The Triisopropylsilyl Group in Organic Chemistry: Just a Protective Group, or More?

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I. Introduction

In 1974, when the trimethylsilyl (TMS) and the *tert*-butyldimethylsilyl (TBDMS) groups were already well-established protective groups for alcohol and enol functionality,[1,2] Ogilvie et al. published the first experiments aimed at selective protection and deprotection of OH groups using the triisopropylsilyl (TIPS) group.[3–5] The bulky substituents on silicon in TIPS were already known to slow down reactions at Si compared to TMS or TBDMS, and to make the Si sensitive to the steric demands of reaction partners, thus rendering TIPS-Cl a selective silylating agent for primary OH in the presence of secondary OH.[6] The expectation proved to be correct,[7] in fact to such an extent that the low rate of attaching TIPS to an organic nucleophile using TIPS-Cl became the limiting factor of its use. Triisopropylsilyl trifluoromethanesulfonate (TIPS-OTf), introduced by Corey et al. in 1981,[8] allowed this limitation to be overcome.

As Corey pointed out, the TIPS group has the potential of being a useful control element in organic synthesis due to its extraordinary bulk, in that steric screening is provided for the atom to which TIPS is attached and even beyond.[8–10] Since then, TIPS has enjoyed ever-increasing popularity among synthetic chemists, and now after 20 years it seems appropriate to review its use in organic chemistry.

The present review, organized mainly by compound classes, cannot deal with the chemical behavior of the particular silane classes, guidance to this material is given in the references. Rather, the aim of this review is to point out where TIPS differs from other R_3Si groups. Here, therefore, the merits of TIPS as a protective group will be briefly discussed, the emphasis, however, is on such reactions where the incremental structural difference between TIPS and other often-used trialkylsilyl groups is translated into a synthetically useful effect, that is where TIPS gives results distinctly different from those for TMS or even TBDMS.

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Table 1. Steric Substituent Constants as Given by Dubois[12] (Revised Taft Values, first column), by Cartledge[11] (Second Column), and by Shimizu[13] (Third Column)

	$-E_s'$	$-E_s$(Si)	$-E_s^{Si}$
Me	0	0	0
Et	0.08	0.149	0.261
^{n}Pr	0.31	0.216	0.315
^{n}Bu	0.31	0.225	0.348
^{i}Pr	0.48	0.556	0.677
Et_2CH	2.00		0.816
^{c}Hx	0.69	1.02	0.757
^{i}Bu	0.93	0.405	0.400
^{t}Bu	1.43	1.46	1.670
^{t}BuCH$_2$	1.63		0.589

II. Reactivity and Structure of the TIPS Group

In spite of the long-standing and widespread use of bulky silyl groups in organic chemistry, there are surprisingly few attempts at quantifying the intuitive concept of bulkiness. Two closely related but different aspects have to be considered. First, there is the influence of the various alkyl groups in a triorganosilyl group on reactions taking place at the Si atom, such as silylation and desilylation reactions. Second, the retarding effect of various triorganosilyl groups on reactions at the point of attachment, or at atoms even farther apart, has to be considered.

As to the first, in 1983 Cartledge noted that steric effects of alkyl groups on reactions at Si are different from the effects observed on reactions at a carbonyl C, as described by the Taft steric parameters, E_s. Using as a model reaction for nucleophilic attack at Si the acid-catalyzed hydrolysis of Si−H compounds he obtained a set of steric parameters for groups at Si, E_s(Si) (Table 1).[11] The major difference between the two sets is that reactions at tetracoordinate Si show a greater effect of branching α and a smaller effect of branching β to the reaction center than do reactions at tricoordinate carbon. However, the database of the Cartledge values is small, and especially the large difference between ^{i}Pr and ^{c}Hx casts some doubt on their validity.

Shimizu et al. in 1992 measured the rates of solvolysis in 89 mol % aqueous dioxane for a large series of triorganosilyl chlorides and obtained a set of steric substituent constants for reactions at Si, E_s^{Si}, which are log k_{rel} values (relative to Me) divided by a constant in order to make their magnitude comparable to the Taft values (Table 1).[13] The trends observed by Cartledge were grossly confirmed. From the same measurements a system of simple equations was obtained allowing the prediction of the reactivity of any trialkylsilyl chloride.[14] Agreement between observation and calculation is very good in most cases (Table 2).

As to the second, it is certainly reasonable to describe the screening action of a bulky group on the atom to which it is attached by an angle, that is a set of directions from which an attack at the screened atom is impossible. This concept of the cone angle (Tolman[15]) was applied to silyl groups seemingly independently by Imyanitov[16] and by Panek and Giering[17] who when trying to separate steric and electronic effects of silyl groups ascribed to the different trialkylsilyl groups the cone angles θ and

Table 2. Relative Reactivities of R_3SiCl Compared to Me_3SiCl (Solvolysis in 89% Aqueous Dioxane)[14]

		$-\log k_{rel}$ obsd	$-\log k_{rel}$ calcd
TMS	Me_3Si	0	0
TES	Et_3Si	1.869	2.00
	^{n}Bu$_3$Si	2.567	2.49
TBDMS	^{t}BuMe$_2$Si	3.507	3.76
TIPS	^{i}Pr$_3$Si	4.968	5.18
	^{t}Bu$_3$Si		13.16
	Ph_2MeSi	2.157	2.00
TPS	Ph_3Si	3.438	3.62
TBDPS	^{t}BuPh$_2$Si	6.889	6.53

Table 3. θ (Cone Angle) and χ for Various R_3Si Groups[17]

		θ, deg	χ, cm^{-1}
TMS	Me_3Si	118	8.55
TES	Et_3Si	132	6.3
	^{n}Bu$_3$Si	136	5.25
	^{n}Hx$_3$Si	136	5.0
TBDMS	^{t}BuMe$_2$Si	139	5.7
TIPS	^{i}Pr$_3$Si	160	3.75[a]
	$ClMe_2Si$	120	21.7
	$PhMe_2Si$	122	10.6
TPS	Ph_3Si	145	13.25

[a] In the sources values of 3.45 and 3.1 are given.

the χ values given in Table 3. These parameters were defined earlier from Ni(CO)$_3$ phosphane complexes: θ, a measure of steric effect, is the apex angle of an imaginary cone whose apex is on the principal axis of the bulky group 2.28 Å (an average Ni−P bond length) outside the group's central atom, and whose mantle touches the van der Waals surfaces of the alkyl groups building the bulky group.[15] The values of θ were obtained from simple measurements of space-filling molecular models. χ is a measure of σ-donicity (electronic effect), obtained as the difference of $\tilde{\nu}$ for the symmetric A_1 CO stretch in the respective Ni(CO)$_3$ phosphane complex and in Ni(CO)$_3$P(^{t}Bu)$_3$. Small values of χ correspond to good donors. The values for the silyl groups were obtained simply by taking the values determined earlier for the corresponding phosphanes. This crude procedure was justified by the "obvious similarity" of $-SiR_3$ and PR_3, and by the excellent linear correlation obtained when the kinetic data for the addition of a diarylcarbenium ion to a series of allylsilanes were described using θ and χ as independent variables.

Although the details of this procedure are open to criticism, the trend in these θ values seems reasonable in that it agrees well with a large body of qualitative experimental evidence. Cone angles for the following groups are either given in ref 15 or easily estimated from data given in refs 15 and 17: ^{t}Bu^{i}Pr$_2$Si, 167°; ^{t}Bu$_2{}^i$PrSi, 174°; ^{t}Bu$_3$Si, 182°; ^{t}BuPh$_2$Si, 157°; ^{t}Bu$_2$PhSi, 170°; (benzyl)$_3$Si, 165°; and (neopentyl)$_3$Si, 180°. Values given for the same groups by Imyanitov are consistently larger by 5°, due to a shorter M−P bond length chosen by this author.[16]

A conventional measure for a group's steric effect is its A value, the energetic preference for the group occupying an equatorial *vs* an axial position on a cyclohexyl ring ($-\Delta G°$ in kcal/mol, e.g. Me 1.74, ^{i}Pr

2.15, ^{t}Bu > 4, TMS 2.5[18]). *A* values for $OSiR_3$ groups were recently measured by ^{13}C-NMR by Eliel and Satici: OTMS, 1.31; OTES, 1.26; OTBDMS, 1.06; OTIPS, 0.94 (in CD_2Cl_2).[19] Three features are notable: (i) The values are small, which is understandable since the alkyl groups are separated from the cyclohexane by no less than three bonds. (ii) Unexpectedly, the more bulky a silyl group is by all other measures, the smaller is the *A* value of the corresponding $OSiR_3$, which suggests that the alkyl groups attached to Si are more sterically interfering when $OSiR_3$ is equatorial than when it is axial. (iii) There is a large unexplained solvent effect: In toluene-d_8 the *A* values for $OSiR_3$ are consistently smaller by ca. 0.5 kcal/mol than those in CD_2Cl_2.

It is conceivable that the isopropyl groups in TIPS may rotate about the C_α–Si bonds not independently of one another, and that they may prefer a particular relative arrangement, such as a propeller-like one. (Hindered rotation was found experimentally in ^{t}Bu$_3$-Si-X compounds.[20]) However, in NMR work a hint to a possible interdependence of the TIPS isopropyl groups in their rotation around the Si–C bonds was not normally found, not even in tetraisopropylsilane (TIPS-^{i}Pr).[21] The molecular structure of this compound was analyzed by electron diffraction,[22] the strain in the S_4 symmetric structure is manifested in an unusually long Si–C bond (1.919 Å, standard 1.870 Å), in widened and compressed C–Si–C angles, and in deviations from the fully staggered conformation for the isopropyl and methyl groups.

From calculations (empirical force field and MNDO) of the structure of tri-*tert*-butylisopropylsilane (^{t}Bu$_3$-Si-^{i}Pr) Weidenbruch concluded that the isopropyl group rotates independently of the other alkyl groups even in this highly loaded molecule.[20] Hindered rotation of the alkyl groups in TIPS was reported in an unusual Rh complex containing two TIPS groups very close to one another,[23] and in a disilylarsane.[24]

MM2 parameters for silanes were derived by Allinger.[25]

Although *ca.* 50 X-ray structure analyses of TIPS-containing compounds are published, the TIPS group was never the focus of these studies, and a comparative evaluation of the data was not undertaken. The only relevant information from these studies at present is that bonds to TIPS are significantly longer than the corresponding standard bonds to Si, as contained in the Cambridge Crystallographic Database (1987), which probably represent mostly bonds to TMS.[26] Data are available for aryl–TIPS (median 1.906 Å,[27,28]) compared to aryl–Si (median 1.868 Å,[26]), and for O–TIPS (median 1.660 Å,[29–33]) compared to O–Si (median 1.630 Å,[26]). Similarly, the Si–C bonds within TIPS are significantly longer (median 1.889 Å,[27–29,31–36]) than Si–CH_3 bonds (median 1.857 Å,[26]).

