic derivatives **72a** (Scheme 35a).[121] The reactions of compounds bearing an acetoxy or benzyloxy group at the α position with respect to the aminal center (compounds **71b**) proceed with high selectivity to give syn isomers **72b**; however, a more polar solvent such as acetonitrile or nitromethane is required. The substantial effect of the medium polarity is apparently associated with solvation of the resulting iminium cation, which is destabilized due to the presence of the adjacent electron-withdrawing alkoxy group.[121] Allylation of amide **73**, which exists as a single atropoisomer, proceeds at −40 °C with nearly 100% selectivity (Scheme 35b). Subsequent oxidative removal of the aryl fragment affords lactam **74** with more than 99% ee.[122] High selectivity of this process is determined by steric hindrance of rotation around the N−C(Ar) bond in the iminium cation and the strong stereodifferentiating effect of the *tert*-butyl group.

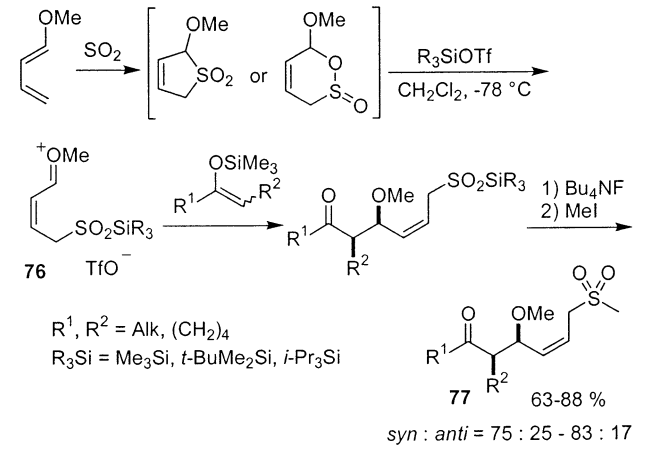
Intramolecular transfer of the allyl fragment in azetidinonium cation **75** is exemplified by eq c in Scheme 35.[123]

The reactions of peroxyacetals with silyl ketene acetals catalyzed by Me_3SiOTf gives rise to 3-peroxy-substituted esters (Scheme 36).[124] In this process, a peroxycarbenium cation acts as the electrophilic species.

Scheme 36



Scheme 37



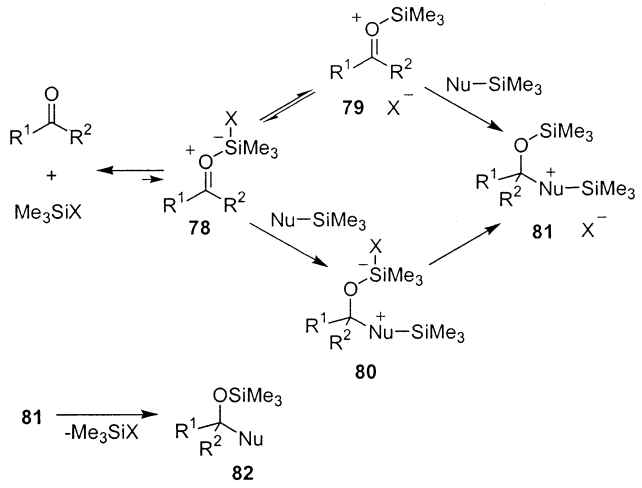
The reaction of 1-methoxy-1,3-butadiene with SO_2 followed by the reaction of intermediate five- or six-membered heterocycle with SLA results in generation of oxocarbenium cation **76**, which can be stereoselectively captured by silyl enol ether (Scheme 37).[125] The initially formed silyl sulfinates can be alkylated at the sulfur atom to give sulfones **77**. The syn isomers are obtained as the major reaction products; moreover, sulfones **77** contain exclusively the *Z*-substituted double bond.

VII. Reactions of Carbonyl Compounds with Nucleophiles

A. Reactions with π-Nucleophiles

The reactions of carbonyl compounds with π-nucleophiles can be described by the mechanism shown in Scheme 38. Thus, the reaction of a substrate with

Scheme 38

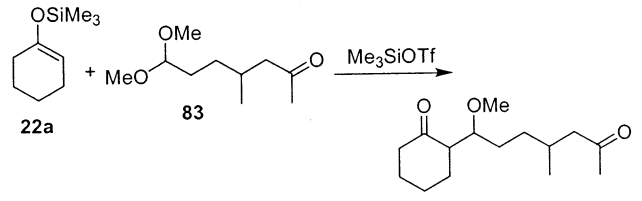


SLA initially affords five-coordinate complex **78**, which can exist in the equilibrium with cation **79**.[126] The subsequent nucleophilic attack on the carbon atom of complexes **78** or **79** is accompanied by the formation of the C,C bond to give intermediates **80** or **81**, respectively. The intermediate **81** is rapidly transformed into the final product, viz., silyl ether **82**. The position of the equilibrium RCHO + Me_3SiX ⇌ **78** ⇌ **79** depends on the cation-stabilizing effect of the substituents R^1 and R^2 and on the nature of the leaving group X.

Attempts to observe complexes **78** or **79** generated from benzaldehyde and Me_3SiOTf by NMR spectroscopy failed (only the starting components were present in the system).[7b] This experiment provided unambiguous evidence for a very small contribution of **78** and **79** to the equilibrium mixture. Hence, it can be tentatively assumed that cation **79** is not formed if the Si-X bond is sufficiently strong, e.g., Si−O bond. Neutral complex **78**, in turn, is a much weaker electrophile compared to **79** or oxocarbenium cation **17** generated from acetals upon elimination of the alkoxy group (see Scheme 9). Consequently, one would expect that carbonyl compounds are less reactive in reactions with nucleophiles as compared to the corresponding acetals.

The difference in the reactivity of the acetal and carbonyl groups is demonstrated with bifunctional substrate **83**, which reacted with 1-silyloxycyclohexene exclusively at the acetal fragment (Scheme 39. In the original study, the yield of the target product was not reported.).[5]

Scheme 39



In the early 1980s, Noyori demonstrated that aldehydes and ketones do not react with 1-silyloxycyclohexene **22a** and allyltrimethylsilane in the presence of Me_3SiOTf in CH_2Cl_2 at −78 °C.[4,5,73,84] The reaction of benzaldehyde with **22a** catalyzed by Me_3SiOTf proceeds only at room temperature to give the target silyl product of aldol condensation (in toluene, the yield was 60%, syn:anti = 49:51) or benzylidenecyclohexanone (in CH_2Cl_2, 85%). Aliphatic aldehydes are not involved in this reaction.

According to the results of other studies, benzaldehyde smoothly reacts with silyl enol ether **22a** upon catalysis by Me_3SiOTf (5 mol %) in CH_2Cl_2 at −78 °C to give the silyl product of the aldol condensation in 89% yield in the ratio syn:anti = 63:37.[127] In the latter case, the reaction is probably catalyzed by traces of TfOH rather than by Me_3SiOTf itself. Actually, the reaction of **22a** with benzaldehyde or isobutyraldehyde in the presence of 5 mol % of TfOH in CH_2Cl_2 at −78 °C is complete in 30 min to give aldol products in 86% (syn:anti = 69:31) and 82% (syn:anti = 73:27) yields, respectively.[5,128]

However, Me_3SiNTf_2, a considerably stronger silyl donor compared to Me_3SiOTf, efficiently catalizes addition of silyl enol ethers toward aldehydes and ketones (Scheme 40a). The reaction is best performed in diethyl ether as solvent at −78 °C with as little as 0.5−1 mol % of SLA, generated in situ from $HNTf_2$

Scheme 40

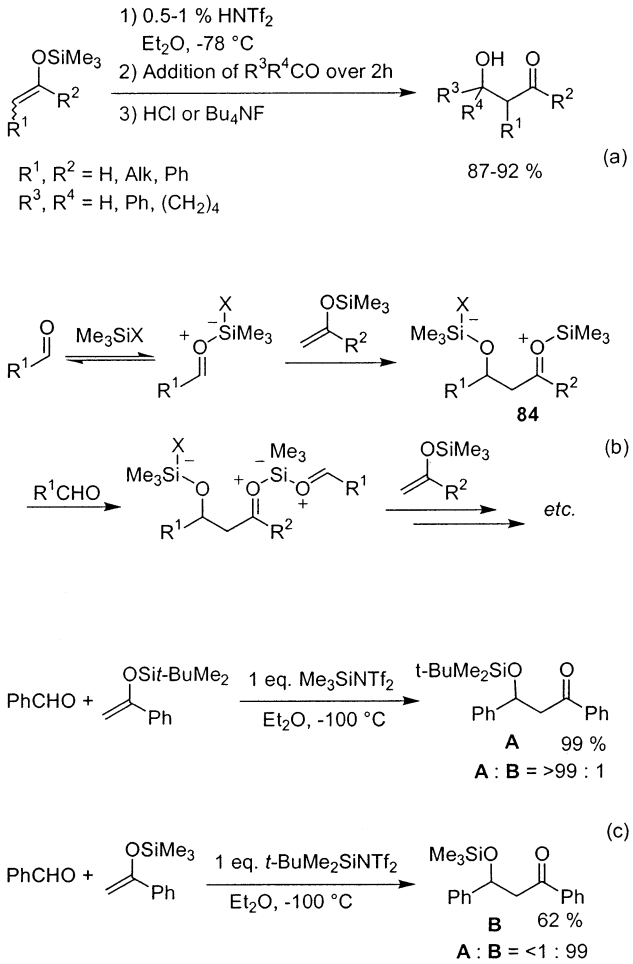
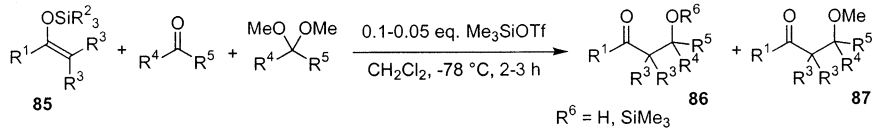
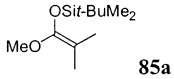
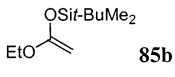


Table 4. Chemoselectivity in Reactions of Silyl Ketene Acetals 85[a]



Entry	85	Carbonyl	Acetal	Yield, % (86 + 87)	Ratio 86 : 87	Ref
1	 85a	$C_6H_{11}CHO$	$C_6H_{11}CH(OMe)_2$	89	26 : 74	134
2	**85a**	$C_7H_{15}CHO$	$C_7H_{15}CH(OMe)_2$	76	58 : 42	134
3	**85a**	PhCHO	$PhCH(OMe)_2$	92	79 :21	134
4	**85a**	$C_9H_{19}COCH_3$	$C_9H_{19}CH(OMe)_2CH_3$	81	11 : 89	134
5	**85a**	$PhCOCH_3$	$PhC(OMe)_2CH_3$	81	57 : 43	134
6	 85b	$PhCOCH_3$	$PhC(OMe)_2CH_3$	91	100 : 0	135
7	**85b**	PhCHO	$PhCH(OMe)_2$	79	89 : 11	135
8	**85b**	$C_7H_{15}CHO$	$C_6H_{13}CH(OMe)_2CH_3$	71	68 : 32	136

[a] Ratio **85**: carbonyl:acetal = 1:1:1 for entries 1−5 and 8 or 1.3:1:1 for entries 6 and 7.

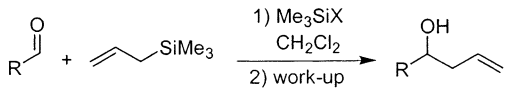
and silyl enol ther. To minimize the formation of side products, it is necessary to do the slow addition of carbonyl compound.[129] The following mechanism for this transformation was proposed:[129b] the electrofilic attack of silyl activated aldehyde species onto silyl enol ether produces cationic species **84**, which subsequently acts as a source of Lewis acidic silyl group without regeneration of Me_3SiNTf_2 (Scheme 40b).[130] In accord with such a mechanism is the observation that the silylated aldol initially formed from the coupling of benzaldehyde and 1-silyloxycyclohexene contains the silyl group derived from nucleophile, and not from silylated amide R_3SiNTf_2 (Scheme 40c).[131] Moreover, when two enol ethers of different ketones bearing different silyl groups are simultaniously used, the scrambling of the silyl groups takes place.[129b]

In the reactions of aldehydes with allyltrimethylsilane the target products can be obtained with the use of Me_3SiOTf, Me_3SiI, or in better yields with Me_3SiNTf_2 (Scheme 41).

Unlike silyl enol ethers, silyl ketene acetals **85** react with aldehydes and ketones upon catalysis by Me_3SiOTf. Moreover, carbonyl compounds often appear to be more reactive in these reactions than their acetals (Table 4).

Analogously, coupling of 2-trimethylsilyloxyfuran with aliphatic aldehydes catalyzed by Me_3SiOTf or Et_3SiOTf proceeds smoothly to give predominantly the *syn* isomers in high yields (Scheme 42a).[137] Bissilyl ketene acetal **88** reacts with aldehydes, ketones, and acetals. The presence of two nucleophilic functions in substrate **88** allows one to carry out consequtive reactions with different electrophiles (Scheme 42b).[138] Trimethylsilyl ketene acetal derived from ethyl α-fluoroacetate reacts with aldehydes in refluxing dichloromethane upon catalysis with 2 mol %

Scheme 41



R	Me_3SiX	Conditions	Yield, %	Ref
Ph	Me_3SiOTf, 0.2 eq.	r.t., 21 h	61	132
$PhCH_2CH_2$	Me_3SiOTf, 0.2 eq.	r.t., 23 h	27	132
$PhCH_2CH_2$	Me_3SiI, 0.2 eq.	r.t., 45 min	65	132
Ar, Alk	Me_3SiNTf_2[a] 0.005 eq.	−78 to 0°C 15 min	84-98	129a

[a] Reaction Is Performed Either in Ether or in Chlorobenzene[133]

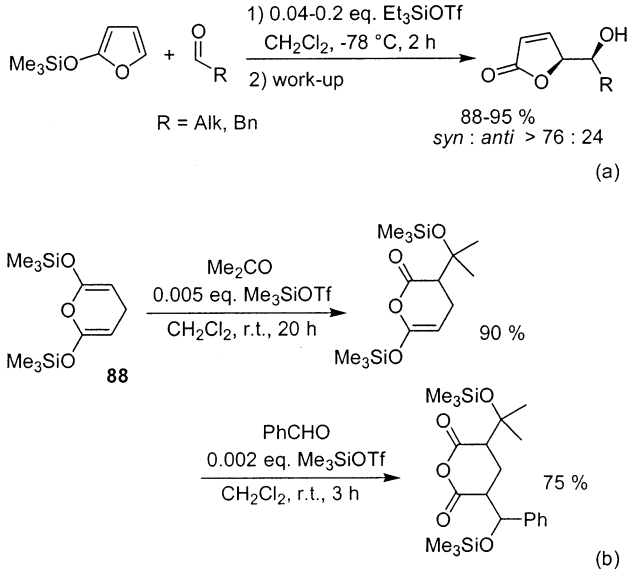
Me_3SiOTf furnishing aldols in good yields but as a 1:1 mixtures of syn/anti isomers.[139]

Apparently, high reactivity of silyl ketene acetals in the above-considered reactions results from their very high nucleophilicity[140] although the contribution of free-radical processes, which is typical of this class of nucleophiles, should not be ruled out.[141]

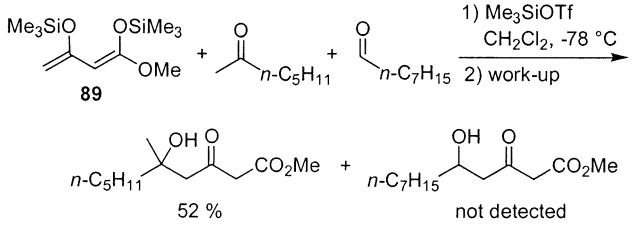
Bis(silyl)methylacetoacetate **89** is a synthetic equivalent of the corresponding dianion and its terminal carbon atom is involved in reactions with carbonyl compounds in the presence of Me_3SiOTf, ketones being more reactive than aldehydes (Scheme 43).[142]

The reactions of 1,4-dicarbonyl compounds **90** with **89** afford bicyclic products **91** (Scheme 44, Table 5).[142,143] It was suggested that this process occurs through the anchimeric interaction between the carbonyl groups arranged in an appropriate way. According to the general scheme, Me_3SiOTf activates one carbonyl group followed by the formation of cyclic

Scheme 42



Scheme 43



oxocarbenium cation **93**, which reacts with the nucleophile to give acetal **94**. Cyclization of intermediate **94** is accompanied by C,C bond formation to give bicyclic compounds **91** as the final products.

This mechanism is consistent with the following observations:

(a) Cyclization proceeds with high regioselectivity (Table 5). In the reactions of 1,4-keto aldehydes and unsymmetrical 1,4-diketones, the initial nucleophilic attack (**93** to **94**) occurs predominantly at the most sterically hindered carbonyl group (Table 5, entries 6−8), whereas the reactivity of monoketones changes in the reverse order (Scheme 45a). In the case of 1,4-dicarbonyl substrates, the observed effects may result from the preferential coordination of Me_3SiOTf to the less sterically crowded oxygen atom. In the case of keto aldehydes, the observed regioselectivity is attributable to the formation of the more stable cyclic oxocarbenium cation **93** derived from keto- rather than from aldehyde carbonyl group.