In a few cases the isopropyl groups were found to be disordered.[31,37,38]

III. Triisopropylsilylating Agents

The silicon hydride TIPS-H was first obtained in 1947 by Gilman from $HSiCl_3$ and isopropyllithium in a hydrocarbon solvent, the chloride TIPS-Cl likewise from $SiCl_4$.[39] In this paper also the first use of TIPS-Cl and TIPS-H as silylating agents, for EtOH or PhLi, respectively, is reported.

The easily available Grignard reagent ^{i}PrMgCl in ether transfers only two ^{i}Pr groups to a silicon.[39–41] The currently best preparation of TIPS-H from $HSiCl_3$ uses ^{i}PrMgCl in THF (room temperature, 3 days).[7] TIPS-Cl can be prepared from TIPS-H by treatment with $CuCl_2$[42] or very easily and efficiently by bubbling Cl_2 into a cold (−30 °C) solution of TIPS-H in petroleum ether.[43]

In the TMS series, the triflate TMS-OTf is a more potent silylating agent than the chloride TMS-Cl by a factor of 6.7×10^8.[44] A similar effect is observed for TIPS-OTf *vs* TIPS-Cl, although no number is available. TIPS-OTf is made by treating TIPS-Cl or simply TIPS-H with trifluoromethanesulfonic acid without a solvent at 0 °C to room temperature. The clear liquid, fuming when exposed to air, is easily purified by distillation; it has to be handled and stored under dry nitrogen.[8] The use of silyl triflates for silylation was recently reviewed.[45]

Both TIPS-Cl and TIPS-OTf are commercially available.

In the overwhelming majority of reported triisopropylsilylations, one of these two agents was used (see below). Others were used occasionally, such as TIPS-F for aryl- and alkyllithiums (notably isopropyllithium) as well as an alcoholate,[21,46] and for Ca cyanamide,[47] TIPS-I for inorganic anions (CN^-,[41] NO_3^-,[48] S^{2-},[49]), TIPS-CN for CN^-,[50] TIPS-F and TIPS-Br for lithiated anilines,[51,52] and TIPS-imidazole for a secondary alcohol.[53] TIPS-H was used in the presence of CsF and imidazole to selectively silylate a primary alcohol in the presence of a secondary alcohol, a primary amine was reported not to react under these conditions.[54,55] TIPS-H is a useful agent for hydrosilylation of C=C bonds (both under Rh or Pt complex catalysis[56–59] and under free radical conditions[60]), and of C≡C bonds (Rh, Pt catalysis).[61–64]

IV. O-TIPS Compounds

A. TIPS Alkyl (or Aryl) Ethers

1. Preparation

For general information on the use of trialkylsilyl as O-protecting groups see recent reviews.[45,65–68]

The TIPS ether can be obtained from a primary or secondary alcohol using TIPS-Cl in DMF in the presence of imidazole[3,4,7,69,70] or DMAP,[71] or pyridine and $AgNO_3$ or $Pb(NO_3)_2$,[72] or in acetonitrile,[73] or in CH_2Cl_2,[74,75] best in presence of both imidazole and DMAP,[76,77] but Et_3N is sufficient.[78] The Li derivative of a secondary alcohol was triisopropylsilylated in THF/HMPA.[79,80] Generally, primary OH reacts much faster than secondary OH.[3,4,74,81–83] A primary alcohol function was triisopropylsilylated selectively in the presence of a secondary alcohol using TIPS-Cl/tetramethylguanidine in *N*-methylpyrrolidone,[84] or TIPS-Cl/imidazole in DMF.[85] Interestingly, the imido nitrogens of thymidine and uridine do not react with TIPS-Cl under the conditions given[3,4,72] (as is also known for lactam nitrogen on treatment with TBDMS-Cl[86]). In ribonucleosides moderate selectivity

for 2′-OH silylation over 3′-OH was observed.[3] TIPS-Cl in THF in the presence of either imidazole or $AgNO_3$ silylated modified ribonucleosides with better 2′-O *vs* 3′-O selectivity (e.g. 10:1) than did TBDMS-Cl or $^tBuPh_2Si$-Cl (TBDPS-Cl).[87-89] TIPS-Cl was found to monosilylate a bissecondary diol more selectively than TBDMS-Cl.[90]

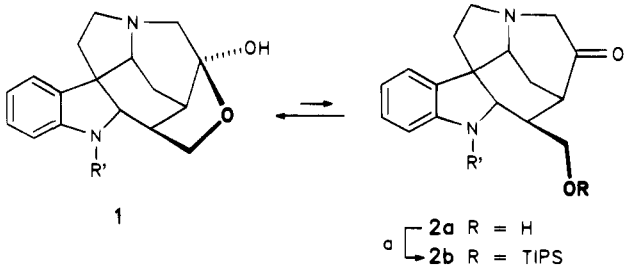
A triol was mono-triisopropylsilylated at a secondary OH in the presence of another secondary OH and a tertiary OH.[69] Tertiary alcohols do not react,[7] nor does a corresponding Li salt,[91] but the K salt of a cyanohydrin (made in situ from a ketone, KCN and 18-C-6) gave the corresponding tertiary TIPS ether when treated with TIPS-Cl.[92] Similarly, the secondary TIPS ether of a cyanohydrin can be prepared from an aldehyde, KCN, and TIPS-Cl under ZnI_2 catalysis.[93]

Phenols are triisopropylsilylated under similar conditions,[33,94-96] their Na or K salts are silylated faster in CH_3CN or DMSO than in THF.[97]

With the more potent silylating agent TIPS-OTf phenols[98] and primary and secondary alcohols react under mild conditions (CH_2Cl_2/2,6-lutidine, −78 °C to 0 °C),[8,99] even secondary neopentyl-type alcohols were successfully reacted with TIPS-OTf in the presence of Et_3N or 2,6-lutidine.[100,101] Primary and secondary alcohols were silylated by TIPS-OTf in excellent yield in benzene or CH_2Cl_2 in the presence of Et_3N or $^iPr_2NEt$.[43,102] Useful selectivity between primary and secondary OH function is still observed (CH_2Cl_2, 2,6-lutidine, −20 °C).[103,104] Moreover, two secondary OH groups were differentiated at −78 °C,[105] at 0 °C,[106a] or even at room temperature.[107] 2′,3′,5′-Tris-*O*-TIPS derivatives of ribonucleosides were synthesized from the nucleosides and TIPS-OTf in DMF/imidazole, seemingly without any N-silylation.[108]

A tertiary alcohol such as ^tBuOH is triisopropylsilylated by TIPS-OTf under similar conditions only sluggishly.[8,43] This fact was exploited in a critical step in Magnus' strychnine synthesis, where keto primary alcohol **2a** present as minor component in equilibrium with hemiketal **1** (tertiary OH) was selectively trapped as the keto TIPS ether **2b** (Scheme 1).[109,110]

Scheme 1[a]



[a] R′= $SO_2C_6H_4$-4-OMe. (a) TIPS-OTf, DBU, CH_2Cl_2, 0−25 °C.

The TIPS ether of a very hindered tertiary alcohol was obtained by silylation, but a procedure is not given.[111] TIPS ethers of tertiary alcohols are formed e.g. as products of Diels−Alder reactions of cyclic 1-(triisopropylsilyl)oxy dienes,[112,113] or by alkylation of α-Li derivatives of TIPS ethers.[80]

Often in compounds containing both OH and NH or NH_2 groups, the OH can be silylated selectively.[53,54,114] Thus, clean O-triisopropylsilylations were claimed as the result of treating ethanolamine or 4-amino-1-butanol with 0.1 equiv TIPS-Cl in CH_2Cl_2 without a base.[115]

2. Chemical Behavior

Alkyl TIPS ethers are inert in the presence of a wide variety of reagents under many conditions. Thus TIPS ethers survived treatment with the following.

Oxidizing: OsO_4,[116-120] Sharpless dihydroxylation;[121] RuO_4;[116] SeO_2;[30,122] O_3;[75,77,100,123-129] *m*-CPBA;[75,130,131] CF_3CO_3H/Na_2HPO_4;[132] ^tBuOOH;[133-136] Sharpless epoxidation;[131] Ph_3C-OOH;[137] $(TMSO)_2$;[131] dimethyl dioxirane;[82,138] H_2O_2/NaOH;[107,120,139] H_2O_2/LiOH;[137,140-143] $NaIO_4$;[116,118,119,129] NaOCl;[116] Dess−Martin periodinane;[96,107,118,126,144-148] $PhI(OTFA)_2$;[126] Jones oxidation;[84,104,150-152] PCC;[54,153] PDC;[130,144] CrO_3/dimethylpyrazole;[104] $Pb(OAc)_4$;[69,105,154-157] $KMnO_4$;[158] $Ce(NH_4)_2(NO_3)_6$, MeCN/H_2O;[159,160] DMSO/triphosgene;[161] DMSO/py·SO_3;[120,162-164] Swern oxidation;[107,141,147,165,166] DDQ;[106a,118,126,141,147,151,167] MoO_5·HMPA[168] (in contrast to O-TES which is cleaved); WO_5·HMPA[168-170] (in contrast to O-TES which is cleaved); I_2;[74,125,127,171-176] anodic oxidation.[177] (For the behavior of various silyl ethers toward many oxidants see a recent review.[178])

Reducing: LAH[30,96,104,106a,126,162] (however, LAH in THF at reflux may cleave an O-TIPS vicinal to an alcohol, amine, or other group capable of binding an aluminum hydride moiety[179]); DIBAL-H/THF or Et_2O;[92,103,134,139-141,151,164,180-182] DIBAL-H/CH_2Cl_2[182-185] (DIBAL-H in chlorinated solvents at room temperature desilylates RO-TBDMS,[186] a secondary OTIPS was not stable to DIBAL-H in refluxing CH_2Cl_2 for 24 h[187]); $NaBH_4$;[30] $NaBH_4/Et_2BOMe$;[77] $NaBH_3CN$;[116] $LiEt_3BH$;[123] Li^sBu_3BH;[139,145,166] $Me_4NBH(OAc)_3$;[163] $Zn(BH_4)_2$;[143] Ph_3PBH_2CN;[188-192] BH_3·Me_2S[137] and Et_2BH·Me_2S;[193] H_2/Rh complex/CO;[194] H_2/Pd/C;[129,144,195] H_2/Pt/C;[196] Zn/Cu/$TiCl_3$ (McMurry);[128] Li/NH_3 (liq);[104,123,197,198] Na/NH_3(liq);[71,197,199] Birch reduction;[77] Na/Hg;[71,106b,200] Li/naphthalene;[107] LiDBB.[103,130,201]

Basic/nucleophilic: NaH/DMF or THF or KH/THF;[120,162,202,203] NaH/HMPA[106b] (which cleaves RO-TBDMS and RO-TBDPS); amide bases, LDA, LTMP,[120,134,180,204] $LiN(TMS)_2$,[134] $NaN(TMS)_2$,[163] $KN(TMS)_2$;[140,141,205] hydroxide/alkoxide bases, LiOH/THF/(H_2O),[156,163] KOH/MeOH [125,127] (by this reagent (16 h, room temperature) a methyl ester was selectively cleaved in presence of a TIPS ether, the corresponding TBDMS ether was cleaved[125]), KOH/MeOH/H_2O,[102,204] $Ba(OH)_2$·$8H_2O$,[144] K_2CO_3/MeOH/(H_2O),[129,204,206] NaOMe/MeOH, [141,164] $LiOCH_2Ph$/THF,[107] KO^tBu/DMF, 105 °C,[207] NH_3/aqueous EtOH or NH_3/anhydrous MeOH;[208,209] organometallic reagents, Grignard reagents,[120,139,166,196,210,211] MeLi,[134,210] EtLi,[212] ^nBuLi,^sBuLi,^tBuLi,[212] ^nBuLi, [131,213] ^nBuLi/TMEDA,[79,141] $^nBuLi/^tBuOK$,[107] ^sBuLi/TMEDA,[162] ^tBuLi,[106a,126,173,214-217] (by which O-TBDMS is metalated), ^tBuLi/TMEDA;[130] organocuprate reagents;[218-220] $[Me_3SnCu(CN)]Li$;[221] $PhMe_2SiLi$;[222] Me_2Mg;[223,224] Me_3Al;[112,131,141] Et_2Zn, Me_2Zn;[193,225,226] various organometallics; [227] Wittig reagents;[96,127,134,135,228] PhSH.[175]

Acidic: HOAc/H_2O/THF, room temperature;[4,120,158,163,195] HOAc/H_2O/THF, 50 °C, several hours[154] (several other O-SiR_3 groups are cleaved by these reagents, e.g. primary and secondary O-TES and O-TBDMS); 80% HOAc, 100 °C, 10−20 min[3,4] (primary O-TBDMS is cleaved under these conditions); HOAc/MeOH, reflux[116] (primary O-TBDMS is cleaved); Zn/HOAc/THF;[141] glyoxylic acid/HOAc, reflux;[141] py·HOTs/^{i}PrOH/CH_3CN, 70 °C, 26 h[107] or py·HOTs/MeOH 60 °C, 8 h;[204] py·HOTs,HOTs,THF/H_2O (secondary OTIPS and ODEIPS are inert, while primary OTBDMS is cleaved);[118] py·HOTs, acetone, 43 °C[118] or py·HOTs, benzene, heat;[187] CF_3CO_2H[126,130,140,165,229-231] (secondary OTES is cleaved; however, a primary OTIPS was cleaved in the presence of a secondary OTBDPS[149] or a secondary OTBDMS[141] by this reagent in THF/H_2O); Cl_3CCO_2H;[175] camphorsulfonic acid;[120,232] HOTs in anhydrous ^{i}PrOH;[151] fuming HNO_3/Ac_2O;[157] aqueous $HClO_4/Et_2O$.[231] 0.05 N Aqueous HCl in Et_2O/CH_2Cl_2 or anhydrous HCl in Et_2O/CH_2Cl_2 did not cleave an ArO-TIPS,[96] nor did HCl/MeOH/H_2O at reflux for 4 h;[233] 3 N HCl cleaved a vinyl ether in presence of a secondary OTIPS.[205]

Lewis acidic: Me_3Al;[112,131,141] Et_2AlCl or Me_2AlCl;[112,234-236] Me_2AlCl;[133,163,235,237] $EtAlCl_2$ [112,145,238] $^iBu_2AlCl$;[122] $AlCl_3$;[112,113,162] $MeAl(OTf)_2$;[239] MABR (methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide), a highly hindered agent which nevertheless complexes an epoxide);[240-242] Cl_2AlOPh;[92] MeAlCl−NMe(OMe);[164] $Me_2Al-NHCH_2Ph$;[114] $BF_3\cdot OEt_2$;[103,106b,144,162,163,182,243] BCl_3;[150] Me_2BBr;[150,158,195] Et_2BOMe;[77] $(^iPrS)_2BBr$;[244] $TiCl_4$[99,234,236] (for a case of cleavage see ref 165); $TiCl_3(O^iPr)$;[245] $TiCl_2(O^iPr)_2$;[163,237] $Ti(O^iPr)_4$;[225] $Sn(OTf)_2$;[246,247] $SnCl_4$;[92,94] $ZnCl_2$;[138] MgI_2;[182] Ag_2CO_3 in ether/MeCN or CH_2Cl_2.[248]

Miscellaneous reagents: CCl_2;[219,249] Burgess reagent,[211] $^nBu_3SnH$;[74,104,127,182] hydrozirconation;[218,250] Pd/Montmorillonite;[129] $Pd(OAc)_2$;[251-255] $Pd(PPh_3)_4$;[96,122] Pd/BINAP;[215] $RhCl(PPh_3)_3$/PhCN, 165 °C, 4 h[241] (O-TBDMS and O-TPS are cleaved); *N*-chlorosuccinimide/$AgNO_3$/lutidine;[106b,107,139-141] oxalyl chloride/DMF/Et_2O, then CH_2N_2, then $PhCO_2Ag$ (Arndt−Eistert conditions);[204] PCl_3, *N*-methylmorpholine, triazole;[89] Mitsunobu reagent;[145,183] Martin sulfurane;[237] peptide coupling reagents BOP [215] and FDPP;[256] $I(coll)_2ClO_4$;[257b] Barton decarboxylation.[102]

Of special interest are reagents that while removing several O-silyl groups do not attack O-TIPS:

$^nBu_4NF$/HOAc/THF, 25 °C removes secondary *O*-TMS in the presence of secondary *O*-TIPS;[105] $^nBu_4NF$ in THF cleaved a secondary *O*-TBDMS in the presence of a secondary *O*-TIPS;[205] H_2SiF_6/10% aqueous CH_3CN at 0 °C cleaves *O*-TBDMS selectively in the presence of *O*-TIPS,[258] at 55 °C, however, *O*-TIPS is cleaved,[116] *O*-TBDPS is even less reactive; the same selectivity is seen for H_2SiF_6 (catalytic amount) in ^{t}BuOH;[259] aqueous HF/catalytic H_2SiF_6 cleaves secondary *O*-TBDMS in the presence of primary allylic *O*-TIPS;[130] OTIPS and OTBDPS are resistant to excess HF/pyridine/THF, conditions which cleave OTES;[117,260] OTIPS was resistant to HOAc in THF/H_2O (OTES and OTBDMS were cleaved),[237] and to $^nBu_4NF$ in THF/HOAc at 50 °C, whereby *O*-TBDMS was cleaved;[245] 1.5 M aqueous HF in MeCN/THF at room temperature cleaved an anomeric OTBDMS selectively in the presence of a secondary OTIPS;[261] anhydrous *p*-TsOH in ^{i}PrOH (4 Å MS) cleaved a secondary OTBDMS in the presence of a secondary OTIPS; use of EtOH as solvent or a small amount of water increased the rate of OTIPS attack and resulted in loss of selectivity;[151] NaH in HMPA (or dimethylpropyleneurea) cleaves both OTBDPS and OTBDMS, leaving OTIPS intact;[106b] palladium oxide hydrate in MeOH/cyclohexene (1:1) cleaves O-TBDMS in the presence of O-TIPS selectively (catalytic transfer hydrogenation);[262] $FeCl_3$ in DMF cleaves O-TMS (presumably via the alkoxy radical), but not O-TIPS.[157]

There are, however, a few reagents/conditions known to affect an O-TIPS group (in addition to those used preparatively to cleave O-TIPS, see below). In most cases, the C_α−H bond is attacked: NBS/dibenzoyl peroxide α-brominates O-TIPS;[94,263] NBS alone in THF was found to brominate the isopropyl groups in *N*-TIPS-pyrrole even at −78 °C;[264] however, 3 equiv of NBS in $CHCl_3$ at 20 °C did not affect an O-TIPS;[180] elemental Br_2 likewise transforms an isopropyl group at Si into an α-bromoisopropyl group;[265,266] a very strong base, such as lithiodihydropyran, can α-metalate a TIPS group;[83,217] an intramolecularly generated alkylidene carbene inserts into the C_α−H bonds in TIPS (as in TMS or TBDMS);[267,268] alkyl TIPS ethers are converted to alkyl bromides by the action of Ph_3PBr_2;[269,270] a secondary alkyl-O-TIPS was cleaved to the alcohol on treatment with $TiCl_4$ in CH_2Cl_2.[165] OTIPS does not normally act as a leaving group, in contrast to OAc;[252,271] however, β-elimination of TIPS-OH can occur if the double bond formed is conjugated, such as in an α,β-unsaturated imine,[78] see also the Peterson reaction to form enynes (Scheme 84).[272]

Desilylation. Generally, primary TIPS ethers are more easily cleaved than secondary TIPS ethers.[4,7] The stability of several (primary and secondary alkyl, aryl) TIPS and other SiR_3 ethers against acidic and alkaline hydrolysis was measured.[7,73] It was concluded that *O*-TIPS is less reactive than all other *O*-SiR_3 groups tested (including *O*-TBDMS), except that *O*-Si^{t}BuPh$_2$ (*O*-TBDPS) and *O*-Si^{t}Bu$(CH_2)_4$ under acidic conditions are even less reactive than *O*-TIPS.[4,7,73] This latter selectivity was used for selective cleavage of primary OTIPS in the presence of secondary OTBDPS on treatment with F_3CCO_2H.[149,225]

Against F^- likewise O-TIPS is more resistant than O-TBDMS.[7]

For preparative cleavage of TIPS ethers to alcohols the following conditions were used: 0.01 N HCl/EtOH/H_2O, 90 °C, 15−80 min;[3] 2 N HCl/MeOH, 16 h;[110,185] 2 N HCl/MeOH or EtOH, 60−80 °C (for ArO-TIPS);[91,273] 3 N HCl/dioxane, reflux;[274,275] 6 N HCl, 25 °C, 5 h;[265] HCl in EtOAc, −30 to 0 °C,[158,195] F_3CCO_2H/THF/H_2O 1/3/3;[148] TsOH/MeOH/Δ[276] (10% TsOH cleaved one of two secondary O-TIPS selectively[277]); 40% KOH in MeOH, reflux, 18 h.[114]