Table 5. Synthesis of Bicycles 91

entry	R^1	R^2	R^3	R^4	yield of **91**, %	diastereo-selectivity	regio-selectivity[a]
1	Me	H	H	Me	56		
2	Me	H	H	H	53		
3	n-Pr	H	H	H	78−90		
4	Ph	H	H	H	87		
5	t-Bu	H	H	H	88		
6	t-Bu	H	H	Me	74		28:1
7	i-Pr	H	H	Me	67		6:1
8	n-Pr	H	H	Me	73		7:1
9	Et	Me	H	H	77	5.4:1	
10	Me	Ph	H	H	68	15:1	
11	i-Bu	i-Pr	H	H	77	15.6:1	
12	Me	H	Me	H	75	13.5:1	
13	Me	H	i-Pr	H	87	27.3:1	
14	Ph	H	i-Pr	H	68	>160:1	

[a] Products from 1,4-keto aldehydes are reported to be produced in regioisomerically pure form.[142,143]

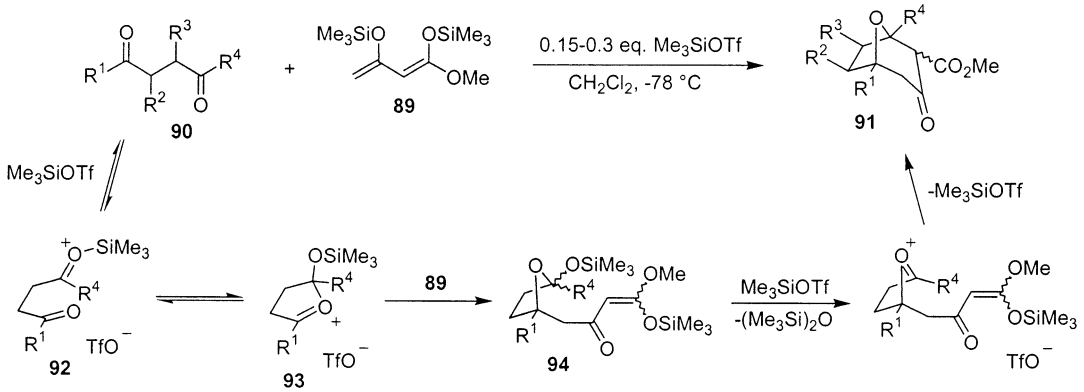
(b) A comparative experiment (see Scheme 45b) showed that 1,4-dicarbonyl compounds are more reactive in this reaction than simple ketones, i.e., one group is activated by another one.

(c) In the presence of additional substituent in the dicarbonyl component R^2 (or R^3), products with exo orientation of R^2 (or R^3) are predominantly formed as depicted in the structure **91** in Scheme 44. The exo:endo selectivity varies from 5.4:1 to >160:1, which is much higher than the selectivity in the reactions of enol ether **89** with monoketones (Scheme 45c).

In addition to the above-described substrates, bis-(silyl) derivatives of 1,3-diketones,[142,143] as well as phenylthio-,[144] benzyloxy-,[145] and methyldiphenylsilyl-containing[146] 1,4- and 1,5-dicarbonyl compounds,[147] can be involved in analogous reactions proceeding through cyclic oxocarbenium cation **93**, to give bi- and polycyclic systems in good yields and with high regio- and diastereoselectivity. This approach to the synthesis of medium-size rings was used for the preparation of some natural compounds.[148]

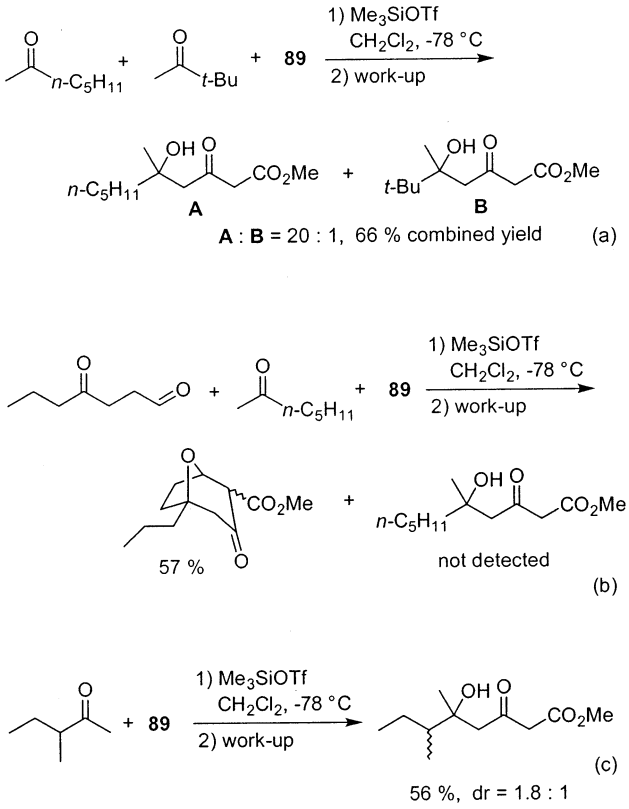
Molecules bearing several oxygen-containing functional groups can undergo more complex cyclizations based on successive intramolecular transfer of cat-

Scheme 44. In Substrates 90 and Products 91, Either R^2 or R^3 Corresponds to Hydrogen Atom, See Table 5[a]



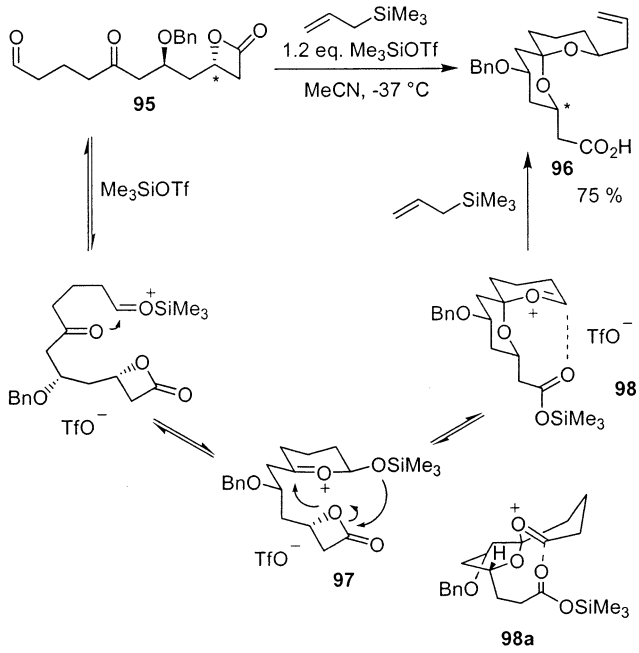
[a] These substituents are omitted in structures **92**−**94**. Complex **92** is shown as a four-coordinate silicon derivative, like in original studies,[142,143] although a five-coordinate adduct of type **78** should not be ruled out (Scheme 38).

Scheme 45



ionic center. For example, the reaction of compound **95** with allyltrimethylsilane in the presence of Me_3SiOTf affords acid **96** after hydrolysis of corresponding trimethylsilyl ester upon workup (Scheme 46).[149]

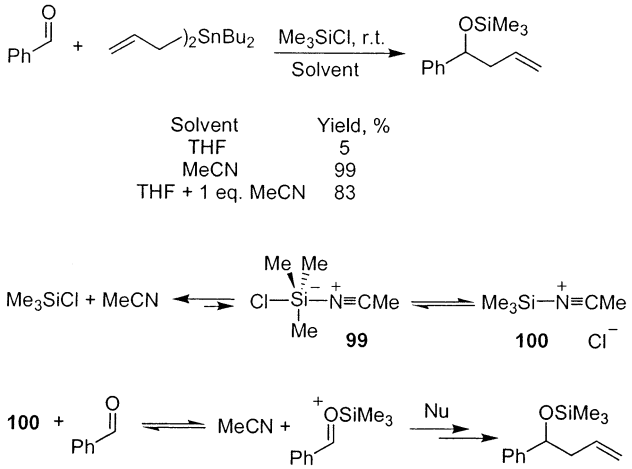
Scheme 46. The Trimethylsilyl Ester Formed in the Reaction Is Hydrolyzed upon Aqueous Workup, Leading to Acid 96



The retention of the configuration at the carbon atom of the lactone ring marked with an asterisk excludes the possibility that the nucleophilic substitution occurs at this center and counts in favor of the mechanism involving the initial formation of six-membered oxocarbenium cation **97**, followed by the β-lactone-ring opening. Cation **98** thus obtained reacts with allylsilane to give the final product bearing the allyl group in the equatorial position. This stereochemical result is attributed to intramolecular stabilization of the cation by the oxygen atom of the ester group thereby hindering the approach of the nucleophile from the axial side (see structure **98a**).

Chlorotrimethylsilane is a very weak donor of the silyl group. However, this reagent in acetonitrile can exhibit properties of strong SLA. For example, diallyldibutylstannane reacts with carbonyl compounds and Me_3SiCl in acetonitrile (Scheme 47).[150] The

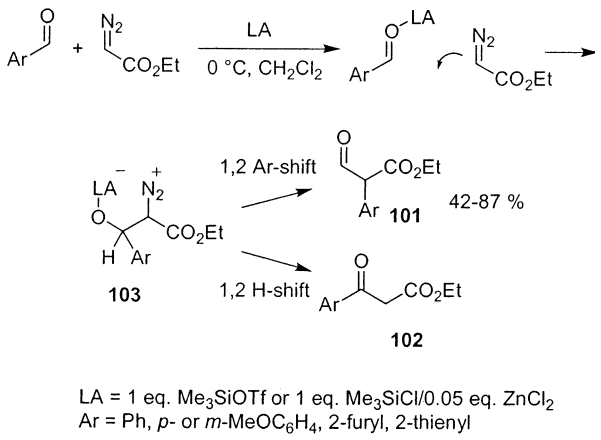
Scheme 47



reactions performed under analogous conditions in benzene, tetrahydrofuran, or dichloromethane afford the target product only in trace amounts. At the same time, the reaction can be carried out in tetrahydrofuran in the presence of only 1 equiv of acetonitrile or benzonitrile, which indicates that the nitrile group is directly involved in this process. The observed effect can be explained assuming the equilibrium formation of silylnitrilium cation **100**,[12a] which is a very powerful SLA, capable of transferring the silyl fragment to the oxygen atom of aldehyde or ketone. Apparently, generation of cation **100** proceeds readily due to low steric requirements of the nitrile group resulting in the relatively low barrier of formation of trigonal-bipyramidal intermediate **99**.

Reactions of aromatic aldehydes with diazoacetic ester under the action of a Lewis acid can give rise to α-formyl esters **101** or β-ketoesters **102** (Scheme 48). The reaction mechanism involves the nucleophilic attack of diazoacetic ester on the activated carbonyl group to form diazonium cation **103**. The subsequent liberation of the nitrogen molecule is accompanied by the 1,2-shift of the aryl group to give ester **101** or by the 1,2-shift of the hydride ion to produce ester **102**. The **101**:**102** ratio depends on the Lewis acid used. In the case of $SnCl_2$ or $SnCl_4$, only α-ketoesters **102** are generated, whereas α-formyl esters **101** are predominantly formed in the presence of SLA.[151] Either Me_3SiOTf or the $ZnCl_2/Me_3SiCl$ system can serve as SLA. It should be noted that neither $ZnCl_2$ nor Me_3SiCl on their own exhibit catalytic activity. It is assumed that the function of

Scheme 48

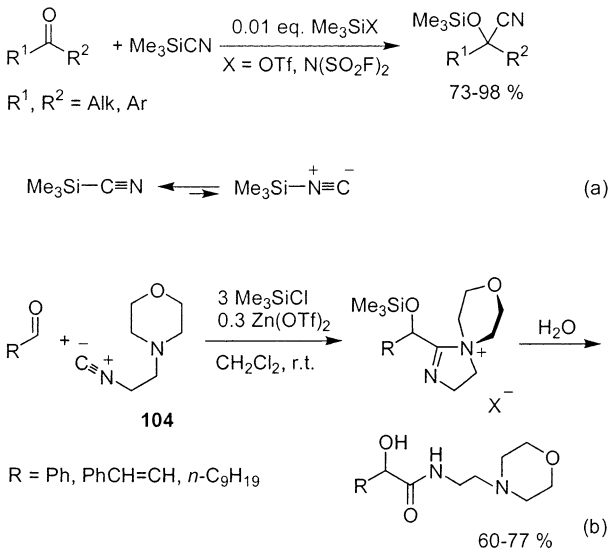


$ZnCl_2$ is to activate Me_3SiCl through complex formation with the chlorine atom (for more detailed information on complex formation of SLA with a metal-centered Lewis acid see section VII.C.). Electron-donating substituents in the aromatic ring favor the formation of α-formyl esters.

B. Reactions with σ-Nucleophiles

Unlike most of π-nucleophiles, trimethylsilyl cyanide smoothly reacts with aldehydes and ketones in the presence of 1 mol % of Me_3SiOTf[4] or $Me_3SiN(SO_2F)_2$[152] to form silyl derivatives of cyanohydrins (Scheme 49a). Probably, Me_3SiCN exhibits high

Scheme 49



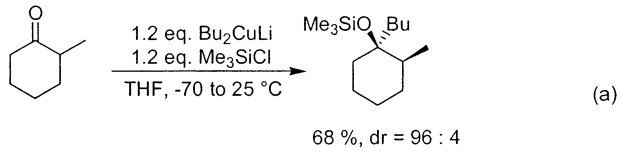
activity due to the presence of more reactive isocyanide containing the Si−N bond in the equilibrium mixture.

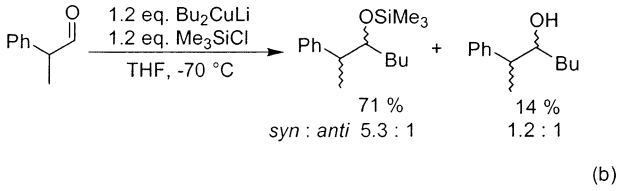
Isocyanide **104** bearing morfoline fragment adds to aliphatic and aromatic aldehydes in the presence of 3 equiv of Me_3SiCl and 0.3 equiv $Zn(OTf)_2$ to yield after hydrolytic workup the products of Passerini reaction (Scheme 49b).[153] No reaction takes place when Me_3SiCl or $Zn(OTf)_2$ are used separately.

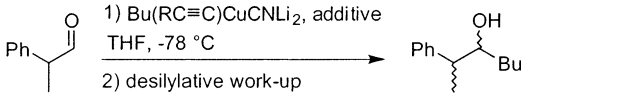
The reactivities of some organometallic reagents toward the carbonyl group can be substantially enhanced in the presence of SLA. This effect was first found for organocopper compounds.

Generally, lithium dialkylcuprates (R_2CuLi, lower order cuprates) do not react with ketones and are moderately active with respect to aldehydes.[154] The addition of an equivalent amount of Me_3SiCl makes it possible to perform the reactions of Bu_2CuLi with ketones and accelerates the reactions with aldehydes (Scheme 50a,b).[155] However, Me_3SiCl has an effect

Scheme 50







additive	time, h	yield, %	*syn* : *anti*
none	4	no reaction	
Me_3SiCl	4	88	10 : 1
Me_3SiBr	1.5	97	18 : 1
Me_3SiI	4	37	7 : 1

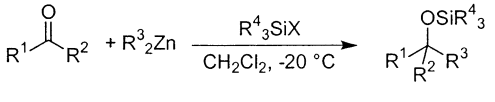
(c)

not only on the rate but also on diastereoselectivity of this process, which is indicative of the participation of SLA in the stereocontrolling step (Scheme 50c). An analogous tendency is observed for higher-order cuprates $R_2CuCNLi_2$. According to the data from low-temperature NMR spectroscopy, lower-order cuprates do not react with Me_3SiCl, whereas the reactions of higher order cuprates performed under the same conditions very rapidly produce Me_3SiCN.[156] The subsequent reaction of R_2CuLi formed with the carbonyl substrate is promoted by the Me_3SiCl/Me_3SiCN system.

In actual practice, the addition of cuprates to aldehydes or ketones is rarely required. Probably, that is the reason the accelerating effect of Me_3SiCl was not studied in detail. It is possible that the mechanism of this reaction is analogous to the well-studied mechanism of conjugate addition, which is substantially accelerated by different SLA (see section XI.A.).