The reagents of choice for cleavage of TIPS ethers are several fluorides: $^nBu_4NF$ in THF (the commercial reagent contains at least 3 equiv of

H_2O,[113,130,254,278-281] this reaction is rapid, e.g. 5 min at 0 °C are enough to cleave both an aliphatic secondary TIPS ether and an aryl TIPS ether[122]); 1 equiv of $^nBu_4NF$ in THF, 23 °C, 30 min cleaved, as a notable exception, a secondary O-TIPS selectively in the presence of two or even four secondary O-TBDMS;[282] CsF alone or in presence of 18-C-6 (for Ar-OTIPS);[94,263] 47% HF/CH_3CN/H_2O (e.g. 0.5/8.5/1);[69,130,141,146,163,278,283] 40% aqueous HF/THF;[204] 10% HF in CH_3CN;[85] py·HF in THF[96,245] or in py/THF;[118] HF in CH_2Cl_2, generated *in situ* from BF_3·Et_2O and 4-methoxysalicylaldehyde, cleaving silyl ethers including secondary O-TBDPS at rates comparable or higher than those of $^nBu_4NF$.[284] Ar-OTIPS were transformed in one-pot procedures into carbamates ArO-CO-NHR by treatment with $^nBu_4NF$, LiCl and RNCO[98] and into ArOMe by $^nBu_4NF$/NaH/Me_2SO_4;[279] NO_2BF_4 cleaved a secondary TIPS ether, but not in the presence of collidine.[157]

Neutral alumina containing 0−3% H_2O can be employed for cleavage of silyl ethers, avoiding exposure to the basic fluoride ion.[285] Useful selectivity among various silyl groups is again observed, the reactivity order being OTMS >> OTBDMS > OTBDPS > OTIPS.

Unconventional reagents for the cleavage of TBDMS ethers were discovered recently, such as DIBAL-H in chlorinated solvents at room temperature,[186] or $^tBuOOH/MoO_2(acac)_2$.[286] The behavior of TIPS ethers toward these reagents was not studied.

3. TIPS as Protecting Group for Alcohols

The features discussed above (TIPS is easily introduced, is inert under many conditions, is easily removed by specific reagents) render TIPS one of the foremost protecting groups for OH (permanent protection). Its value is clearly seen in ambitious syntheses of complex natural products and analogues, such as the immunosuppressant FK-506;[106a,107,126,140,141,154-156,164,211,277,287-291] rapamycin;[105,106b,118,131,245,260] bryostatin;[100] didemnins;[158,195] strychnine[84,110,135,185,292] macrolides;[144,163,237] phyllanthocin;[129,293] anthracycline C-glycosides;[294] hemibrevetoxin ring system;[162] ciguatoxin partial structure;[120] branched oligosaccharides;[257] polycyclic natural drug ingredients paeoniflorin[283] and miroestrol.[122]

A first study on the use of TIPS for side chain protection in peptide synthesis appeared recently.[73]

RNA synthesis: 2′-O-protection is of central concern in the synthesis of oligoribonucleotides and RNA. Bulky silyl groups are well suited for this purpose, as was first shown in the work of Ogilvie. A systematic strict comparison of TIPS and TBDMS in RNA synthesis has not been performed. Generally, both TBDMS and TIPS groups are in use, the latter for base-protected guanosine nucleotides, the former for the other three nucleotides.[70,136,175,208,209] There seems to be no scientific reason for this difference, rather, it is a matter of commercial availability and price of building blocks.[295] TIPS exhibited higher resistence to cleavage compared to TBDMS, particularly when exposed to aqueous NH_3/EtOH, where harsher conditions are required for the base-deprotection of guanosine residues than of the other three nucleotides.[208,209]

Silylation of ribonucleosides generally shows moderate 2′ over 3′ selectivity.[88] Good 2′-selectivity was achieved using TIPS-Cl and $AgNO_3$ in pyridine/THF.[87,89,296] However, a high 3′ over 2′ selectivity can be achieved using TIPS-Cl, $AgNO_3$ and DABCO in THF.[297,298]

Interestingly, N-silylation was never observed on treatment of nucleosides with TIPS-Cl[190,191,299,300] or even TIPS-OTf.[108]

2′-*O*-silyl groups do not normally migrate to 3′-O in dry aprotic solvents.[175,296,301,302] In protic solvents at least TBDMS and TBDPS tend to migrate;[303] TIPS demonstratedly less so.[87] OTIPS and OTBDMS survive the procedures used for phosphitylation,[175,301,302] detritylation (5% Cl_3CCO_2H or 2.5% Cl_2HCCO_2H/CH_2Cl_2), oxidation of phosphite to phosphate (I_2), cleavage of methyl phosphate (PhSH/Et_3N/dioxane), and conversion to a phosphonate (PCl_3, *N*-methylmorpholine, triazole).[87,89] However, deprotection of acylated nucleobases (aqueous NH_3 in EtOH) is problematic at least in the presence of 2′-OTBDMS which is deprotected to some extent causing internucleotide cleavage. This problem can be minimized by the use of phenoxyacetyl as nucleobase-protecting group, which is cleaved under mild conditions (anhydrous NH_3 in MeOH, room temperature, 1 h) not affecting the 2′-O silyl groups.[208]

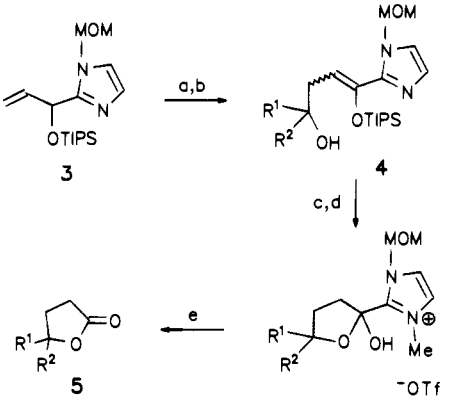
4. O-TIPS as Regiodirecting Group

TIPS was used successfully as a regiodirecting group in that it protects the atom to which it is attached or a nearby atom from being attacked by a reagent.

A classical problem of this kind is the allyl anion α/γ problem.

The Li derivative of an allyl ether reacts with a carbonyl electrophile usually preferentially at the α-position. This preference could not be altered by using the TMS or TBDMS allyl ether. In contrast, the TIPS group did provide the necessary bulk. Thus the imidazole substituted allyl TIPS ether **3** was lithiated at −90 °C (in order to prevent 1,4 O→C Si migration) and reacted with carbonyl compounds to provide preferentially or exclusively γ-products **4** (Scheme 2). These were converted to γ-butyrolactones **5** by desilylation, N-quaternization, and elimination.[79,80]

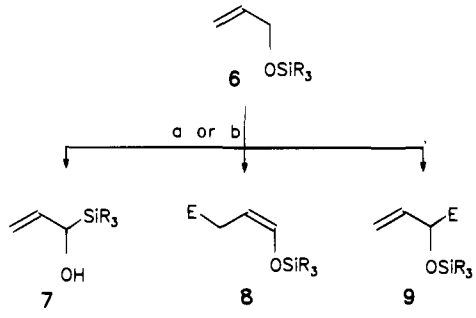
Scheme 2[a]



[a] (a) ^nBuLi/TMEDA. (b) R^1R^2CO. (c) $^nBu_4NF$,THF/H_2O. (d) MeOTf,CH_2Cl_2. (e) NEt_3.

A more demanding test, with disappointing result, had been performed earlier. The Li derivative of unsubstituted allyl TIPS ether **6** (SiR_3 = TIPS) suffered 1,2 O→C Si migration (at −78 °C in THF, → **7**, SiR_3 = TIPS), and the γ-directing effect of TIPS proved to be not strong enough (Scheme 3). Of

Scheme 3[a]



[a] (a) (1) ^{s}BuLi; (2) E-X; (3) H_2O. (b) (1) ^{s}BuLi; (2) BaI_2; (3) E-X; (4) H_2O.

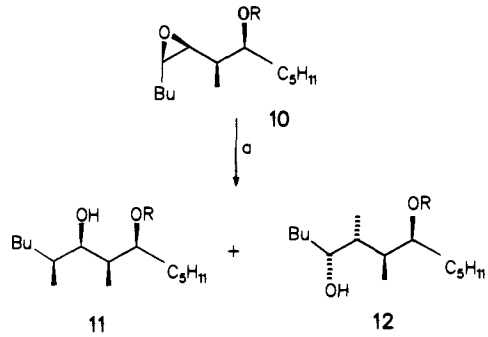
SiR_3	EX	cond.	7	8	9	ref
TIPS	^{i}PrI	a	50%	trace	trace	43
TIPS	TIPS-OTf	a	−[†]	42%	−	43
TES	$C_5H_{11}CHO$	b	−	76.5%	9.5%	304
TIPS	$C_5H_{11}CHO$	b	−	89.3%	5.7%	304

[†] The corresponding TIPS ether was not formed.

several electrophiles tried, only TIPS-OTf provided selectively the γ-product, as the single *Z* isomer **8**, E = SiR_3 = TIPS.[43] Recently, however, high γ-selectivity in the reaction of a metalated silyl alkyl ether with carbonyl electrophiles or alkyl halides was obtained when the TIPS ether was metalated at low temperature *and* the counterion was changed to Ba^{2+}.[304] Si migration was not observed under these conditions. The γ-products **8** were all exclusively *Z*. Without the transmetalation lower or even opposite selectivity was observed. Less bulky silyl groups resulted in lower selectivity.

The regioselectivity of the reaction of an epoxide with carbon nucleophiles can be influenced by a nearby OTIPS group. While free γ,δ-epoxy alcohols **10** (R = H) did not generally show good regioselectivity in reactions with $Li_2Cu(CN)R'_2$, the corresponding TIPS ethers **10** (R = TIPS) provided exclusively the ethers of 1,3-diols **11** (terminal attack, Scheme 4).[169,305]

Scheme 4[a]



[a] (a) (1) $Li_2Cu(CN)Me_2$, Me_2S, PBu_3; (2) H_2O.

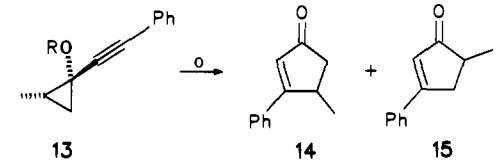
R	11	12
H	26%	58%
TIPS	45%[†]	0%

[†] Fifty-four percent of the starting material was recovered.

2-[[(Triisopropylsilyl)oxy]methyl]-3-alkyloxiranes are attacked by $Et_2AlC{\equiv}CCH_3$ at position 3 highly regioselectively (≥15:1); the behavior of other O-derivatives unfortunately was not studied.[306]

The $Co_2(CO)_8$ induced rearrangement of 1-(phenylethynyl)-2-methylcyclopropanol **13** (R = H) is not regioselective (Scheme 5), producing two methylphenylcyclopentenones **14** and **15** in equal amounts. Silyl groups of increasing bulk on the oxygen, however, cause increasing regioselectivity. The effect was tentatively explained in terms of a conformational bias in the starting materials.[307]

Scheme 5[a]



[a] (a) $Co_2(CO)_8$, DME, reflux.

R	14:15
H	50:50
TMS	70:30
TBDMS	91: 9
TIPS	93: 7

Chromium tricarbonyl complexes of phenol TIPS ethers such as **16** are easily metalated by BuLi to give, after treatment with an electrophile, mostly products of *meta* substitution, e.g. **17**, **21** (Scheme 6).[33,95,308] The reason for this unusual regioselectivity is only partially clear. The sterically crowded O-Si^{i}Pr$_3$ cannot preassociate with the alkyllithium, therefore not favoring *ortho* lithiation. On the contrary, by its bulk it precludes attack at this position; in this sense, the silyl ether provides lateral protection. The reason for *meta* activation is a matter of debate. Anyway, TIPS ether **22** allows a complete reversal of regioselectivity, compared to the corresponding Me ether **24**.[309] The TBDMS ether is less efficient.[308]

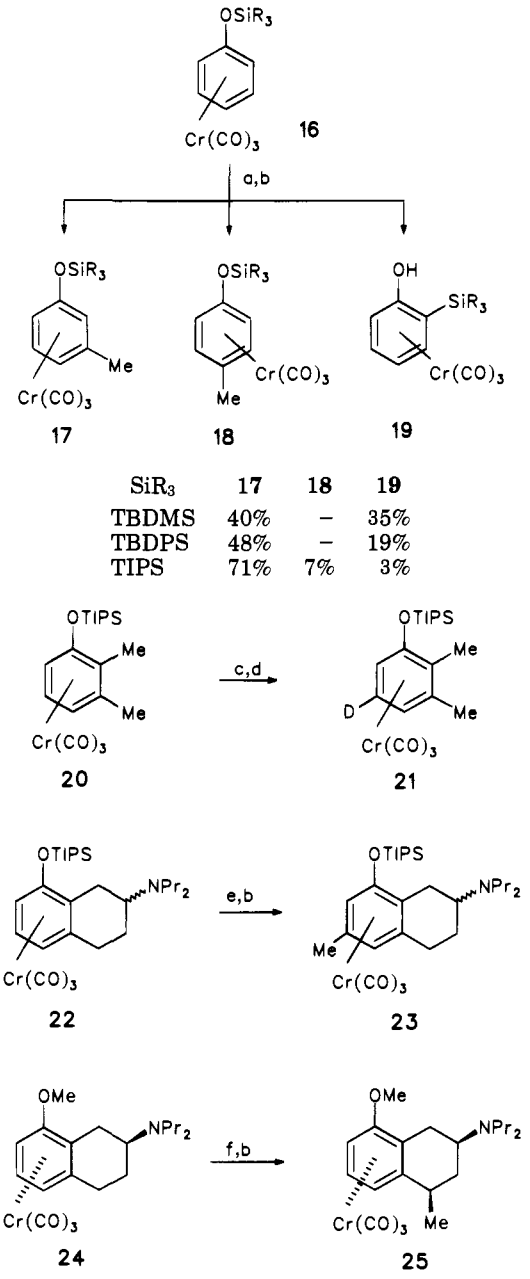
This chemistry was used for an elegant synthesis of phytoalexins Moracin M and C[279,310] as well as a tetrasubstituted arene.[311] Other electronic or steric factors, however, can overwhelm the *meta*-directing effect.[312]

In nucleophilic substitution in OTIPS arenes a similar effect is seen (Scheme 7). Intramolecular anionic cyclization of (ω-cyanoalkyl)arenes **26** can result in both spiranes and annulated systems. While TBDMS aryl ether **26** (SiR_3 = TBDMS) gave the spirane **27** exclusively in 72% yield, the corresponding TIPS ether **26** (SiR_3 = TIPS) under identical conditions cyclized to the linearly condensed ring system **28** in 62% yield.[313]

Regioselectivity could be induced in a Lewis acid promoted ring-enlargening rearrangement of 2,2-disubstituted 1-(silyloxy)cyclohexanecarboxaldehydes. From the TIPS ether **29** both regioisomers **30** and **31** can be obtained at will depending on the conditions (Scheme 8).[92] The corresponding TBDMS ether reacts less regioselectively.

Mikami found the carbonyl−ene reaction of methyl glyoxylate with bishomoallylic ethers **32** to be regi-

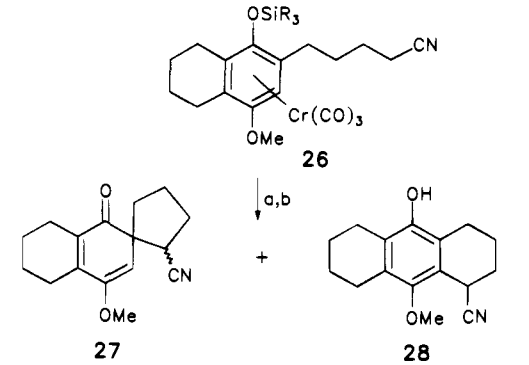
Scheme 6[a]



SiR_3	17	18	19
TBDMS	40%	–	35%
TBDPS	48%	–	19%
TIPS	71%	7%	3%

[a] (a) ^{t}BuLi. (b) MeI. (c) ^{n}BuLi. (d) CF_3CO_2D. (e) ^{n}BuLi, TMEDA, THF. (f) ^{t}BuOK, DMSO.

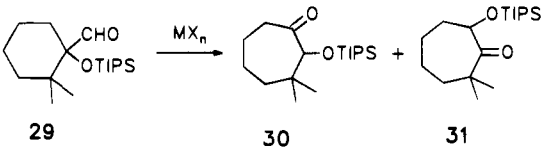
Scheme 7[a]



[a] (a)LDA/THF, −78 °C. (b) excess I_2, from −78 to 25 °C.

SiR_3	27	28
TBDMS	72%	–
TIPS	–	62%

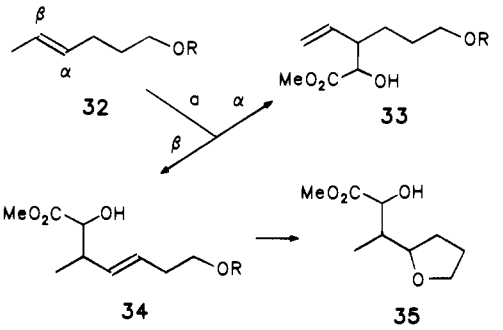
Scheme 8



MX_n	30 : 31		yield, %
$PhOAlCl_2$	1	30	70
$SnCl_4$	7	1	60
$FeCl_3$	26	1	82

oselective in the case of bulky silyl ethers in favor of the β-ene products **34** and **35** (Scheme 9), while alkyl

Scheme 9[a]



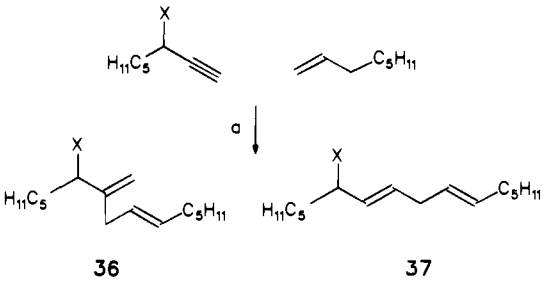
[a] (a) MeO_2C-CHO, $SnCl_4$, CH_2Cl_2, −78 °C.

R	33 : 34 : 35		
Bn	12	52	36
^{i}PrMe$_2$Si	2	18	80
^{t}HxMe$_2$Si	–	50	50
TIPS	–	67	33
TBDPS	1	81	18

ethers gave mixtures of α- and β-ene products **33**–**35**. TIPS and ^{t}HxMe$_2$Si were best in this respect. The reaction is also highly stereoselective, and a cyclic transition state model was proposed to account for these facts. Compound **35** is formed in a cationic cyclization of **34** with loss of the silyl group (Prins cyclization). The TIPS derivative underwent this secondary reaction to a lesser extent than the other trialkylsilyl derivatives. Only the TBDPS compound was even more reluctant.[314,315]

The ruthenium-catalyzed addition of an 1-alkene to an 1-alkyne normally is selective for C(2)-attack on the acetylene providing branched product **36** (Scheme 10). If the propargylic position, however,

Scheme 10[a]



[a] (a) 5% Cp(COD)RuCl, DMF/H_2O 3/1, 100 °C.

X	36 : 37	
H	5	1
OBn	1	2
OTBDMS	1	2.5
OTIPS	1	4

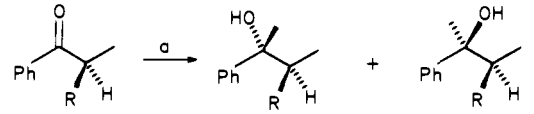
bears a R_3SiO substituent, predominantly C(1)-attack is found resulting in linear chain product **37**. TIPS is more efficient in this respect than TBDMS.[316]

A carbenoid (from an α-diazo ketone and Rh(II)) inserted regioselectively into one of two structurally similar CH bonds, one geminal to a MeO and the other geminal to an RO group. The carbenoid was attracted by the OH group (R = H, selectivity 1:1.4), while for R = TIPS the geminal CH was not easily accessible resulting in 6:1 selectivity.[317]

5. O-TIPS as Stereodirecting Group

Whenever an alcohol derivative is required which does not complex to a metal, the TIPS ether is first choice. This was impressively demonstrated in a series of papers by Eliel, where he studied the kinetics and stereochemistry (Cram's chelation control *vs* nonchelation) of the addition of organometallics to α- and β-alkoxy and siloxy ketones.[139,166,223,224,318] Thus Me_2Mg added to 1-(benzyloxy)acetone 140 times faster than to 1-[(triisopropylsilyl)oxy]acetone.[224] The rate constants and isomer ratios **39/40** found in the reaction of Me_2Mg with α-alkoxy- or α-silyloxy-substituted propiophenones **38** are given in Scheme 11.[224] The most reactive substrates are, remarkably, the most stereoselective.