In the past decade, organozinc compounds found wide use in organic synthesis. The reactions of these compounds with aldehydes promoted by amino alcohols were studied in detail,[157] whereas the reactions with ketones are poorly known. Recently, it was demonstrated that in the presence of SLA, various organozinc compounds, including functionalized derivatives, smoothly add to ketones to form silyl ethers

Scheme 51



R^1, R^2 = Alk, Ar, CH_2Br, $(CH_2)_5$
R^3 = Et, $(CH_2)_4OAc$
$R^4{}_3SiX$ = Me_3SiCl, Et_3SiCl, *t*-$BuMe_2SiOTf$

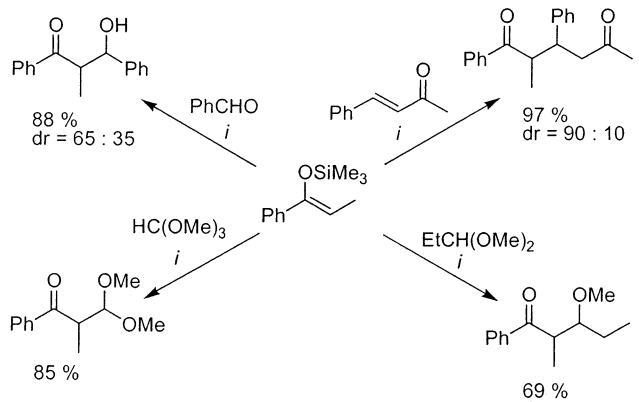
of tertiary alcohols (Scheme 51).[158] The mechanism of this transformation was not investigated.

C. Activation of Carbonyl Compounds by Combinations of Lewis Acids

Attempts to prepare the Me_3Si^+ cation by analogy with the *tert*-butyl cation by the reaction of Me_3SiX with strong Lewis acids failed. Olah and co-workers demonstrated that the reaction of Me_3SiBr with $AlBr_3$ produces the $Me_3SiBr{\rightarrow}AlBr_3$ complex (^{29}Si NMR, $\delta = 62.7$).[52] Even SbF_5, which is one of the strongest Lewis acids, cannot abstract the fluoride anion from Me_3SiF and gives the $Me_3SiF{\rightarrow}SbF_5$ complex (^{29}Si NMR, $\delta = 102$) instead of the silyl cation.[62] Binding of SLA with another Lewis acid leads to the shift of the electron density from the silicon atom, which is confirmed by the ^{29}Si NMR spectroscopic data (the chemical shifts of different SLA−LA complexes are given in Table 2; section III). As a consequence, the resulting SLA−LA complexes are much stronger donors of the silyl group than the starting SLA.

The possibility of the use of SLA−LA complex as the mediator in C,C bond forming reactions was first demonstrated by Mukaiyama in 1987.[159] While quite inactive in the individual form, Lewis acids Me_3SiCl and $SnCl_2$, taken together, exhibit properties of strong SLA. Thus, aldehydes, α,β-unsaturated ketones, and acetals smoothly react with silyl enol ethers in the presence of this LA pair (Scheme 52).

Scheme 52

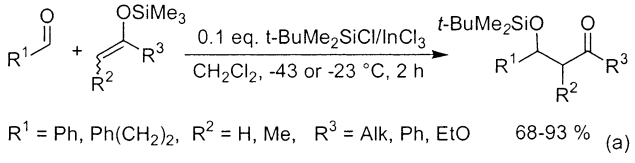


i: 0.15-0.2 eq. Me_3SiCl/0.08-0.12 eq. $SnCl_2$
CH_2Cl_2, -78 °C; work-up

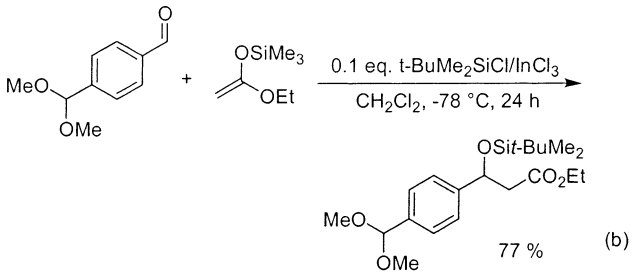
The $Me_3SiCl/ZnCl_2$ system can function analogously although it is less efficient compared to $Me_3SiCl/SnCl_2$.[159]

It was also reported that trialkylchlorosilanes could be activated by adding indium trichloride.[160] The reactivity of the $R_3SiCl/InCl_3$ mixture depends substantially on the nature of the alkyl groups at the silicon atom. For example, the $Me_3SiCl/InCl_3$ system catalyzes the reactions of trimethylsilyl enol ethers both with aldehydes and acetals (Scheme 53a). At the same time, only aldehydes react with *tert*-butyldimethyl silyl enol ethers in the presence of *t*-$BuMe_2SiCl/InCl_3$. The latter fact allows one to perform selective nucleophilic addition at the carbonyl group in the presence of the acetal fragment (Scheme 53b).

Scheme 53



R^1 = Ph, $Ph(CH_2)_2$, R^2 = H, Me, R^3 = Alk, Ph, EtO



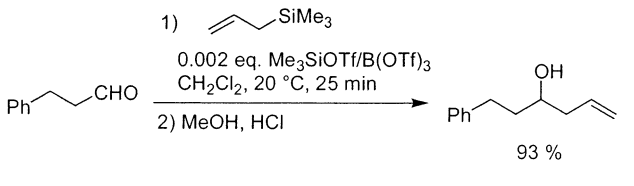
Boron and aluminum compounds can also activate SLA, leading to silicon species, which exhibit very high catalytic activity. High reactivity of these systems is probably associated with the complete transfer of the silyl group to the carbonyl oxygen atom to form the silyloxycarbenium species $RCH{=}OSiR_3^+$.

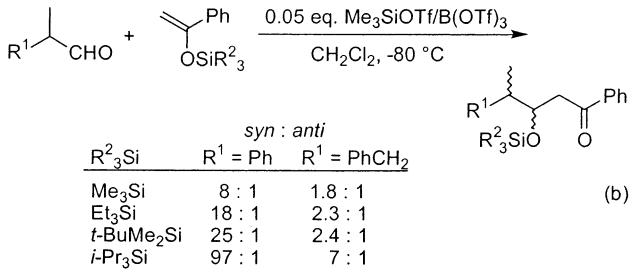
The reaction of $B(OTf)_3$ with Me_3SiOTf exothermically gives the $Me_3SiB(OTf)_4$ adduct (^{29}Si NMR, $\delta =$ 62.0). The ^{11}B NMR spectrum ($\delta = -3.17$, $\Delta\nu_{1/2} = 28$ Hz) corresponds to the $B(OTf)_4^-$ anion, whereas the ^{13}C NMR spectrum shows the presence of only one trifluoromethyl group ($\delta = 118$, q, $^1J_{C,F} = 318$ Hz).[132] Most likely, the trimethylsilyl group in this complex very rapidly migrates among all triflate residues. Trace amounts of $Me_3SiB(OTf)_4$ are sufficient for the reactions of aldehydes with silyl enol ethers and allylsilanes to proceed (Scheme 54a). In the presence of an asymmetric center adjacent to the carbonyl group, the diastereoselectivity of the process can be changed by varying the volumes of the substituents at the silicon atom (Scheme 54b). Apparently, an increase in the size of the silyl group, which binds to the carbonyl oxygen, leads to the limitation of possible pathways of approach of the nucleophile, thereby improving diastereoselectivity of the reaction.[161]

A particularly useful property of $B(OTf)_3$ is its ability to form complexes with chlorosilanes R_3SiCl, giving silylating reagents, which compare favorably with the $R_3SiOTf/B(OTf)_3$ system.[53] The possibility of generation of very strong silylating reagents based on sterically hindered chlorosilanes allows the use of these compounds instead of more expensive silyl triflates.

A combination of Me_3SiOTf and sterically hindered organoaluminum compounds MAD or MABR (Scheme 55) is another example of the formation of very active

Scheme 54

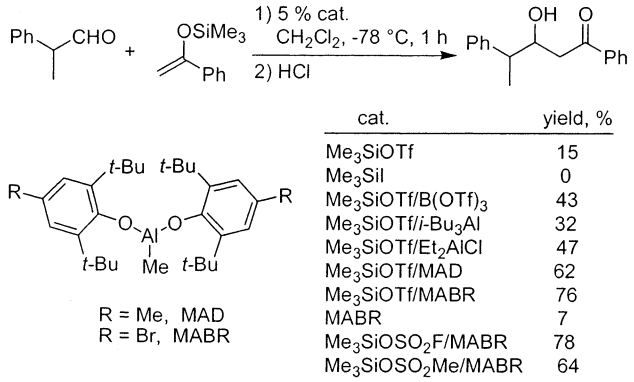




R^2_3Si	R^1 = Ph	R^1 = $PhCH_2$
Me_3Si	8 : 1	1.8 : 1
Et_3Si	18 : 1	2.3 : 1
t-$BuMe_2Si$	25 : 1	2.4 : 1
i-Pr_3Si	97 : 1	7 : 1

(b)

Scheme 55



cat.	yield, %
Me_3SiOTf	15
Me_3SiI	0
$Me_3SiOTf/B(OTf)_3$	43
$Me_3SiOTf/i\text{-}Bu_3Al$	32
Me_3SiOTf/Et_2AlCl	47
Me_3SiOTf/MAD	62
Me_3SiOTf/MABR	76
MABR	7
Me_3SiOSO_2F/MABR	78
Me_3SiOSO_2Me/MABR	64

SLA.[162] As follows from Scheme 55, these organoaluminum compounds coordinate the triflate anion more efficiently than $B(OTf)_3$. The Me_3SiOTf/MABR system makes it possible to carry out the reactions of silyl enol ethers even with poorly reactive carbonyl compounds, such as pivalaldehyde and methyl isopropyl ketone.

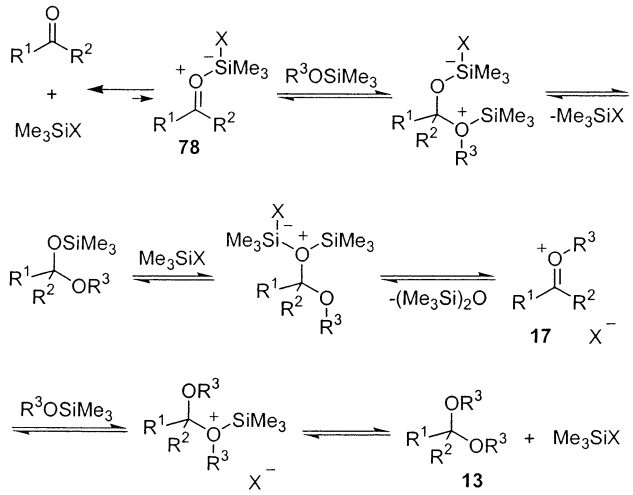
The study of complex formation between benzaldehyde, with MAD, and Me_3SiOTf by ^{13}C NMR spectroscopy at −50 °C showed that the addition of 2 equiv of Me_3SiOTf to the PhCHO→MAD adduct affords a new electrophilic species of unknown nature. The ^{13}C NMR spectrum of the latter has a signal, which is shifted downfield by approximately 3 ppm compared to the signal of the PhCHO→MAD complex. Probably, this species consists of benzaldehyde and two different Lewis acids, and it behaves as a true electrophile, which attacks the double bond of silyl enol ether.[163]

In addition to the above-considered examples, it should be noted that activation of SLA might cause undesirable transformations. Thus, it is difficult to achieve high enantioselectivity when performing catalytic asymmetric aldol reactions of aldehydes with silyl enol ethers in the presence of chiral metal-centered Lewis acids. These difficulties are generally attributed to the effect of SLA, which is generated in the early steps of the process and then promotes C,C cross-coupling yielding a racemic product.[29b,164] At the same time, Noyori demonstrated that aldehydes do not react with silyl enol ethers under the action of Me_3SiOTf.[4,5,73] In this connection, it is reasonable to assume that the observed low enantioselectivity might result from complex formation of SLA with a chiral Lewis acid. Under the action of this complex, the trialkylsilyl fragment can be transferred to the carbonyl group, producing a racemic product.

VIII. Three-Component Coupling of a Carbonyl Compound, an Alkoxysilane, and a Nucleophile

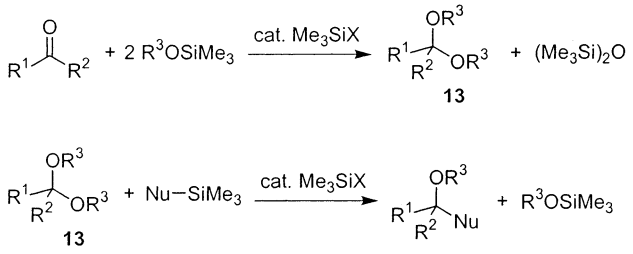
As mentioned above (section VII.A.), five-coordinate species **78** (Schemes 38 and 56), which are presumably generated in a low equilibrium concentration from carbonyl compounds and SLA, are weak electrophiles unable to couple with silyl enol ethers and allylsilanes. However, O-nucleophiles, such as alkoxysilanes, react with aldehydes or ketones under the action of SLA to give acetals **13** and hexamethyldisiloxane (Scheme 56).[4,165]

Scheme 56



Hence, to carry out the nucleophilic addition of a C-nucleophile at the carbonyl group, the following two successive steps sould be performed: (1) acetalization of the substrate using two equivalents of alkoxysilane and (2) the reaction of acetal with the C-nucleophile to form the target product and 1 equiv of alkoxysilane (Scheme 57).

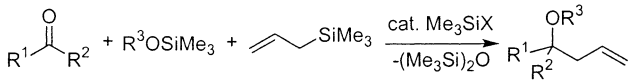
Scheme 57



It should be noted that oxocarbenium intermediate **17** derived from carbonyl substrates under the action of alkoxysilanes and SLA is identical to the carbocation generated from acetals under the action of

SLA. Consequently, a mixture of a carbonyl substrate with alkoxysilane in the presence of SLA is equivalent to acetal. On the basis of this principle, the general equation of the reaction of a three-component coupling, which has received wide acceptance, can be written (Scheme 58).[21,90g,166−168]

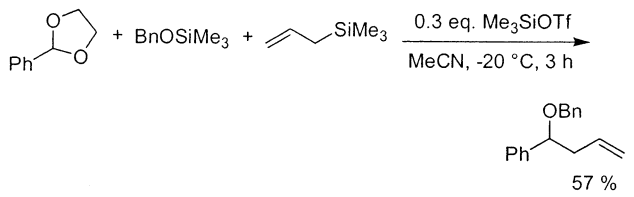
Scheme 58



Thus, a carbonyl compound, an alkoxysilane, and a silyl nucleophile are taken in equivalent amounts and the overall process is catalyzed by SLA to form the product and $(Me_3Si)_2O$ as a byproduct. At the same time, mixing of aldehyde and alkoxysilane in the 1:1 ratio in the presence of SLA but in the absence of a nucleophile gives rise to an equimolar mixture of the starting aldehyde, acetal, and $(Me_3Si)_2O$.[168]

Generally, the above-described approach is employed using allylsilanes as C-nucleophiles. It was mentioned that acetalization of the carbonyl group proceeds more slowly than the reactions of acetals with C-nucleophiles.[166] Conceivably, this is the reason coupling of acetals with silyl enol ethers (see section V.A.) affords β-alkoxycarbonyl compounds and alkoxysilanes in high yields without subsequent transformations of the target products. Though containing the carbonyl group, the latter compounds coexist with alkoxysilane formed. Higher reactivity of alkoxysilanes compared to that of allylsilanes is also manifested by the fact that acetals and alkoxysilanes readily undergo transacetalization, which proceeds more rapidly than C,C cross-coupling (Scheme 59).[169]

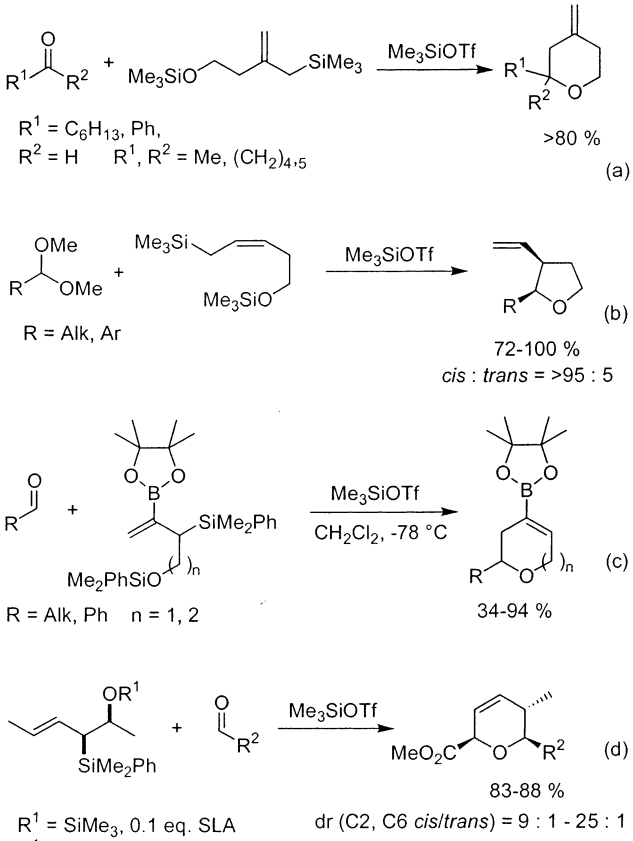
Scheme 59. Ratio of Reagents: Acetal:BnOSiMe$_3$:Allylsilane = 1:2:1.4



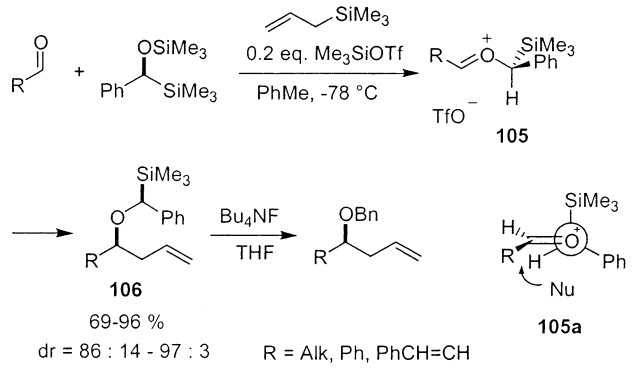
If allylsilane bears the silyloxy fragment, the three-component reaction becomes two-component and is accompanied by the intramolecular formation of the C,C bond. (Scheme 60a−c[170−172]). In some cases, C,C cross-coupling can be carried out with the use of allylsilane bearing the free hydroxy group (Scheme 60d).[173]

If alkoxysilane contains an asymmetric center, three-component coupling can give rise to diastereomerically enriched products. Thus, the reaction of aldehydes with silyl ether of (S)-α-trimethylsilylbenzyl alcohol and allylsilane furnishes products **106** with high diastereoselectivity (Scheme 61).[174] It is assumed that intermediate oxocarbenium cation **105** adopts a conformation with the maximum overlap of σ C−Si with π^* C=O (structure **105a**). The subsequent nucleophilic attack occurs preferentially from the side opposite to the bulky trimethylsilyl group. Products **106** can be transformed into usual benzyl ethers under the action of Bu_4NF.