Scheme 11[a]



38 **39** **40**

[a] (a) (1) Me_2Mg/THF; (2) H_2O.

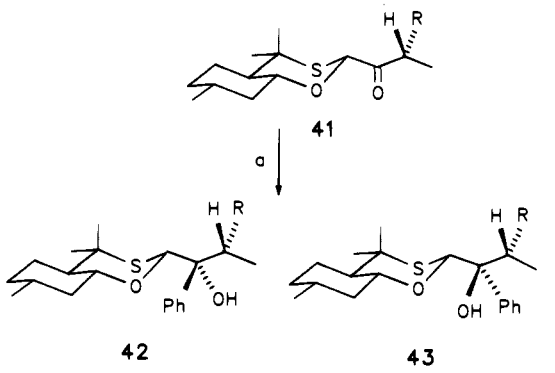
R	rel. rate	39	: 40
OMe	1000	>99	1
OTMS	100	99	1
OTES	7.9	96	4
OTBDMS	2.5	88	12
OTBDPS	0.82	63	37
OTIPS	0.45	42	58
H	0.54		

The conclusion drawn from this was that there are two independent reaction paths. The nonchelation one is slow and almost completely stereorandom (this is the only contributing pathway for R = H or OTIPS), the chelation one is fast and completely stereoselective, as for R = OMe. "The very large difference between the TMS and TIPS group is remarkable, with the former one impeding chelation very little and the latter preventing it totally." [224] As a consequence, the stereoselectivity of such a reaction sometimes can be completely reversed just by replacing OMe by OTIPS (e.g. **41** → **42** or **43**, Scheme 12).[319] Conversely, when in a reaction no difference was seen between the results for a OMe or OTIPS (or even Me) group in a particular position, it was concluded that this group is not involved in chelation.[99,139,320,321]

For β-alkoxy *vs* β-silyloxy there are generally only small or no effects.[322,323]

The noncomplexing behavior of OTIPS was used to advantage in a synthesis of frontalin.[76]

Scheme 12[a]



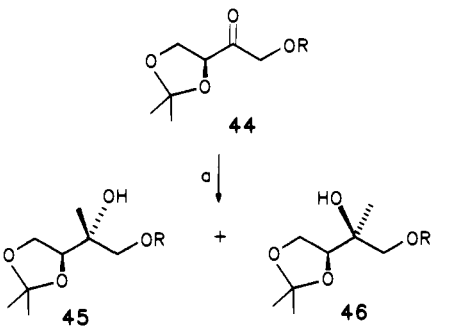
41 **42** **43**

[a] (a) (1) PhMgBr or PhLi; (2) H_2O.

R	42	: 43
OMe	0	100
OTIPS	100	0

Similar observations were made by Marco in the addition of organometallics to erythrulose derivatives (**44** → **45/46**, Scheme 13),[324] by Guanti in the addition

Scheme 13[a]



44 **45** **46**

[a] (a) (1) MeLi, Et_2O, −78 °C; (2) H_2O.

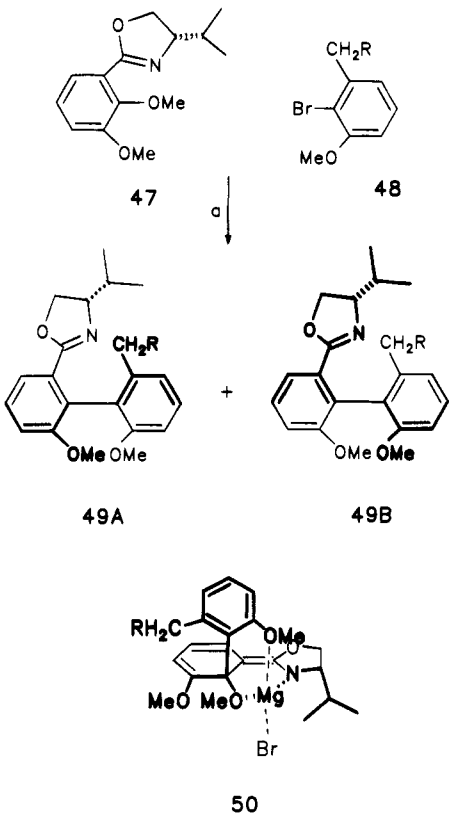
R	45	: 46	yield, %
H	50	50	53
TMS	50	50	65
TBDMS	63	37	85
TIPS	75	25	85
TBDPS	86	14	86

of allyl- or crotyltributyltin[151,325] to a β-alkoxy-β-silyloxy-disubstituted aldehyde and in the DIBAL-H reduction of similar ketones,[151] by Noyori in the binap/Ru catalyzed hydrogenation of alkoxy substituted β-keto esters,[326] and by Wender in the addition of an azide group to alkoxy- and silyloxy substituted β-keto esters.[207]

Two diastereomeric enantiopure biphenyls **49A** and **49B** can arise from coupling of a 2,6-disubstituted aryl Grignard reagent (from **48**, Scheme 14) to an enantiopure oxazolinylbenzene **47**. High selectivity for **49A** is achieved if R in **48** is unable to compete with the OMe group for chelating the Mg in the intermediate complex (R = H or OTIPS, OTBDMS).[327] If, on the other hand, the complexing abilities of OMe and CH_2R are comparable (R = OMe or OBn), then both products are obtained. These results were rationalized by postulating the intermediate **50** as a precursor for **49A**.

A TIPS-protected oxygen atom does not add to a iodonium or mercuronium intermediate.[74] However, in an aldol reaction using Sn(II) enolates, Paterson

Scheme 14[a]



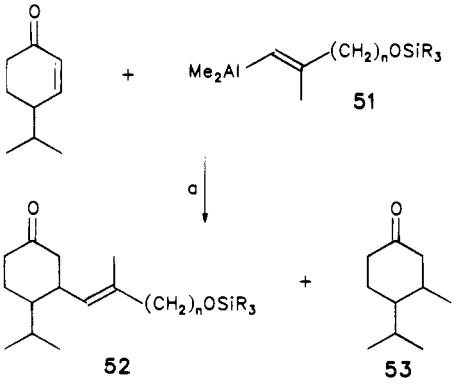
[a] (a) Mg, THF, heat.

R	49A	: 49B
H	90	10
OMe	40	60
OBn	42	58
OTBDMS	93	7
OTIPS	93	7

found some evidence that even OTIPS may complex to some extent.[328]

In the Cu(I)-catalyzed Michael addition of dimethylvinylalanes **51** to α,β-enones Lipshutz found that a TBDMS or TBDPS protected primary hydroxy function in the reagent completely suppresses the desired vinyl transfer, while a TIPS-protected one is compatible (→ **52** rather than **53**, Scheme 15).[329] It

Scheme 15[a]



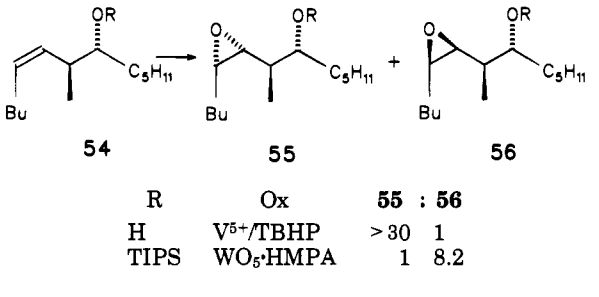
[a] (a) Catalyst CuCN.

SiR_3	n	52	53
TBDMS	2	7%	87%
TIPS	4	76%	10%

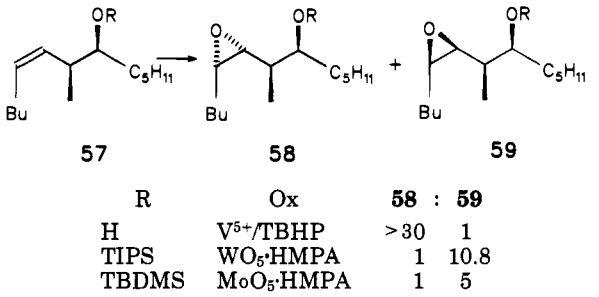
was suspected that the chelating/nonchelating behavior of these silyl ethers plays an important role. A Zr- and Zn-based version of the same reaction is compatible with both OTIPS and OTBDMS.[227]

In homoallylic alcohols Katsuki used TIPS etherification to redirect the stereochemistry of epoxidation (Scheme 16). Thus epoxidation of alcohol **54** (R = H) resulted in a >30:1 preference for "back-side attack" (in the zigzag projection shown, **55** over **56**) when V^{5+}/TBHP was used, thought to result from complexation of the reagent to the OH group. On the other hand, when complexation was prevented by using TIPS ether **54** (R = TIPS) and a reagent (WO_5·HMPA) less prone to complexation, then a 8.2:1 preference for "front attack" (**56** over **55**) was achieved.[168,169] Surprisingly, in substrate **57** (diastereomeric to **54**) again complexing conditions favored back-side attack (**58**), noncomplexing conditions favored front attack (**59**). No explanation was given. TBDMS was less efficient. The method was used in the synthesis of a rifamycin S intermediate.[170] See also refs 167 and 330.

Scheme 16



R	Ox	55 : 56
H	V^{5+}/TBHP	>30 1
TIPS	WO_5·HMPA	1 8.2

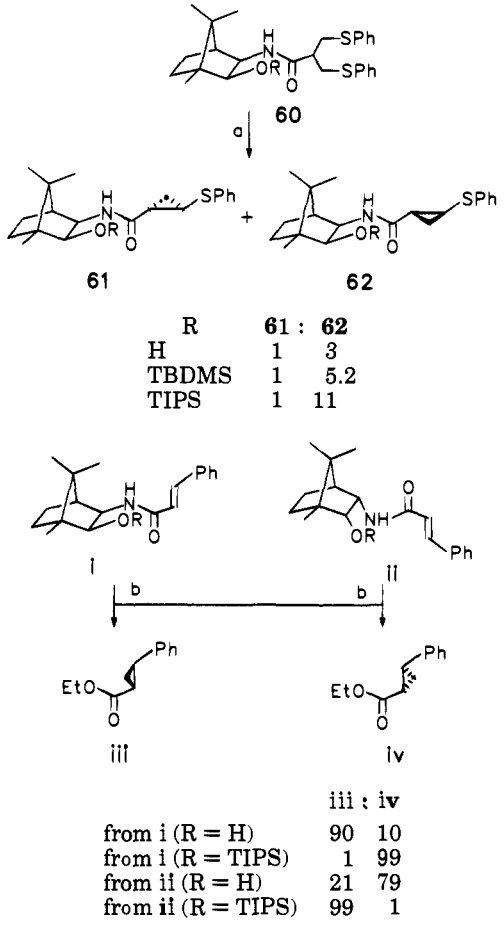


R	Ox	58 : 59
H	V^{5+}/TBHP	>30 1
TIPS	WO_5·HMPA	1 10.8
TBDMS	MoO_5·HMPA	1 5

Asymmetric derivatives of 2-alkenyl-1,3-propanediols were epoxidized by Guanti using *m*-CPBA or V^{5+}/TBHP, with the stereoselectivity moderately depending on the protective group. Bulky silyl groups such as TIPS or TBDPS gave particularly high selectivity (>95:5).[331] Attack of organocopper reagents at the epoxides obtained is likewise regioselective.[220]