Scheme 60

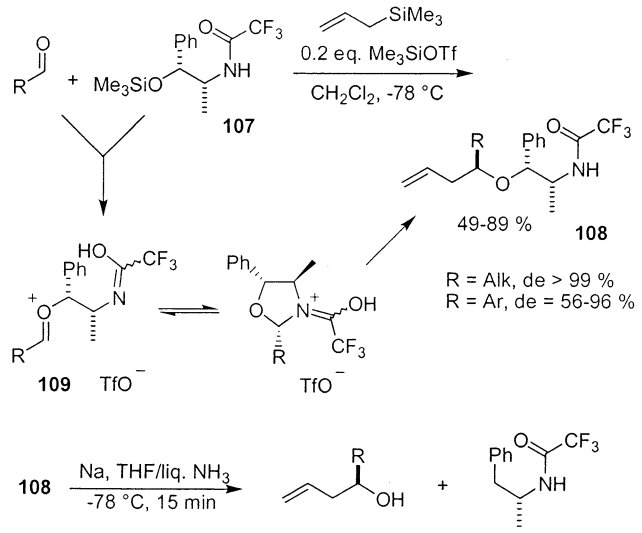


Scheme 61



Even higher selectivity can be achieved if the alkoxysilane molecule contains additional chelating groups capable of interacting with the positive charge of the carboxonium cation. According to this principle, allylation of aldehydes in the presence of *N*-trifluoroacetyl-*O*-trimethylsilylnorpseudoephedrine **107** furnishes products **108**, with one diastereomer substantially predominating. Removal of the chiral auxiliary allows the preparation of optically active homoallylic alcohols (Scheme 62).[175] Low-temperature NMR spectroscopic study of this reaction revealed the mechanism shown in Scheme 62. Higher diastereoselectivity is achieved for aliphatic rather than for aromatic

Scheme 62



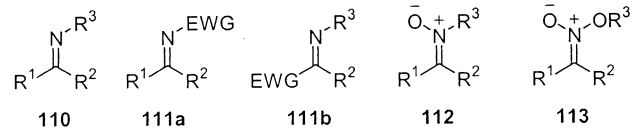
derivatives. This tendency was attributed to the large contribution of S_N1 mechanism in the step of C,C bond formation in the case of aromatic derivatives through additional stabilization of carbocation **109** by the aromatic ring.

IX. Activation of the C=N Bond

The nucleophilic addition to substrates containing the C=N bond is of great importance in modern organic synthesis. These reactions yield either amines or their derivatives; otherwise the reaction products can be transformed into these compounds by simple means. In addition, the construction of a new asymmetric center bound to the nitrogen atom represents the problem of asymmetric synthesis.

In general, substrates possessing the C=N fragment are less electrophilic than carbonyl compounds. Like aldehydes and ketones, imines **110** (Scheme 63),

Scheme 63



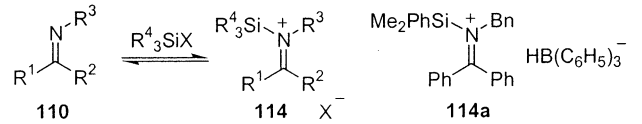
which are the simplest compounds containing the C=N group, are not sufficiently electrophilic to react with soft π-nucleophiles in the absence of an acid mediator. One would expect activation of such "imines" by introducing electron-withdrawing substituents (EWG, structures **111a**,**b**) or oxygen atoms at the nitrogen atom (nitrones **112**, nitronates **113**). However, even in these cases, Lewis acids must be used for activating the electrophilic component in reactions of C,C bond formation.

This section covers the reactions of compounds **110**−**113** with nucleophiles in the presence of SLA.

A. Reactions of Unfunctionalized Imines

The reactions of imines with SLA would be expected to produce N-silyliminium cations **114** (Scheme 64). In some cases, salts **114** precipitate.[176] The ^{1}H

Scheme 64



NMR spectrum of the iminium cation generated from benzylideneaniline and Me_3SiOTf has a signal of the azomethine proton at δ 9.34; i.e., it is shifted downfield by 1.0 ppm compared to the signal in the spectrum of the starting imine.[176a]

Recently, a new procedure was proposed for generation of iminium cations based on the three-component reaction of imine, trisubstituted silane R_3SiH, and $B(C_6F_5)_3$ (Scheme 64). Cation **114a** thus obtained was characterized by NMR spectroscopy.[177]

In the presence of SLA, imines react with the multitude of π-nucleophiles, such as allylstannanes (a),[176b] silyl enol ethers (b),[176a] and silyl ketene acetals (c)[178] (Scheme 65). Traditionally, Me_3SiOTf is used as SLA. Chlorosilanes, which are weaker activators, can also promote reactions of imines providing that acetonitrile is used as the solvent. The reactions of silyl ketene acetals with imines containing an aliphatic R^1 substituent, catalyzed by Me_3SiOTf, afford the target products in lower yields due probably to consumption of SLA through silylation of the C=N bond of the starting imine.[178a]

Compared to aldehydes, imines are less reactive with respect to organometallic reagents. In particular, simple aldimines do not react with organozinc compounds even in the presence of amino alcohols, which are generally used as catalysts for the addition of R_2Zn to aldehydes. However, imines **110** containing either aliphatic or aromatic substituents smoothly react with diethylzinc under the action of Me_3SiCl to give secondary amines in good yields (Scheme 65d).[179]

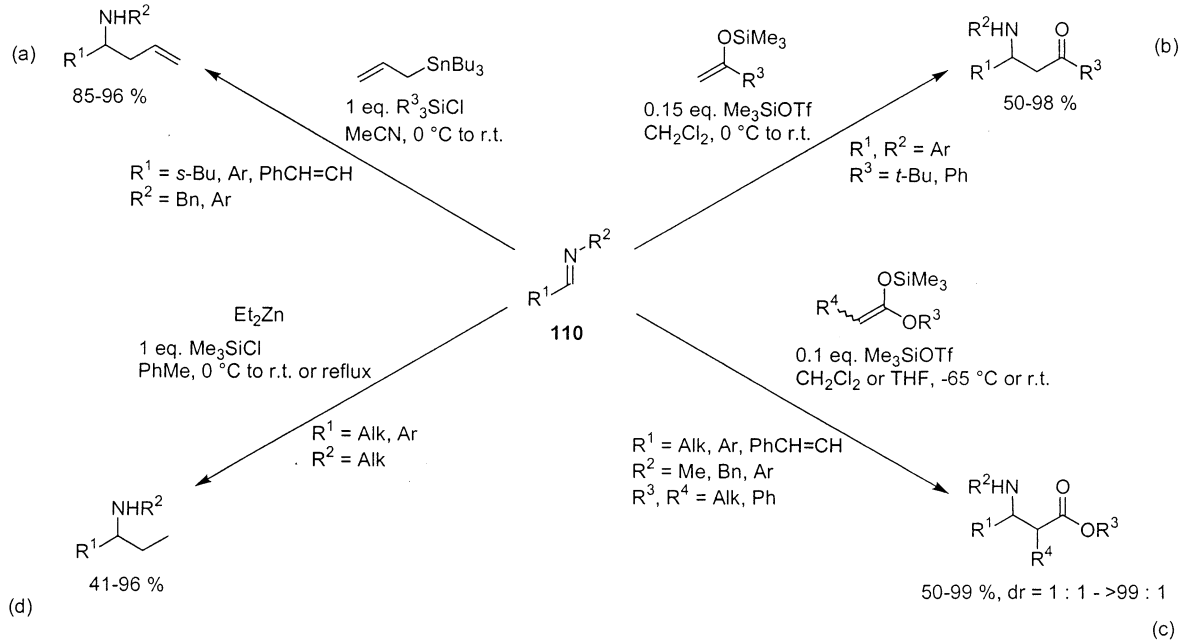
Nucleophilic addition to imines is sometimes mediated by combination of SLA and $Yb(OTf)_3$. The examples are offered by the addition of unprotected acyl group from acylzirconium reagents[180] and Pictet−Spengler type cyclization[181] (Scheme 66). The exact mechanisms of these reactions have not been determined. This enables one to speculate that the observed reactivity of imines is due to ytterbium species, as is follows from azophilicity of lanthanides. However, the presence of SLA is essential for successful realization of the reactions, since without SLA much lower yields of the products are achieved.

In the presence of Me_3SiOTf, the addition of Grignard reagents proceeds in low yields.[182] The addition of some (4-pyridyl)methyllithium derivatives occurs at the C,N double bond in 3,4-dihydroisoquinolines (Scheme 67). Under analogous conditions, usual alkyllithium compounds react predominantly at the silicon atom of the iminium cation.[182]

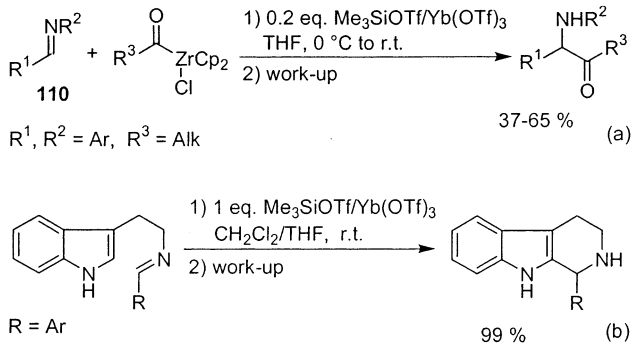
B. Addition to Imines Containing Electron-Withdrawing Groups

The insertion of electron-withdrawing groups into imines at the nitrogen or carbon atoms (structures **111a**,**b**, Scheme 63) leads to enhancement of elec-

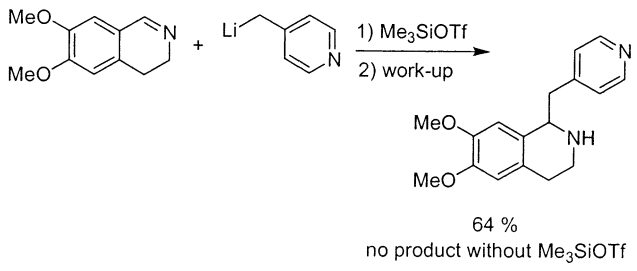
Scheme 65. In All Reactions Appropriate Aqueous Workup Was Applied to Give Desilylated Products Shown



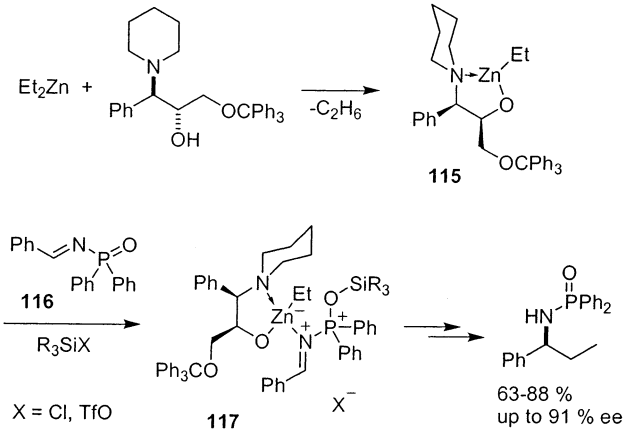
Scheme 66



Scheme 67



Scheme 68

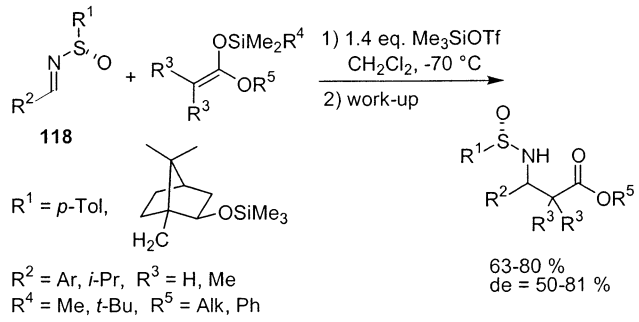


trophilicity of the C=N bond. The sulfono, sulfoxy, phosphinoyl, or ester groups can serve as activating substituents. SLA preferentially binds to the oxygen atom of these groups, thereby providing an opportunity for a second equivalent of Lewis acid to be additionally complexed with the nitrogen atom of the imino fragment. For example, a model of double activation of benzaldehyde (diphenylphosphinoyl)-imine **116** was proposed for the enantioselective addition of Et_2Zn (Scheme 68). According to the proposed mechanism, SLA and chiral reagent **115**, generated from Et_2Zn and amino alcohol, bind with oxygen and nitrogen atoms of the imine, respectively. Hence, the nucleophilic attack occurs at doubly activated intermediate **117**. The reaction with the use of the powerful silylating reagent (Me_3SiOTf) is very rapid, but the enantiomeric excess is only 17%. The enantioselectivity can be substantially improved (up to 91% ee) in the presence of bulky SLA, such as *t*-$BuPh_2SiCl$ or *i*-Pr_3SiCl, in combination with a stoichiometric amount of an asymmetric inducing agent.[183]

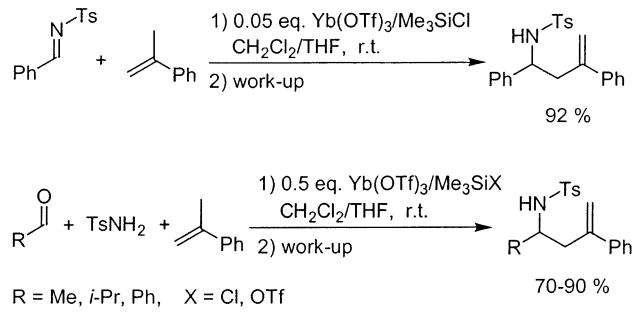
The reaction of sulfinylimine **118** containing the asymmetric sulfur atom as the chirality source with silyl ketene acetals in the presence of a stoichiometric amount of Me_3SiOTf furnishes derivatives of β-amino acids (Scheme 69).[184] Presumably, in these reactions the N-silyliminium cation is generated in a low equilibrium concentration, since no changes in the chemical shifts are observed upon mixing of imine **118** and Me_3SiOTf in an NMR tube at room temperature.

The ene reaction of N-toluenesulfonylbenzaldimine with α-methylstyrene proceeds smoothly under the action of 5 mol % of the $Yb(OTf)_3/Me_3SiCl$ system (Scheme 70). The reaction with the use of each of

Scheme 69



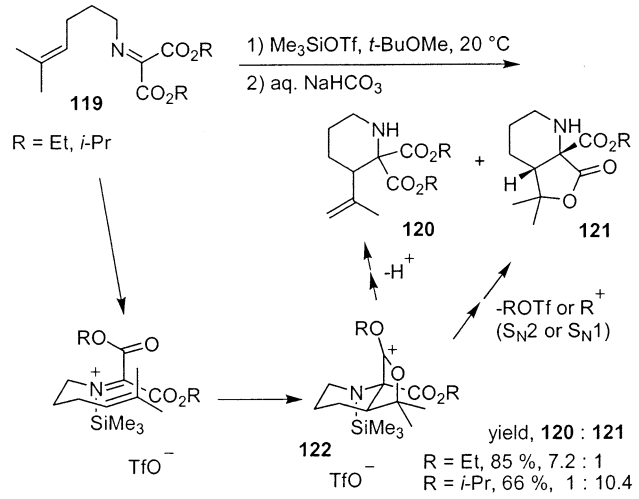
Scheme 70



these Lewis acids by itself either is very slow, giving the target product in low yield (in the case of Yb(OTf)$_3$), or does not proceed at all (in the case of Me_3SiCl).[185] On the basis of this transformation, a three-component coupling of toluenesulfonamide, α-methylstyrene, and aldehydes can be performed, although it requires 50 mol % of Yb(OTf)$_3$ and SLA.