Tanaka studied the stereochemistry of cyclopropane formation by PhSH elimination from 1,3-bis(phenylthio)propanes linked to a camphor-derived chiral auxiliary (**60**, Scheme 17).[332] When the OH function was free, moderate 1:3 stereoselectivity was observed (**61**:**62**), which could be enhanced to 1:11 for the TIPS ether. An explanation was not given. This is a complex situation, since one out of four diastereotopic protons can be removed by the base, each leading to a different product. The fact that only *trans* cyclopropanes are formed (in high yield) demonstrates that only two of these deprotonations actually occur (or that the Li derivatives are not

Scheme 17[a]



R	61 : 62	
H	1	3
TBDMS	1	5.2
TIPS	1	11

	iii : iv	
from i (R = H)	90	10
from i (R = TIPS)	1	99
from ii (R = H)	21	79
from ii (R = TIPS)	99	1

[a] (a) Excess ^{n}BuLi,THF. (b) (1) Et_2Zn/CH_2I_2; (2) $(^{t}BuO_2C)_2O$, Et_3N, DMAP; (3) EtOH/EtONa.

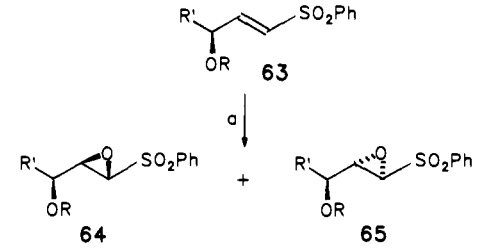
configurationally stable). Compound **62** results from removal of the *pro-S* proton in the *pro-S* CH_2SPh group in **60**, while **61** stems from removal of the *pro-S* proton in the *pro-R* CH_2SPh group. Even if the amide conformation in **60** (*s-trans*) and effective shielding of the molecule's front hemisphere by TIPS are taken for granted, the result would certainly not have been predicted.

The same chiral auxiliary allowed stereoselective cyclopropanation (Simmons–Smith) of cinnamic acid. An impressive selectivity reversal depending on the presence or absence of the TIPS group was observed in the *exo,exo*-amide i (Scheme 17 bottom).[333] Gratifyingly, use of the *endo,endo* diastereomer ii resulted in selectivity reversal compared to i.

A similar effect on the stereoselectivity of a photochemical cyclization was seen in a synthesis of a [7]helicene.[334,335]

The stereochemistry of nucleophilic attack of peroxide to γ-oxygenated α,β-unsaturated sulfones **63** resulting in epoxidation was studied by Jackson (Scheme 18).[336] In the isopropyl series (**63**, R′ = ^{i}Pr), the 25:1 preference for *syn* attack (**64**:**65**) found in the free alcohol could be reversed to a 1:40 selectivity for *anti* attack in the TIPS ether. TBDPS was less efficient. In the methyl series (**63**, R′ = Me), the free alcohol likewise gave preferentially *syn* attack (3:1), but now TIPS enhanced this *syn* selectivity to 10:1. The conformational uncertainties in these acyclic

Scheme 18[a]



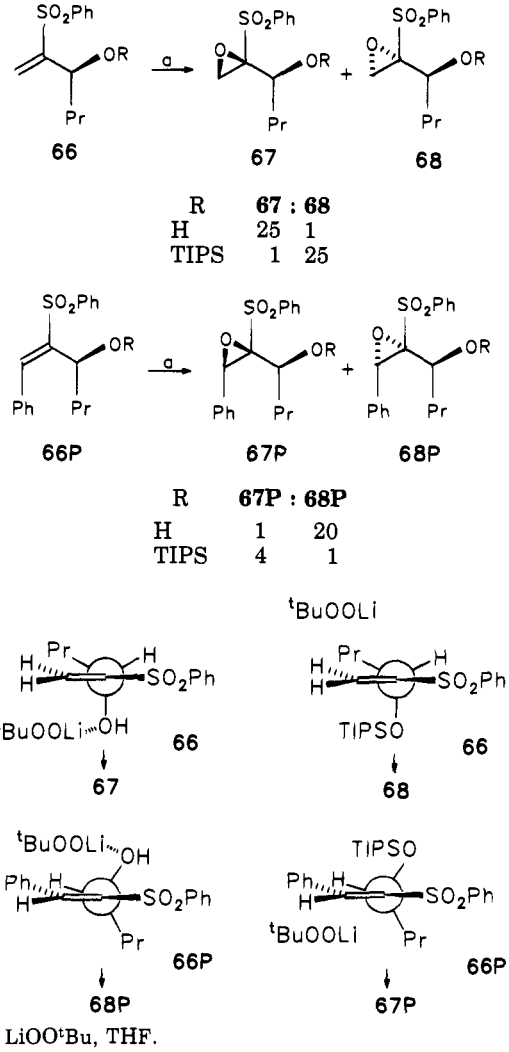
[a] (a) LiOO^{t}Bu,THF.

	R′ = ^{i}Pr		R′ = Me	
R	64 :	65	64 :	65
H	25	1	3	1
TBDPS	1	4	4	1
TPS	1	25	3	1
MEM	1	30	1	1.5
TIPS	1	40	10	1

systems precluded a coherent rationalization of all these results.

Similar reversals of stereoselectivity caused by OTIPS *vs* OH were observed in the epoxidation of acyclic β′-oxygenated α,β-unsaturated sulfones, e.g. **66** (Scheme 19).[337] In a sulfone bearing an additional

Scheme 19[a]



R	67 :	68
H	25	1
TIPS	1	25

R	67P :	68P
H	1	20
TIPS	4	1

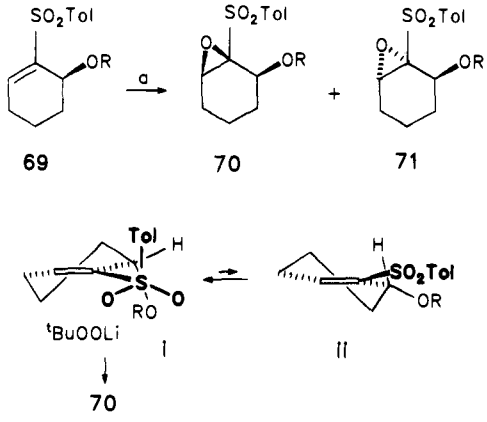
[a] (a) LiOO^{t}Bu, THF.

E-β-Ph group, **66P**, the stereoselectivities are reversed compared to **66**. These results were rational-

ized as shown in Scheme 19, bottom, where the additional Ph group in **66P** tolerates none but the smallest substituent (H) on the stereogenic center in its vicinity.

Cyclic β'-oxygenated α,β-unsaturated sulfones **69** were epoxidized under similar conditions by Carreno and Ruano (Scheme 20).[338] The results are similar

Scheme 20[a]



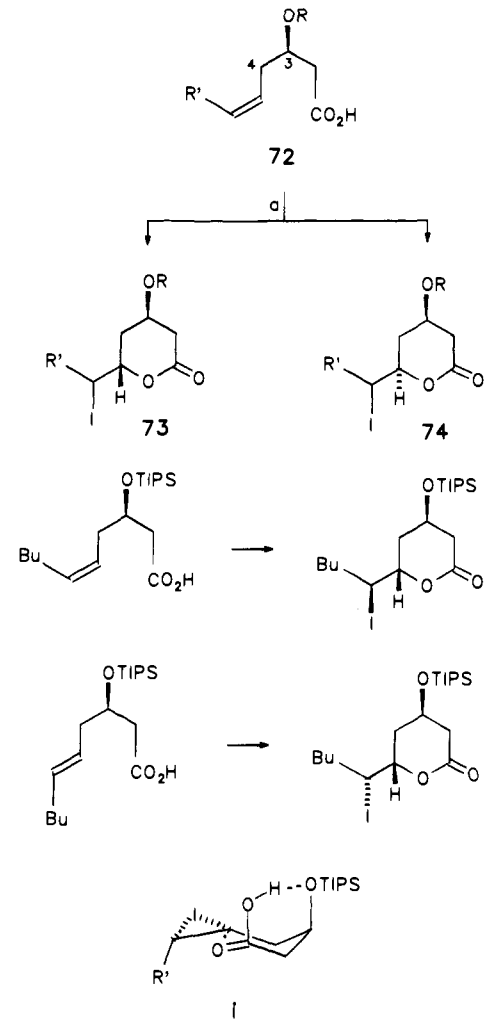
[a] (a) LiOO^{t}Bu/THF.

R	70 : 71	
H	100	0
TIPS	63	37

to those for **66** above, the free alcohol gives the *syn* epoxide **70**, the TIPS ether displaces the outcome somewhat toward *anti* epoxide **71**. Since **69** is cyclic, there is no problem with the gross conformation, and the results are easily explained in terms of precomplexation of the reagent (for R = H) and steric access control (for R = TIPS), respectively, with the additional constraint that **71** cannot be the major product even for R = TIPS, since the side of the ring opposite to OTIPS is occupied by the bulky tolyl group. The authors assume that **69** adopts the most favorable half-chair conformation i (shown in Scheme 20, bottom), which on attack from below (→ **70**) will give a chairlike transition state, while formation of **71** (attack from above) requires a twistlike transition state. This difference may be an additional factor favoring **70**.

The stereoselectivity of the iodolactonization of 3-oxygenated 5-enoic acids was studied as a key step in the synthesis of mevinic acids by Knight (Scheme 21). While the free alcohol **72** (R = R'= H) provided the *trans*-(iodomethyl)-δ-lactone **73** (R = R'= H) in modest stereoselectivity and yield, the TIPS ethers **72** (R = TIPS, R' = H or ^{n}Bu) gave products **73** (R = TIPS, R'= H or ^{n}Bu) both more stereoselectively and in higher yield. TBDMS and TBDPS were less stereodirecting than TIPS.[125,171,172,174] The stereochemistry of the double bond was found to influence the stereochemistry of the exocyclic carbon only (Scheme 21, middle).[171] With a methyl group in place of the OR, in contrast, *cis*-disubstituted valerolactones are preferentially formed. The stereochemical results could not be convincingly explained. A tentative rationalization postulates H-bonding between the carboxyl OH and the TIPS-O (in an axial position on a chair transition state, i in Scheme 21, bottom), which seems rather speculative when compared to the results cited earlier in this section.