Iminomalonates **119** bearing two activating ester groups undergo cyclization in the presence of Me_3SiOTf in *tert*-butylmethyl ether to give piperidines **120** and piperidine lactones **121** (Scheme 71). Ap-

Scheme 71

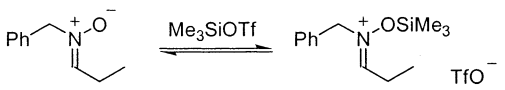


parently, the mechanism of this process involves the intramolecular attack of the silyliminium cation to the trisubstituted double bond accompanied by lactonization. The subsequent elimination of the proton or the alkyl group from intermediate **122** completes the process. The ratio of the products **120**:**121** depends primarily on the nature of the ester group.[186]

C. Addition to Nitrones[187]

The reactions of nitrones with SLA afford the corresponding N-silyloxyiminium cations wich can be identified by NMR spectroscopy (Scheme 72).[188]

Scheme 72

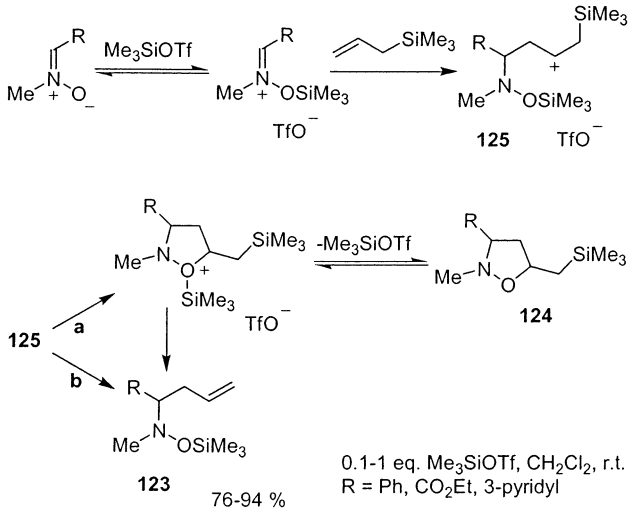


	Nitrone	Iminium cation
	δ, ppm	δ, ppm
C*H*=N	6.60	8.60
PhCH_2	4.85	5.33
$SiMe_3$	–	0.48
*C*H=N	140.5	167.4
Ph*C*H$_2$	68.9	66.0

Let us consider the reactions of nitrones with nucleophiles catalyzed by SLA. In these reactions, Me_3SiOTf is most commonly used as the catalyst. Due to the presence of the electron-withdrawing silyloxy group at the nitrogen atom, N-silyloxyiminium cations are more electrophilic than N-silyliminium derivatives.

Thus, the N-silyloxyiminium cations smoothly react with allylsilanes even at 20 °C to give mixtures of O-silylhydoxylamines **123** and isoxazolidines **124** (Scheme 73). Upon prolonged reaction times, hy-

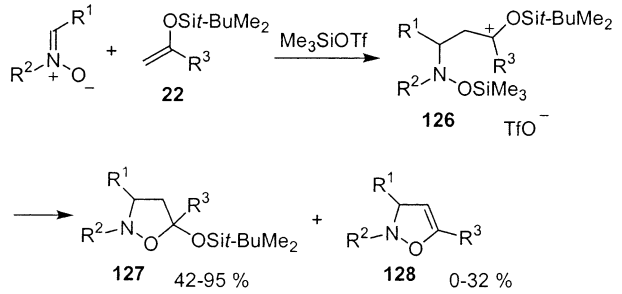
Scheme 73



droxylamines **123** are obtained as the only reaction products. A mixture of **123** and **124** results from two competitive reactions of intermediate **125**, viz., intramolecular capture of the cation by the N-silyloxy group followed by desilylation (path a) and elimination of the silyl group from the β position with respect to the cationic center (path b).[189]

Allyltributylstannanes react with nitrones in the presence of Me_3SiOTf under analogous conditions to

Scheme 74



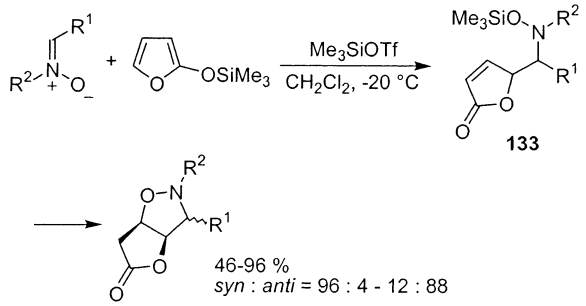
give hydroxylamines exclusively due apparently to the fact that Bu_3Sn is the better leaving group.[190]

The reactions of the nitrone/Me_3SiOTf system with silyl enol ethers afford 5-silyloxyisoxazolidines **127** as mixtures of diastereomers in the cis:trans ratio (R^1-R^3) ranging from 4:1 to 1:4 (Scheme 74).[188a,191] Low diastereoselectivity of the process is apparently associated with configurational instability of the products in a mixture with Me_3SiOTf. The reactions involving silyl enol ethers of ketones (**22**, R^3 = Me or Ph) give rise to small amounts of isoxazolines **128** as byproducts through the elimination of silanol. It should be noted that the reactions of silyl enol ethers with nitrones do not produce acyclic derivatives analogous to **123**. This fact is attributable both to higher stability of the cyclic form compared to the acyclic form and to a relatively larger lifetime of carbocationic intermediate **126**, compared to β-silyl carbocation **125**, that undergoes cyclization.

Trimethylsilyl triflate can be coordinated to the heteroatoms of isoxazolidines to give cations **129**−**131** (Scheme 75). Binding of the silyl group with the endocyclic oxygen atom can cause the epimerization of the acetal center through open oxocarbenium cation **126**. The coordination of the nitrogen atom is evidenced by the ^1H NMR spectroscopic data. Thus, the signals for two benzyl protons and the signal for the third proton (C*H*Et) in the spectrum of an equimolar mixture of **127** (R^1 = Et, R^2 = $PhCH_2$, R^3 = H) and Me_3SiOTf are shifted downfield by 0.37, 0.32, and 0.44 ppm, respectively, compared to the signals of individual **127**. Coordination at the oxygen atom of the silyloxy group (structure **131**) allows to realize the electrophilic potential of the acetal center in 5-silyloxyisoxazolidines. For C,C cross-coupling with silyl nucleophiles to proceed, the reaction mixture must be heated to 50−70 °C, which may correspond to slow dissociation of **131** to oxocarbenium cation **132** directly interacting with the nucleophile.[188a]

Since isoxazolidines are prone to be involved in equilibrium binding with SLA, stoichiometric amounts of Me_3SiOTf are generally used in the above-mentioned processes. Nevertheless, nitrones can react with silyl nucleophiles under the action of 5−35% of Me_3SiOTf due to reversible coordination of the silyl group. Thus, 2-silyloxyfuran couples with nitrones at −20 °C under the action of Me_3SiOTf as the catalyst (Scheme 76). The resulting silyloxyhydroxylamines **133** readily undergo cyclization on silica gel or in the presence of fluoride ions.[192]

Scheme 76



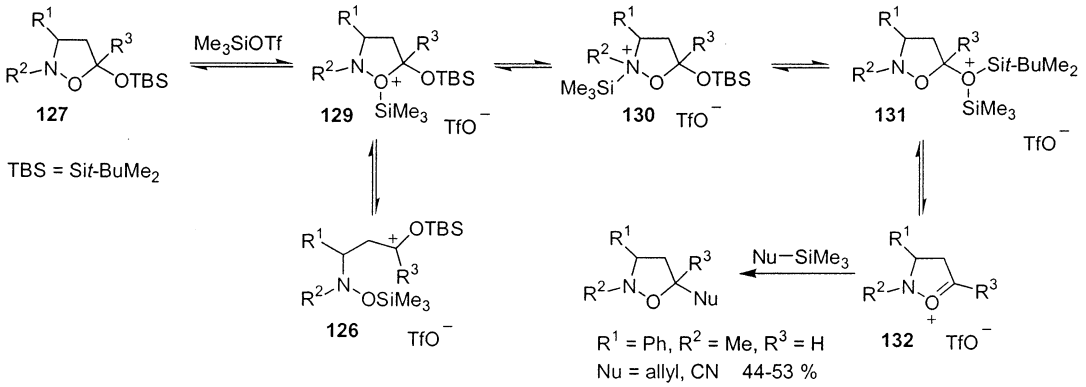
Activation of nitrones with chlorosilanes is uncommon. As an example we refer to the reactions of nitrones with indoles (Scheme 77). The reaction mechanism involves the nucleophilic attack of the heterocycle on the N-silyliminium cation. The subsequent proton transfer, elimination of hydroxylamine, and coupling of the carbocation stabilized by the indole fragment with the second molecule of the nucleophile afford bis-indoles in satisfactory yields.[188b,193]

D. Addition to Nitronates

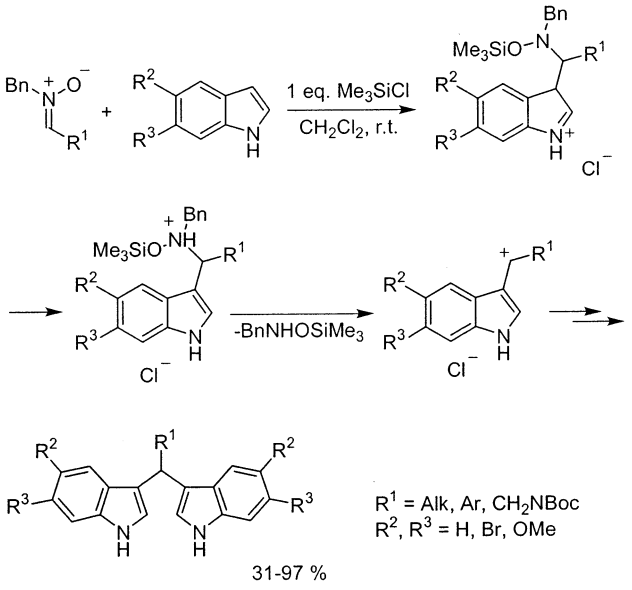
Conceivably, the iminium cation bearing two oxygen-containing substituents at the nitrogen atom (structure **134**, Scheme 78) is the strongest electrophile possessing the C,N double bond.

A cyclic analogue of cation **134** was first proposed as an intermediate upon solvolityc substitution of the nitro group in bicyclic α-nitro-*N*,*N*-dialkoxyamines.[194] However, its reactions with C-nucleophiles remained unknown. Another more general approach to species of this type may be represented as the electrophile

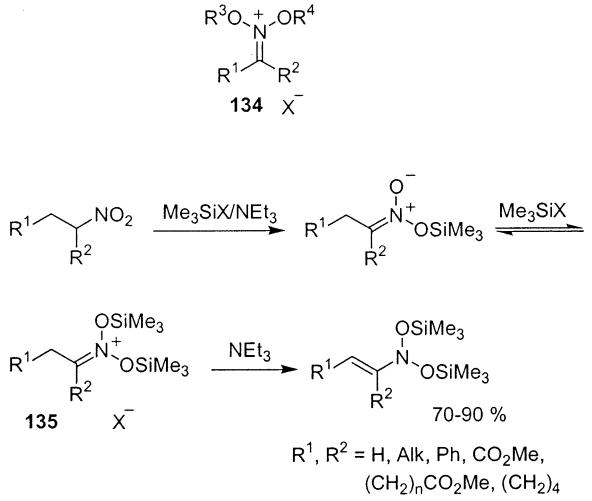
Scheme 75



Scheme 77



Scheme 78

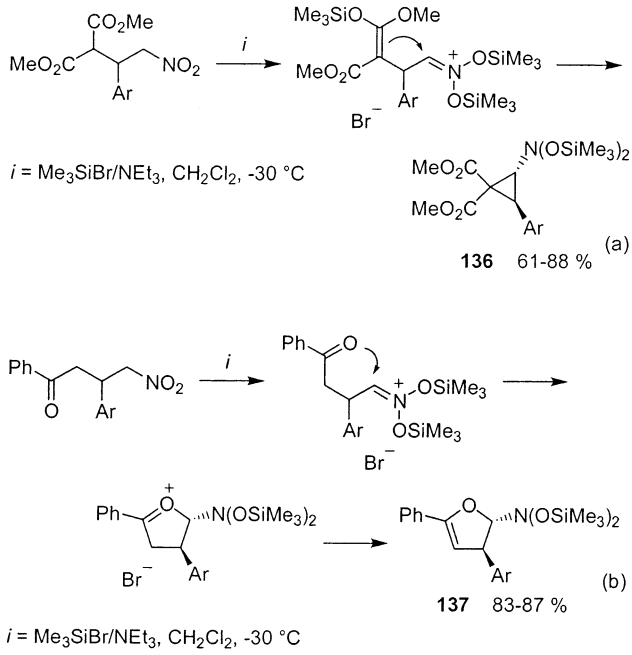


transfer to the oxygen atom of the nitronate molecule. Silylation of aliphatic nitro compounds giving rise to *N*,*N*-bis(silyloxy)enamines through silyl nitronates (Scheme 78) is an example of reactions proceeding through the intermediate formation of *N*,*N*-bis(silyloxy)iminium cation **135**.[99,195]

Despite the apparent great potential of this approach, only one example of the formation of the C,C bond presumably involving cation **135** is presently known. The silylation of nitro compounds containing a fragment of malonic ester with the Me_3SiBr/NEt_3 system affords *N*,*N*-bis(silyloxy)aminocyclopropanes **136** (Scheme 79a).[196] In this reaction, the C,C bond is formed by an intramolecular mechanism through the nucleophilic attack of silyl ketene acetal at the iminium carbon atom. The related process involving the reaction of the iminium cation with the suitably positioned oxygen atom of the carbonyl group to give *N*,*N*-bis(silyloxy)aminodihydrofurans **137** is represented by eq b.[196]

Presently, the chemistry of *N*,*N*-bis(silyloxy)-iminium cations is in its infancy. One would expect the discovery of new transformations, which will

Scheme 79



extend the possibilities of the synthetic use of derivatives of aliphatic nitro compounds.

X. Cycloaddition Reactions

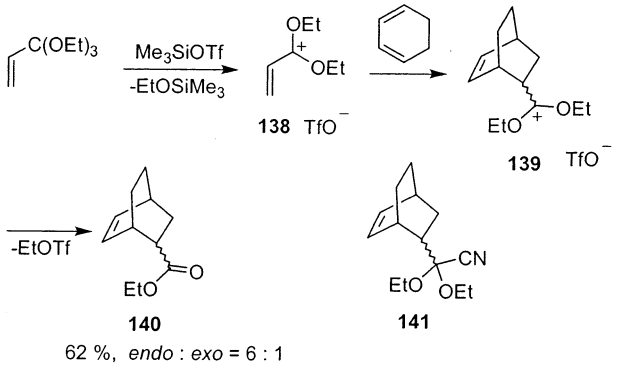
Lewis acids are frequently employed for the acceleration of cycloaddition reactions. However, not so much of research has been devoted to the application of SLA.

In contrast to the metal centered catalysts, SLA form weaker complexes with keto and ester groups—standard fragments of dienophiles. Nevertheless, when dienophile contains acetal function instead of carbonyl group, SLA may be conviniently used for the generation of carbocationic center, the resulting species may be quite active to couple with diene.

A. Reactions of Acetals of α,β-Unsaturated Carbonyl Compounds

The interaction of triethyl orthoacrylate with Me_3SiOTf affords stabilized carbocation **138** characterized by ^1H NMR spectroscopy (Scheme 80).[197] The

Scheme 80

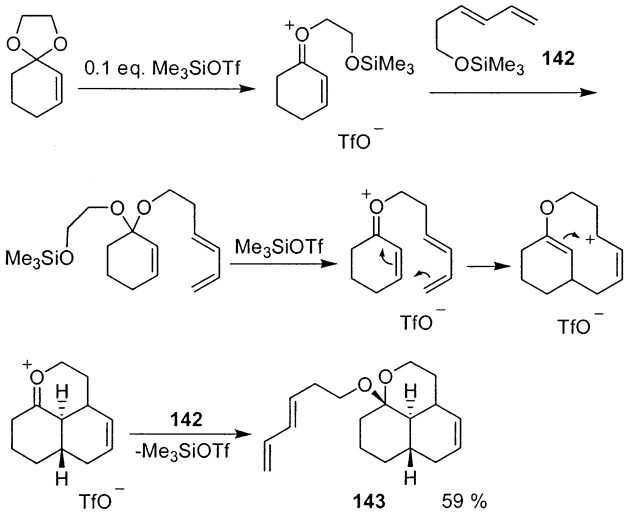


adjacent positive charge lowers the LUMO energy of **138**, which smoothly reacts with dienes at zero or

below-zero temperatures. The resulting cation **139** eliminates the ethyl group to form the ester functional group and EtOTf.[198] Cycloaddition can proceed by either concerted or stepwise mechanism. However, the addition of Me_3SiOTf to a mixture of cyclohexadiene, triethyl orthoacrylate, and Me_3SiCN affords compounds **140** (25%) and **141** (24%). Since Me_3SiCN is more nucleophilic than cyclohexadiene, the result observed is better consistent with the concerted mechanism.

An analogous process can be realized based on acetals of conjugated enones and silyloxydiene **142** (Scheme 81).[199] In this case, the acetal fragment

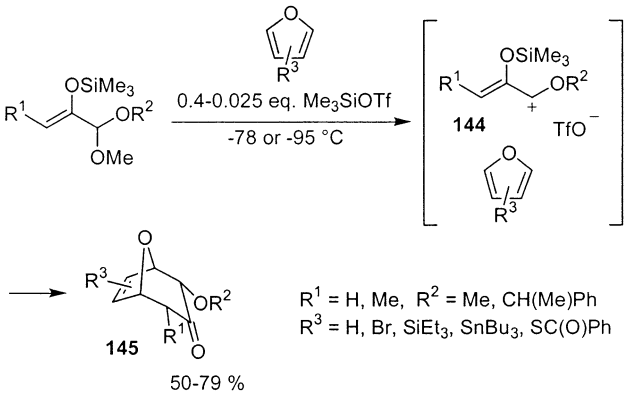
Scheme 81



serves to bind the diene and dienophile molecules through transacetalization. The subsequent intramolecular cycloaddition proceeds stepwise, as evidenced by the trans fusion of the cyclohexane rings in the final product **143**. The reaction with the use of cyclohexenone instead of its acetal also gives rise to tricyclic compound **143**. However, as would be expected, the process is slower in case of cyclohexenone because carbonyl compounds are much less active with respect to SLA than acetals (see sections V and VII).

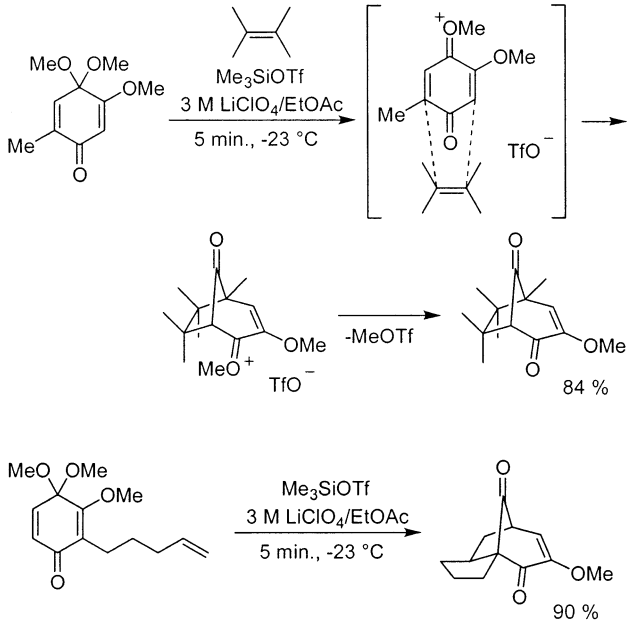
Oxyallyl cations **144** bearing the silyloxy group at position 2 can react with dienes as three-carbon two-electron systems by a [4+3]-cycloaddition mechanism (Scheme 82). Their reactions with furans have received the most study.[200] Cycloaddition is carried out in the presence of a catalytic amount of Me_3SiOTf and proceeds very rapidly even at low temperatures to give bicyclic products **145**. Subsequent elimination of the oxygen atom of the furan fragment under the action of Me_3SiOTf/NEt_3 opens a way to the preparation of tropone systems.[200a,201] Several natural products were synthesized using the approach shown in Scheme 82.[201,202]

Scheme 82



The reactions of trimethoxycyclohexadienone derivatives with alkenes promoted by Me_3SiOTf are interesting examples of [5+2]-cycloaddition (Scheme 83). Both inter- and intramolecular cycloaddition can take place. The reactions are carried out in ethyl acetate/3 M $LiClO_4$ and are complete in few minutes at −23 °C. In the absence of $LiClO_4$, the target products are formed in substantially lower yields.[203]

Scheme 83



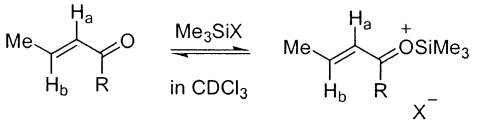
B. Activation of α,β-Unsaturated Carbonyl Compounds

The efficiency of SLA as the catalyst of [4+2]-cycloaddition depends primarily on the efficiency of complex formation between SLA and the dienophile. Standard silyl derivatives, such as R_3SiCl or R_3SiOTf, are not sufficiently strong reagents for the transfer of the silyl fragment to the carbonyl group of α,β-unsaturated aldehydes, ketones, and esters.[204a] To accomplish this, more powerful SLA are required[204b] (see section VII).

Complex formation between Me_3SiOTf or Me_3SiNTf_2 and crotonaldehyde or methyl crotonate was studied by NMR spectroscopy (Scheme 84).[17a,c]

These data demonstrate that high concentration of the complex dienophile−LA is achieved only with the use of Me_3SiNTf_2. As a consequence, the reactions of 1,3-dienes with methyl acrylate work only in the presence of Me_3SiNTf_2 (Scheme 85).[17a,c] It should be emphasized that the reversible character of SLA coordination allows the use catalytic amounts of SLA.

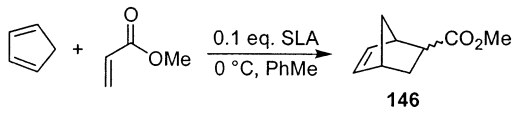
Scheme 84



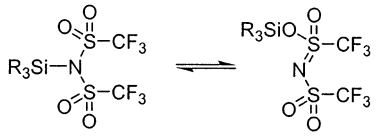
R		Me_3SiNTf_2	Me_3SiOTf
H	$\Delta\delta(H_a)^a$	0.80	0.03
	$\Delta\delta(H_b)^a$	1.81	0.06
OMe	$\Delta\delta(H_a)^b$	0.37	0.00
	$\Delta\delta(H_b)^b$	0.85	0.01

[a] At –40 °C. [b] At 0 °C.

Scheme 85



SLA	Yield, %	*endo* : *exo*
Me_3SiOTf	<5	13.3 : 1
Me_3SiNTf_2	83	24 : 1



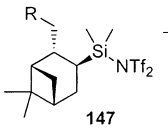
Interestingly, triisopropylsilyl derivative *i*-Pr_3-$SiNTf_2$ is more reactive compared to Me_3SiNTf_2.[205] In fact, cycloaddition of methyl acrylate with cyclohexadiene proceeds approximately 4 times faster with bulkier SLA. Consistent with this is the observation of stronger downfield shift of β-proton of methyl crotonate when combined with *i*-Pr_3SiNTf_2, $\Delta\delta(H_b) = 1.09$ ppm, suggesting that equilibrium transfer of silyl group from SLA onto dienophile is more significant with triisopropylsilyl rather then with trimethylsilyl counterpart. Similar trend is supported by ^{29}Si NMR studies.[205] The grater reactivity of bulkier SLA may be explained either by strain release upon silyl group transfer from bis(sulfonyl)-imide residue to the smaller carbonyl function or by different constitution of SLA due to silylotropic migration (Scheme 85).[206]

A set of chiral sterically hindered SLA **147** was synthesiszed and tested in asymmetric Diels−Alder reaction of cyclopentadiene with methyl acrylate (Table 6). The 54% ee is achieved when side chain R of the catalyst contains ether function.

α,β-Unsaturated amides are poor dienophiles in thermal reactions. However, the positive charge in their complexes with silylating reagents is better stabilized than in analogous complexes of aldehydes and esters. Hence, R_3SiOTf is sufficient for [4+2]-cycloaddition of α,β-unsaturated amides to proceed (Scheme 86).[207]

The solvated silyl cation is among the strongest SLA. Recently, a chiral C_2-symmetrical positively

Table 6. Reaction of Cyclopentadiene with Methyl Acrylate Catalized by 147[a]

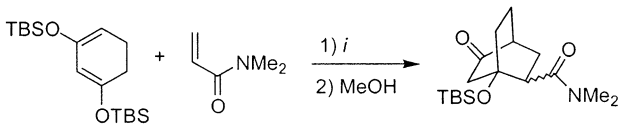


147

R	Yield of **146**, %	Ee (*endo*[b])
Et	83	7
OMe	83	54
OBn	79	26
OBz	80	13

[a] Conditions: toluene, 0.1 equiv **147**, −78 °C, 1.5 h. [b] endo: exo = 99:1.

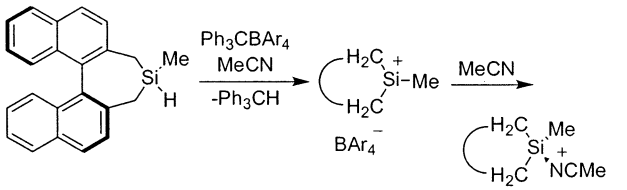
Scheme 86



i: without TBSOTf: 170 °C, 6 days, 73 %, *endo* : *exo* = 30 : 70
with 0.1 eq. TBSOTf: 20 °C, 30 min, 87 %, *endo* : *exo* = 92 : 8

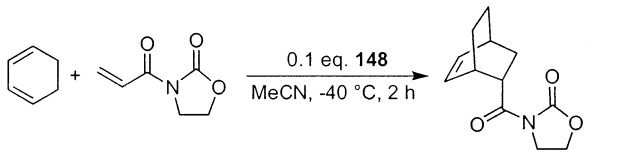
TBS = *t*-$BuMe_2Si$

Scheme 87



Ar = C_6F_5 or 3,5-$(CF_3)_2C_6F_3$ **148** BAr_4^-

(a)

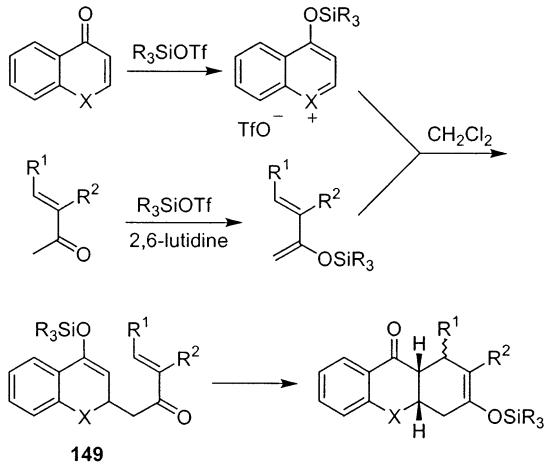


95 %
10 % ee, >95 % *endo* (b)

charged SLA was prepared by the hydride transfer reaction (Scheme 87a).[208] Solvated nature of cation **148** is evident from the chemical shift in the ^{29}Si NMR spectrum ($\delta = 34.0$), which is very close to that of the $MeCN^+$—$SiMe_3$ complex ($\delta = 36.7$).[209] The ^{1}H NMR spectrum of cation **148** has two doublets at δ 2.30 and 2.59 corresponding to homotopic pairs of the protons of the methylene groups. This is indicative of the rapid acetonitrile−ligand exchange (the authors also assumed the existence of the five-coordinate silicon atom with two solvent molecules; however, this structure is inconsistent with the chemical shift in the ^{29}Si NMR spectrum). Cation **148** is a very active catalyst of cycloaddition of 1,3-cyclohexadiene to acryloyloxazolidinone (Scheme 87b). The reaction product is isolated in high yield but with low enantioselectivity.[208]

The reactions of various silyloxy pyrylium, thiopyrilium, and quinidinium salts generated from corresponding heterocycles under the action of silyltri-

Scheme 88



flates, with silyloxydienes follows the formal [4+2]-cycloaddition scheme (Scheme 88).[210] However, these reactions proceed by a ionic (multistep) rather than by a concerted mechanism. The process begins with the nucleophilic attack of the silyl enol ether fragment of the diene on the pyrylium salt. The subsequent intramolecular conjugate addition affords the final product. According to this scheme, early quenching of the reaction mixture allows isolation of α,β-unsaturated ketones **149**.[210a,b]

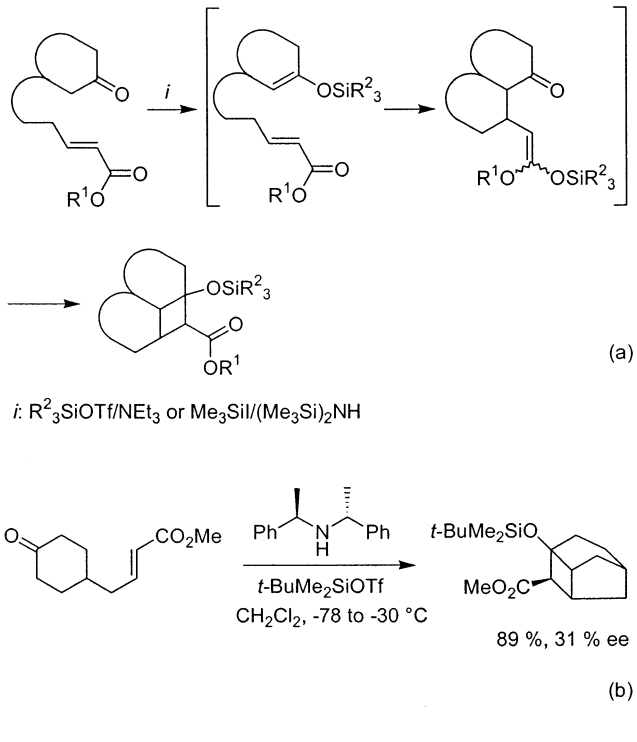
Various α,β-unsaturated esters possessing a ketone function at the appropriate position undergo stepwise [2+2] cycloaddition, leading to polycyclic cyclobutanes (Scheme 89a).[211] In this transformation SLA plays a dual role: at the beginning it converts the ketone to the silyl enol ether, while afterward it promotes consecutive reactions of conjugate and aldol addition. Attempts to render this multistep process enantioselective by employing either chiral amine instead of triethylamine (eq b)[211c] or 8-phenylmenthyl auxiliary substituent in the ester group (eq c)[211d,e] have been made.

C. Cycloaddition of Heterodienes and Heterodienophiles

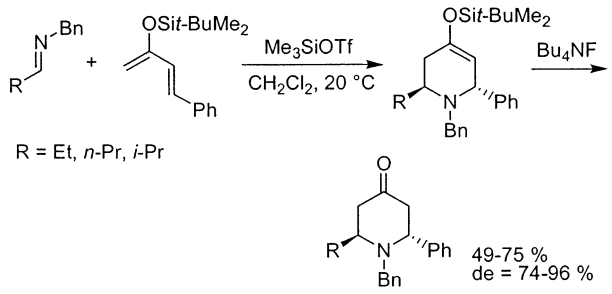
Strong Lewis acids can be used for activating both heterodienophiles and heterodienes. For example, activation of aldimines under the action of Me_3SiOTf allows their use as heterodienophiles in [4+2]-cycloaddition. For example, the reaction of *N*-benzylaldimines with 4-phenyl-2-silyloxy-1,3-butadiene in the presence of Me_3SiOTf furnishes (after desilylation of the intermediate silyl enol ethers) 2,6-disubstituted 4-pyridones (Scheme 90). The increase of bulkiness of the substituent R leads to higher trans/cis ratio in the product.[212]

Silyl enol ether of acetone undergoes cycloaddition to β-nitrostyrene in the presence of the Me_3SiOTf/NEt_3 system at 20 °C. Under the reaction conditions, silylation of the resulting oxazole *N*-oxide **150** gives rise to unstable intermediate **151**, which undergoes [4+2]-cyclofragmentation to give ene oxime **152** in 20% yield along with silyl acetate (Scheme 91). This

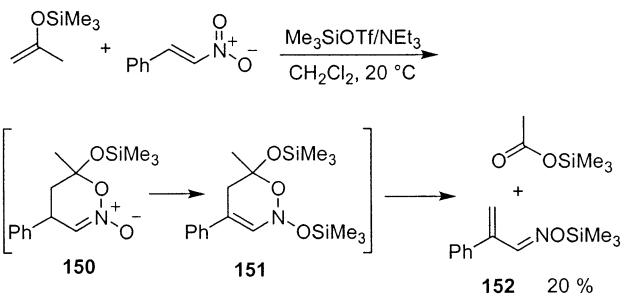
Scheme 89



Scheme 90



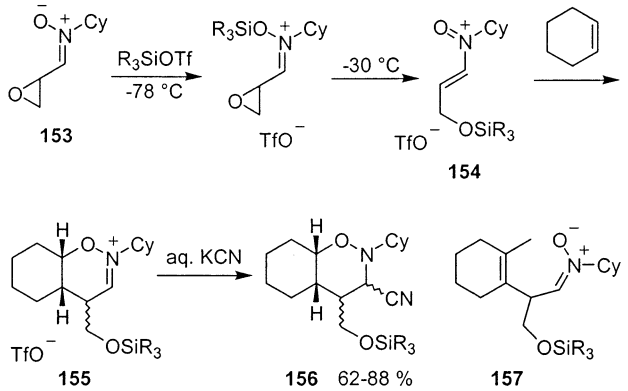
Scheme 91



oxime can also be prepared in 80% yield by silylation of authentic compound **150** with the Me_3SiBr/NEt_3 system.[213]

Under the action of silyl triflates, epoxinitrones **153** can be transformed into positively charged heterodienes **154** (Scheme 92).[214] According to the results of ^1H and ^{13}C NMR spectroscopy at −78 °C, the silyl

Scheme 92



group is initially transferred from SLA to the oxygen atom of *N*-oxide, whereas the epoxide-ring opening occurs only at −30 °C. The resulting heterodiene **154** reacts with alkenes via [4+2]-cycloaddition to give adduct **155**. Stable products **156** can be prepared by introducing cyanide ion, which adds at the C,N double bond. In the reactions involving trisubstituted dienophiles, the electrophilic attack of cation **154** at the double bond of the dienophile is a dominant reaction followed by proton abstraction to yield nitrones of type **157**.

XI. Conjugate Addition

A. Reactions of Organocopper Compounds

The reactions of C-nucleophiles with α,*β*-unsaturated carbonyl compounds can follow two pathways: (a) 1,2-addition at the carbonyl group to form an alkoxide anion; (b) the Michael reaction yielding an enolate ion. In the latter case, the resulting enolate can be used in reactions with electrophiles, that allows the formation of two C,C bonds by coupling three independent components, viz., a Michael acceptor, a nucleophile, and an electrophile.[215]

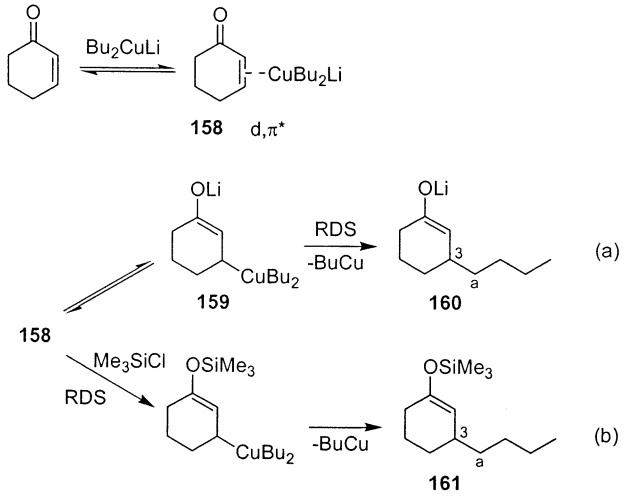
Organocopper compounds have found widespread use for 1,4-addition reactions.[154] However, the synthetic applications of these reagents are sometimes limited due to their low activity with respect to some Michael acceptors. Thus, unsaturated esters and *β*,*β*-disubstituted α,*β*-unsaturated ketones poorly react with R_2CuLi, whereas α,*β*-unsaturated amides do not react at all. In reactions of R_2CuLi, simlpe organocopper species RCu are formed which are absolutely unreactive, thereby resulting in the loss of one group.

The above-mentioned problems can be solved by adding to the reaction mixture SLA, which substantially accelerates couplings of cuprates with Michael acceptors.[216] Generally, Me_3SiCl serves as a rather efficient reagent although other SLA, for example, Me_3SiBr, Me_3SiI, or Me_3SiOTf, are also used.[154,217]

The mechanism of conjugate addition of cuprates to Michael acceptors and the nature of the activating effect of SLA are debated. Among numerous mechanistic concepts, the scheme, which was proposed by Corey in 1985[218] and was refined by Singleton at a later time,[219] seems to be most reasonable.

The reaction proceeding in the absence of Me_3SiCl includes the rapid equilibrium formation of d,*π**-complex **158** from R_2CuLi and enone and its transformation into Cu (III) derivative **159** followed by rate-limiting reductive elimination to form enolate anion **160** (Scheme 93, path a).[220] The observation of the kinetic isotopic effect for the C_3 and C_a atoms in the reaction of cyclohexenone with Bu_2CuLi [$C_3(k^{12}_C/k^{13}_C = 1.020-1.026)$ and $C_a(k^{12}_C/k^{13}_C = 1.011-1.016)$] correlates well with the above scheme.[219b]

Scheme 93. RDS = Rate-Determining Step

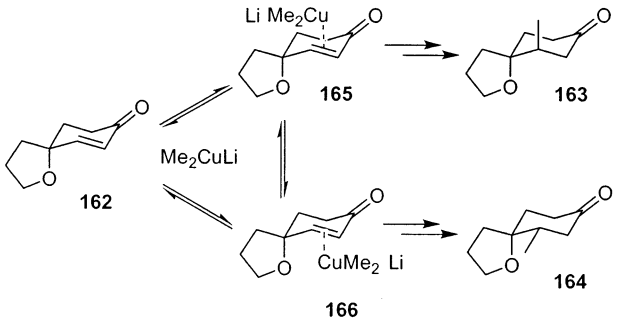


No visible changes occurred upon mixing of R_2CuLi with Me_3SiCl in tetrahydrofuran at −78 °C.[218] The α,*β*-unsaturated ketone too does not react with Me_3SiCl, although once it was suggested that the carbonyl group of enone may be involved in complex formation with Me_3SiCl.[221] The formation of this complex is unlikely, due to the low Lewis acidity of Me_3SiCl. At the same time, coupling of α,*β*-unsaturated ketone with R_2CuLi and Me_3SiCl results in very rapid conjugate addition. It is believed that in the presence of Me_3SiCl, silylation of d,*π**-complex **158** is the rate-limiting step followed by reductive elimination to give silyl enol ether **161** (Scheme 93, path b). This mechanism is evidenced by a comparison of the isotopic effects of the oxygen atom of the carbonyl group and of C_3 and C_a atoms: O ($k^{16}_O/k^{17}_O = 1.018-1.019$), C_3 ($k^{12}_C/k^{13}_C = 1.004-1.008$), and C_a ($k_{12C}/k^{13}_C = 0.996-1.002$).[219a]

It was also noted that the reactions of conjugated acyclic *Z*-enones with Me_2CuLi in tetrahydrofuran in the absence of Me_3SiCl at −78 °C is accompanied by rapid *Z*-*E* isomerization of the starting substrate preceding the formation of the conjugate addition product. In the presence of Me_3SiCl, this *Z*-*E* isomerization is suppressed, and the formation of the target products is accelerated.[218a]

The mechanism shown in Scheme 93 provides an explanation for the results of the addition of Me_2CuLi to enone **162** (Scheme 94).[218a] In the absence of Me_3SiCl, the reaction affords two isomers **163** and **164** in a ratio of 8:92, whereas the addition of Me_3SiCl leads to substantial acceleration of the reaction, yielding a product with reverse stereoselectivity (**163**:**164** = 99:1). According to the proposed interpretation, the equilibrium between two diastereomeric d,*π**-complexes **165** and **166** is initially established, with isomer **165** predominating; however, isomer **166** is

Scheme 94

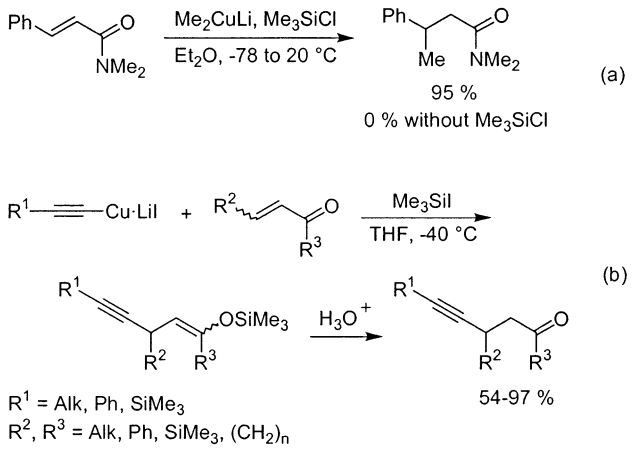


much more rapidly transformed into the final product **164**. Chlorotrimethylsilane, on the contrary, silylates dominant complex **165** to give isomeric ketone **163**.

Hence, the mechanistic observations concerning primarily the α,β-unsaturated enone/R_2CuLi or R^1R^2-CuLi systems confirm the validity of the processes presented in Scheme 93. It can also be proposed that the conjugate addition of other organocopper reagents to other types of Michael acceptors considered below proceeds analogously.

Silicon Lewis acids can influence the reaction rate of 1,4-addition of various copper derivatives to a wide range of unsaturated substrates. Some processes can be realized only in the presence of SLA. This effect is illustrated with two examples given below. α,β-Unsaturated amides are, as a rule, inactive toward lithium dialkylcuprates. At the same time, the addition of Me_3SiCl to the reaction mixture allows the preparation of the desired conjugate addition products in high yields (Scheme 95a).[222] Copper acetylides

Scheme 95

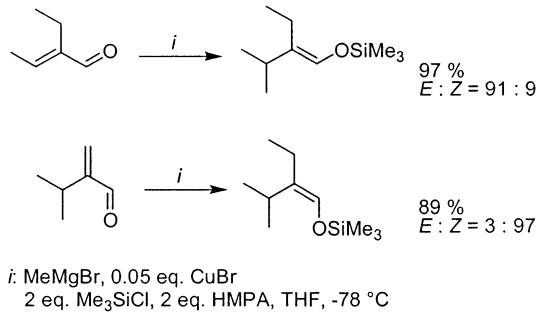


are very weak nucleophiles. Moreover, acetylide substituents are often used as nontransferable ligands in mixed cuprates $R^1(R^2C{\equiv}C)CuLi$. However, the Michael reactions of copper acetylides with unsaturated aldehydes or ketones can be realized in the presence of SLA (Scheme 95b).[223]

Silicon Lewis acids can also facilitate 1,4-addition of simple organocopper reagents RCu prepared from equimolar amounts of RLi or RMgX and a copper(I) salt.[224] In addition, SLA allow to perform conjugate addition of various organometallic reagents, such as RMgBr,[225] R_2Zn,[216] and R_3Al,[226] in the presence of a catalytic amount of copper(I) salts. In some cases additives such as HMPA,[225,227] DMAP,[227] or TMEDA[228] are used in combination with SLA due to which the reactions proceed more smoothly.

The selective synthesis of silyl enol ethers performed in the presence of Me_3SiCl and HMPA is exemplified by 1,4-addition of Grignard reagents to α,β-unsaturated aldehydes catalyzed by CuBr (Scheme 96). The observed dependence of the double-bond

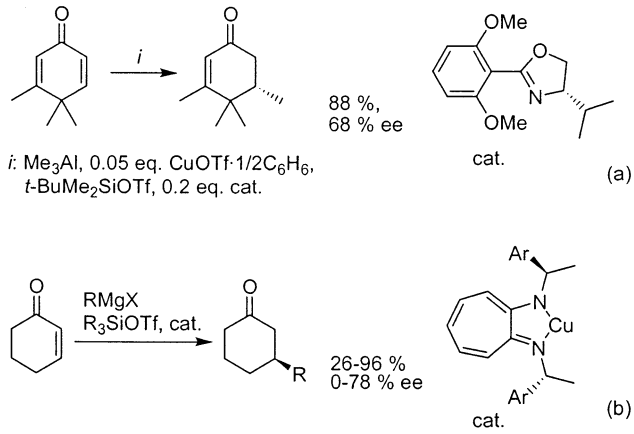
Scheme 96



configuration of silyl enol ether on the structure of the starting substrate indicates that the nucleophile adds to the aldehyde adopting the s-trans conformation.[224]

The involvement of an additional ligand in the process offers possibilities for studying the enantioselective version of the Michael reaction. This approach is demonstrated in Scheme 97a,b.[229,230]

Scheme 97

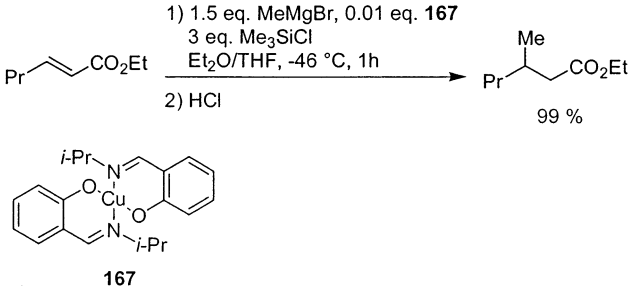


In the chemistry of organocopper compounds the Cu(I) species are usually operative. Even if the reactions are carried out with the use of copper(II) salts, the latter are rapidly reduced under the reaction conditions. However, Me_3SiCl prevents this reduction. On the basis of the results of varying the ligand environment around the copper atom, N-*iso*-propyliminosalicyl complex **167** was proposed as a very efficient catalyst of conjugate addition (Scheme 98).[231]

B. Other Conjugate Addition Reactions

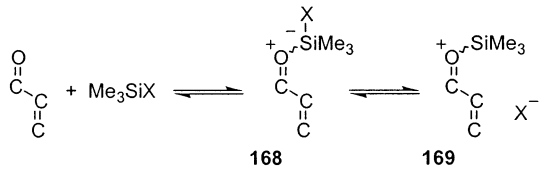
The conjugate addition of allyl nucleophiles is promoted by different Lewis acids (for example, $TiCl_4$, $SnCl_4$, BF_3, $EtAlCl_2$, etc.).[71a] Compared to these reagents, the most widely used SLA, viz., trialkylsilyl triflates, are much weaker activators of α,β-enones.

Scheme 98



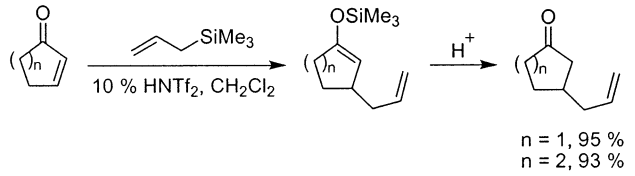
As mentioned in section VII.A, the interaction of R_3-SiOTf with carbonyl group results only in the equilibrium formation of a five-coordinate intermediate. Hence, for the addition at the double bond of a substrate to occur, either a strong nucleophiles capable of attacking five-coordinate species **168** or a strong SLA, which can form cationic complex **169**, must be used (Scheme 99).

Scheme 99



Thus, allylsilanes, which are inert with respect to α,β-enones, smoothly react with cyclopentenone and cyclohexenone under the action of Me_3SiNTf_2 generated in situ from allylsilane and $HNTf_2$ (Scheme 100).[17b]

Scheme 100

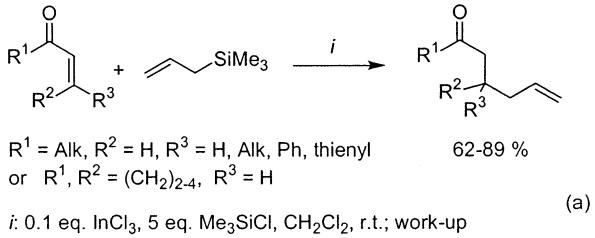


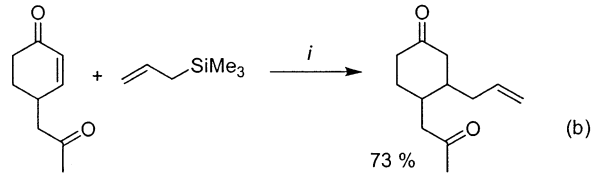
In the presence of the $InCl_3/Me_3SiCl$ system, allylsilane adds to cyclic and acyclic α,β-unsaturated ketones to give 1,4-addition products in good yields (Scheme 101a).[232] Under these conditions, allylsilane can chemoselectively react with enone in the presence of a free keto group (Scheme 101b).

Allylstannanes are approximately 4 orders of magnitude more nucleophilic than analogous allylsilanes.[107,108] Because of this the reactions of allylstannanes with α,β-enones mediated by SLA proceed very rapidly even at −78 °C (Scheme 102).[233] The resulting Bu_3SnOTf does not promote the addition of allylstannanes and, therefore, a stoichiometric amount of R_3-SiOTf must be used (*t*-$BuMe_2SiOTf$ is preferable to Me_3SiOTf because the corresponding silyl enol ethers are more resistant to hydrolysis).

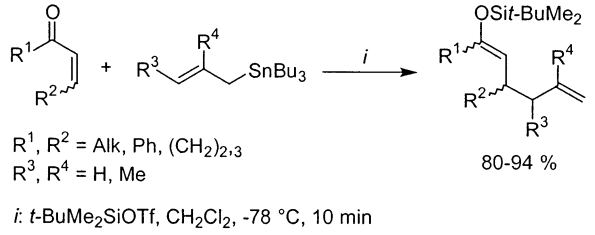
In case of substrates having suffuciently basic carbonyl group the equilibrium shown in Scheme 99 may be completely shifted to the formation of cationic species **169**. Such situation frequently happens when enone fragment is a part of heterocyclic ring. Thus, silyloxy pyrylium, thiopyrilium, their benzoannulated

Scheme 101



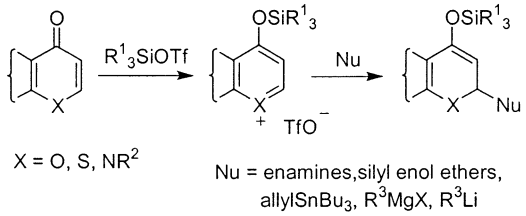


Scheme 102



analogues, and silyloxy quinidinium salts, formed from heterocycles and silyltriflate, couple efficiently with enamines, silyl enol ethers, allylic stannanes, and Grignard reagents (Scheme 103).[234]

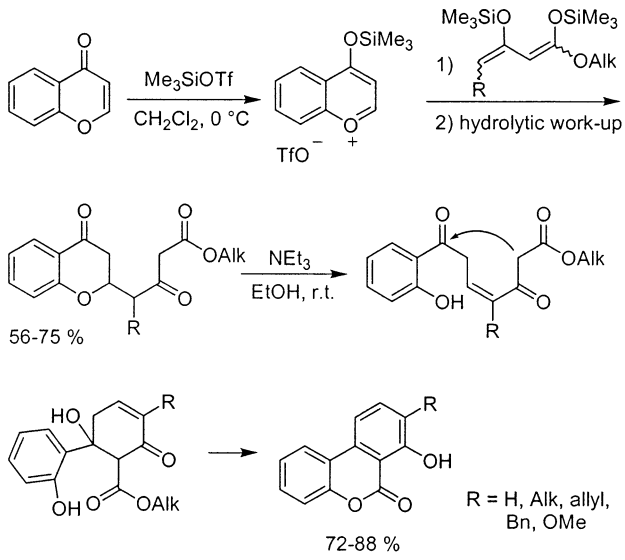
Scheme 103



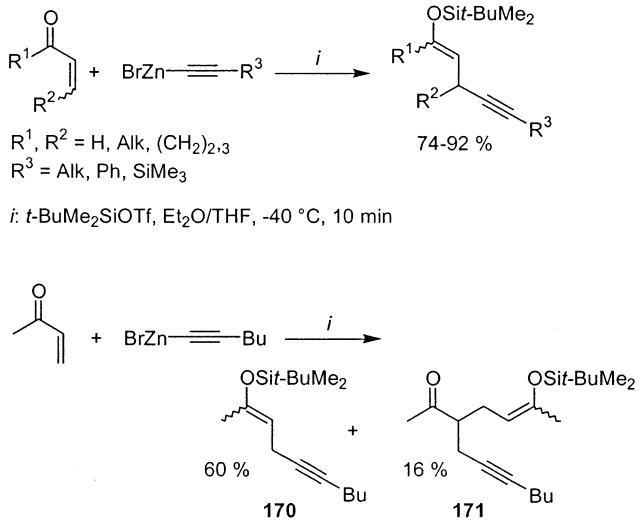
In some cases the obtained products may be used for the synthesis of polycyclic compounds. For example, reaction of benzopyrylium triflate with 1,3-bis silyl enol ethers in the presence of Me_3SiOTf afforded functionalized 2,3-dihydrobenzopyranes. These compounds underwent a novel domino retro-Michael-aldol-lactonization reaction upon treatment with base to give biaryl lactones (Scheme 104).[234a]

Alkynylzinc reagents are also readily involved in the Michael reactions with unsaturated ketones in the presence of the *t*-$BuMe_2SiOTf$ system.[235] Higher yields are achieved for cyclic α,β-enones (Scheme 105). The reaction of methyl vinyl ketone with hexynylzinc bromide affords product **170** along with compound **171**. Formally, this could be a result of the reaction of derivative **170** with the second molecule of methyl vinyl ketone. However, it is demonstrated by a special experiment that this process does not take place under the reaction conditions. Presumably,

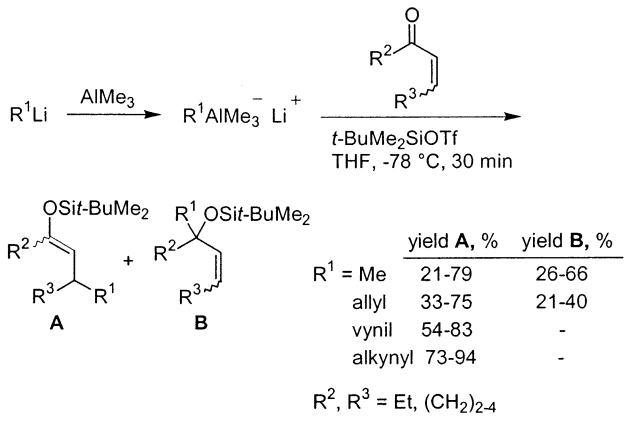
Scheme 104



Scheme 105



Scheme 106



in this system Zn enolate is initially formed followed by its silylation.

The reactions of aluminum ate complexes R_4Al^- with α,β-unsaturated ketones and *t*-$BuMe_2SiOTf$ can give rise to both 1,4- and 1,2-addition products whose ratio depends on the character of the substituent that is transferred (Scheme 106).[236] Vinyl- and alkynyl-aluminum complexes react exclusively in 1,4-fashion, whereas methyl and allyl derivatives produce mixtures of 1,4- and 1,2-addition products.

The 1,4-addition of vinylstannanes to α,β-unsaturated aldehydes in the presence of trialkylchlorosilanes is catalyzed by $Ni(COD)_2$ (COD = 1,5-cyclooctadiene) (Scheme 107).[237] In these reactions, the Michael acceptor initially reacts with $Ni(COD)_2$ and R_3SiCl to form allyl complex **172**. The subsequent transfer of the vinyl group from tin to nickel affords intermediate **173** followed by reductive elimination furnishing silyl enol ether **174**. The latter step is also accompanied by regeneration of the nickel catalyst. This mechanism, whose initial steps resemble reactions of cuprates, is supported by kinetic studies. In addition, allyl intermediates **172** can be isolated and fully characterized in the individual form upon mixing of enal, $Ni(COD)_2$, and R_3SiCl in a stoichiometric ratio.[238] Complex **172** also efficiently catalyzes coupling of vinylstannanes with α,β-enals.

In most cases, silyl enol ethers **174** are obtained as mixtures with respect to the geometry of the double bond in which *E* isomers substantially predominate. The reactions of unsaturated aldehydes bearing the substituent R^1 at the β-carbon atom can also be accompanied by 1,2-addition of vinylstannanes leading to regioisomers **175**.

Kim utilized an interesting approach to the two-step conjugate addition (Scheme 108).[239] In the first step, dimethyl sulfide[239a] or triphenylphosphine[239b] add to α,β-enone in the presence of R_3SiOTf. The corresponding sulfonium salts **176**, which are stable below −20 °C, are characterized by low-temperature NMR spectroscopy. Phosphonium salts **177** are stable at room or even higher temperatures. Derivatives **176** and **177** react both with C-nucleophiles and heteroatom-centered nucleophiles according to a formal scheme of replacement of the sulfide or phosphine residues. Of special note is highly regioselective coupling of sulfonium salts **176** with allylindium reagents generated from allyl bromides (Scheme 109).[240] The substitution mechanism in derivatives **176** and **177** was not studied.

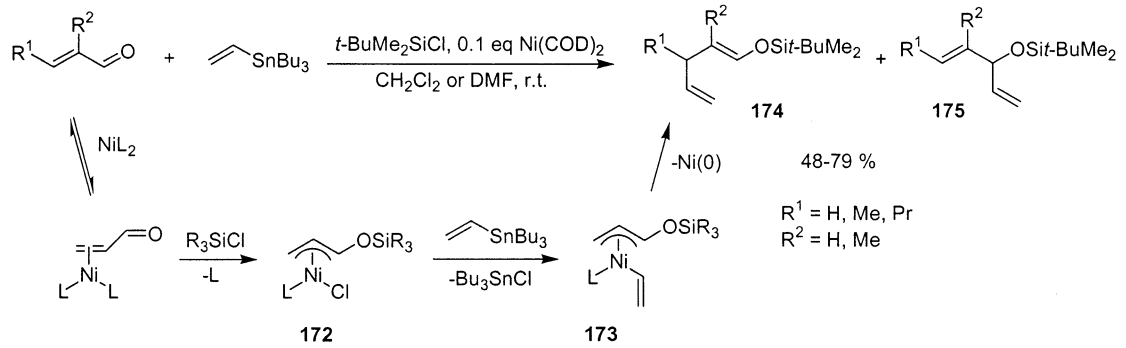
Optically active formaldehyde hydrazone **178** reacts with α,β-enones in the presence of dimethylthexylsilyl triflate (Scheme 110).[241] Desilylation of the primary products affords compounds **179** with high diastereoselectivity. The chiral pyrrolidine fragment can be removed from **179** by oxidative methods. Presumably, the process is initiated by complexation of α,β-enone with SLA followed by nucleophilic attack by the hydrazone.

XII. Miscellaneous Reactions

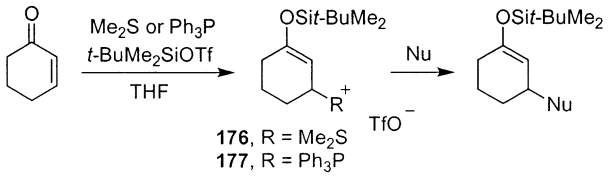
There are also many interesting processes of C,C bond formation promoted by SLA, which do not belong to the above-considered classes of reactions. Usually, these reactions proceed according to the same general scheme involving the initial transfer of the trialkylsilyl group to the heteroatom of a Lewis base followed by transformations of the resulting cationic species.

For example, the Pummerer rearrangement can be carried out under the action of the $Me_3SiOTf/i\text{-}Pr_2$-

Scheme 107. In the Representation of the Mechanism, the Substituents R^1 and R^2 Are Omitted



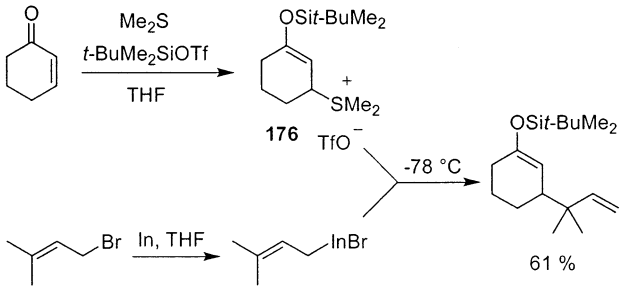
Scheme 108



for **176** + Nu, -70 °C, 10 min, Nu = malonate anion, RMgX, enamines Bu_3SnH, Bu_3SnN_3, pyridine

for **177** + Nu, 65 °C, 3 h, Nu = malonate anion, RSLi, Et_2NH

Scheme 109



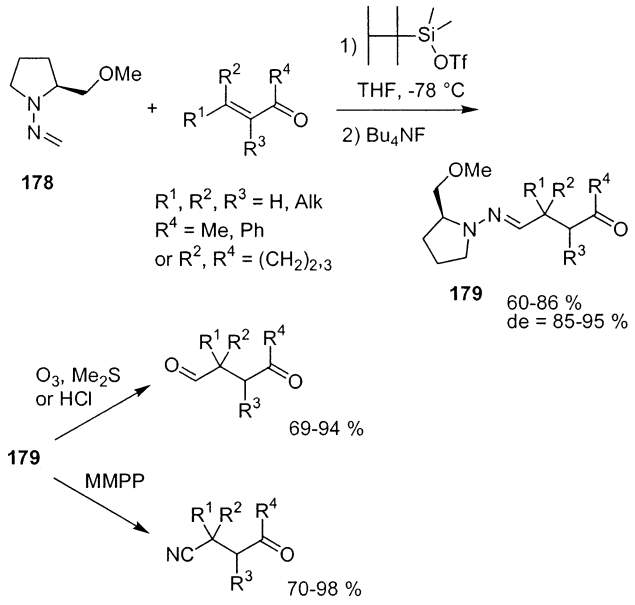
NEt system on sulfoxides as shown in Scheme 111. Intermediate thio-stabilized cation **180** is captured by silyl enol ether. In the absence of the C-nucleophilic component in the system, cation **180** reacts with Hünig's base to give a quaternary ammonium salt.[242]

The reactions of 2,3-methanochromanones **181** with silyl enol ethers in the presence of Me_3SiOTf afford mixtures of compounds **182** and **183** (Scheme 112). The most probable mechanism of this reaction involves the equilibrium generation of electrophilic species **184**, which is subjected to the attack of silyl enol ether. The resulting silyloxycarbenium cation **185** is either captured intramolecularly to give polycyclic ketone **182** or desilylated to produce (after treatment with water) diketone **183**. The ratio of the products depends on the steric requirements of the substituent R^1 in the starting substrate. Thus, the increase in the volume of the substituent R^1 favors the formation of product **183**.[243]

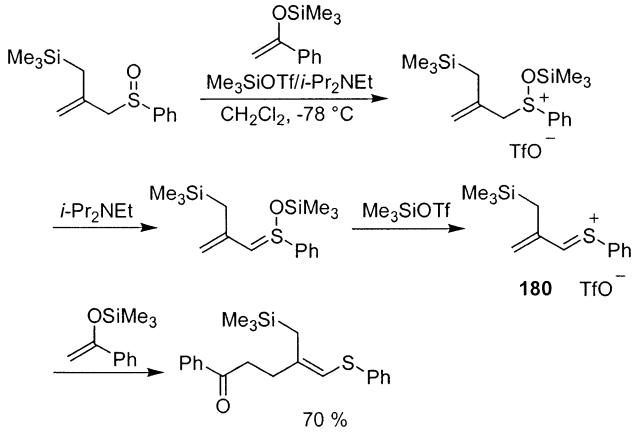
Cyclopropanation of glycal **186** followed by the reaction of bicyclic adduct **187** with Me_3SiCN under the action of Me_3SiOTf can be considered as a means for expansion of six-membered rings of carbohydrates to form oxepane derivatives (Scheme 113).[244]

Silyl triflates can activate carboxylic acid chlorides toward the attack of strong π-nucleophiles. This

Scheme 110. MMPP = Magnesium Monoperoxyphthalate

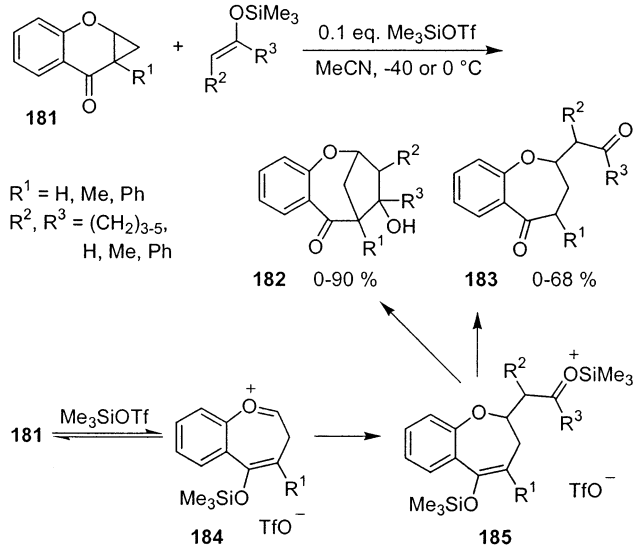


Scheme 111

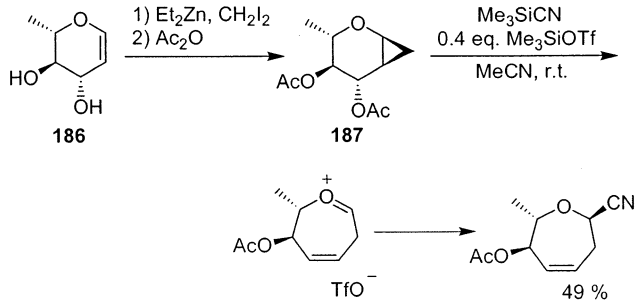


methodology was recently developped by Langer.[245] Thus, the silyl enol ethers, prepared by double silylation of β-ketoesters, react with acid chlorides under the action of Me_3SiOTf. Quenching of the reaction mixture affords 1,3,5-tricarbonyl compounds which may undergo further cyclizations (Scheme 114).[246,79] Acyl chlorides are activated either through coordination of SLA to the oxygen atom of the carbonyl group or through generation of acyl triflate (or an acyl cation).[247]

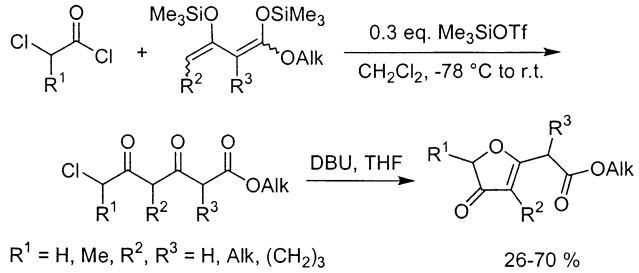
Scheme 112



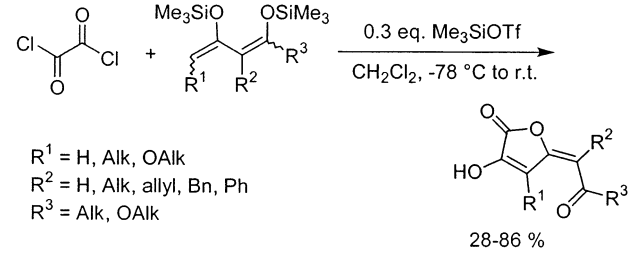
Scheme 113



Scheme 114



Scheme 115



Analogous reactions of oxalyl chloride with silyl enol ethers give rise to γ-alkoxybutenolides (Scheme 115).[245,248] The latter reaction is quite general, on its basis several approaches toward fragments of some natural products were elaborated.[245,248]

XIII. Acknowledgment

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XIV. References

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