Scheme 21[a]



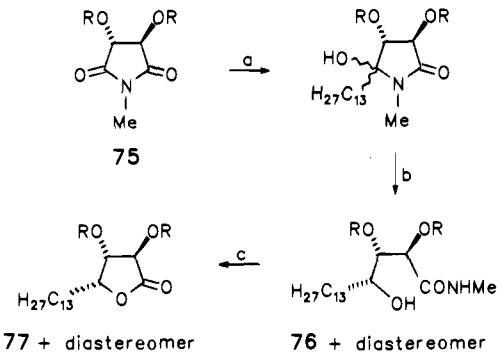
[a] (a) I_2, $NaHCO_3$, MeCN, 0 °C.

R'	R	73	: 74	yield, %
H	H	3	1	23
H	TBDMS	3	1	84
H	TBDPS	4	1	87
H	TIPS	5.5	1	81
Bu	TIPS	10.5	1	93

The stereoselectivity of the iodocarbonatation of homoallylic alcohols bearing an additional TIPSO group was studied.[306] The silyl group was not varied, so its influence is not known.

The stereochemistry of addition of Grignard reagents to C=O under the directing influence of two conflicting silyl ether groups was studied by Yoda and Takabe (Scheme 22). Addition of n-$C_{13}H_{27}MgBr$ to *N*-methyl-2,3-di-*O*-TIPS-tartrimide **75** (R = TIPS) followed by $NaBH_4$ reduction resulted in >99:1 diastereomer selectivity, 74% yield, whereas the TBDMS or IPDMS derivatives each gave both lower stereoselectivity and yield (with n-$C_8H_{17}MgBr$, however, the TIPS ether reacted less stereoselectively than the TBDMS ether). The products **76** were converted into optically active γ-lactones **77** and butenolides.[274,275] The absolute configuration of the newly formed stereocenter in the latter was determined to be *R* in the major product **77**, but the authors did not specify the stereochemistry of the initial step, probably since they are not completely sure of the stereochemical course of the reduction

Scheme 22[a]



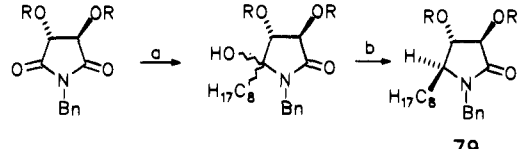
77 + diastereomer 76 + diastereomer

[a] (a) $^{n}C_{13}H_{27}MgBr$. (b) $NaBH_4$. (c) HCl, dioxane.

R	**76** : diastereomer	
IPDMS	92	8
TBDMS	93	7
TIPS	>99	1

step. The initial Grignard addition products **78** can be deoxygenated (Et_3SiH, $BF_3{\cdot}Et_2O$, −78 °C) to provide stereoselectively 4-substituted butyrolactams **79** of 4*S*-configuration (Scheme 23).[339]

Scheme 23[a]



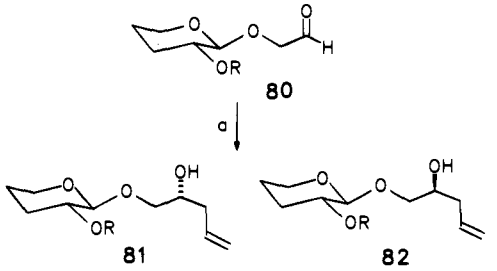
78 **79** + diastereomer

[a] (a) $C_8H_{17}MgBr$. (b) Et_3SiH, $BF_3{\cdot}Et_2O$, −78 °C.

R	**79**	: diastereomer	overall yield, %
TBDMS	95.5	4.5	75
TIPS	97.2	2.8	98

Chelation or nonchelation by a remote O atom was shown to be decisive in the $MgBr_2{\cdot}OEt_2$-promoted addition of allyltri-*n*-butylstannane to glycosyl-substituted 2-hydroxyacetaldehydes **80** (three out of a total of four oxygen atoms present themselves as points of complexation, Scheme 24). Benzylation or

Scheme 24[a]



80 **81** **82**

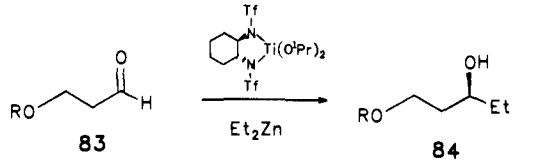
[a] (a) Allyl-$SnBu_3$, $MgBr_2{\cdot}OEt_2$, from −55 °C to room temperature.

R	**81**	: **82**
Bn	97.6	2.4
TIPS	7.2	92.8

triisopropylsilylation of the 2-OH function in the sugarlike moiety resulted in completely reversed stereoselectivity, **81**:**82** = 97.6:2.4 for *O*-benzyl, 7.2:92.8 for *O*-TIPS.[119] TIPS is better in this respect than TBDPS. See also the reaction of allyltri-*n*-butylstannane with β-(silyloxy)aldehydes in the presence of $MgBr_2$.[340]

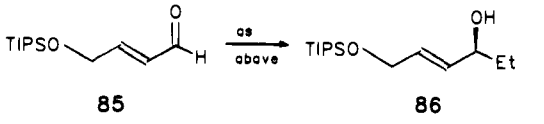
Similarly, addition of Et_2Zn to O-protected β-hydroxyaldehydes **83** in the presence of an enantiopure chiral Ti catalyst was found by Knochel to proceed highly stereoselectively, better with R = TIPS than with R = TBDMS or Bn (Scheme 25).[149] Alkylation

Scheme 25



83 **84**

R	yield, %	ee, %
Bn	88	83
TBDMS	62	85
TIPS	92	93



85 **86**

yield 68%, ee 93%

of the γ-triisopropylsilyloxy α,β-unsaturated aldehyde **85** likewise exhibits high stereoselectivity.[193,216]

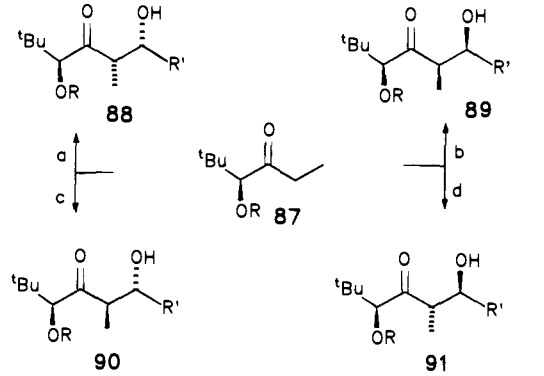
Similar results were obtained for α-silyloxy acetaldehydes where addition of (functionalized) dialkylzincs in the presence of the same enantiopure catalyst proceeds highly stereoselectively for the TIPS- or TBDPS-protected compound.[148]

Addition of Et_2Zn to a chiral α-OTIPS- or α-OTBDPS-aldehyde in the presence of an enantiopure amino alcohol catalyst likewise is highly stereoselective, the configuration of the new stereocenter is controlled by the catalyst, not by the existing chirality.[341]

Stereoselectivity in the Simmons–Smith cyclopropanation of glycosides of allyl alcohols and in epoxidation of the same substrates by *m*-CPBA seems to require a free 2-OH group, since both the 2-benzyl and the 2-TIPS ether resulted in low diastereoselectivity.[203,342,343]

An interesting case of stereochemistry influenced by a silyl ether was found by Heathcock (Scheme 26).[101] The stereochemistry of the newly formed CC

Scheme 26[a]



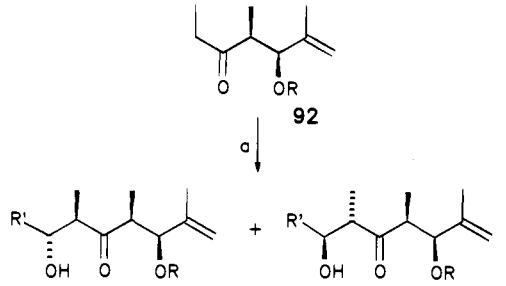
88 **89** **87** **90** **91**

[a] (a) (R = TMS) (1) LDA/THF; (2) TMEDA; (3) R'CHO; (4) H_2O. (b) (R = TMS) (1) $^{i}Pr_2NEt$, Bu_2BOTf; (2) R'CHO; (3) H_2O; (4) H_2O_2/MeOH. (c) (R = TMS) (1) BrMgTMP; (2) R'CHO; (3) H_2O. (d) (R = TBDMS) (1) BrMgTMP, $(^{i}PrO)_3TiCl$, HMPA/dioxane/THF, sonication; (2) R'CHO; (3) H_2O.

bond in aldol reactions of enolates formed from enantiopure α'-(silyloxy) ketones **87** could be directed to one of the four possible substitution patterns **88**–**91** at will depending on the conditions (*Z- vs E*-enolate) and on the use of a chelating (TMS) or nonchelating (TBDMS) silyl ether. Although the ketone enolate of the TBDMS ether is formed without difficulty, the corresponding TIPS ether is ineffective. Presumably, α'-OTIPS sterically prevents removal of an α-proton.

Such a prohibitive protection was not found for β'-(silyloxy) ketones **92** by Paterson. The TIPS group is one bond farther apart from the reaction center here (Scheme 27). Nevertheless it exhibits a small

Scheme 27[a]



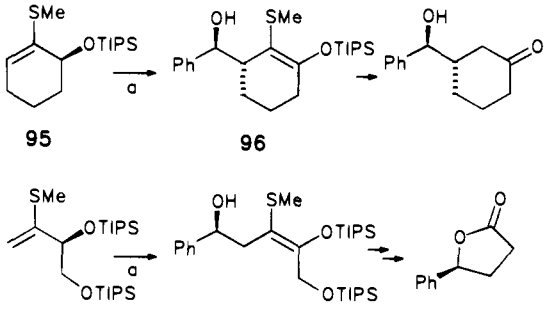
[a] (a) (1) $^{c}Hx_2BCl$; (2) R'-CHO (R'- = $H_2C{=}CMe{-}$).

R	93 : 94	
TBDMS	82	18
TIPS	87	13

effect on the stereoselectivity (when compared to the TBDMS group).[344,345] Experimental data for corresponding TMS or benzyl ethers are unfortunately lacking.

Thiosubstituted silyl allyl ethers (TBDMS or TIPS, e.g. **95**) are useful reagents for the stereocontrolled synthesis of γ-hydroxyketones from aldehydes by an ene reaction under chirality transfer (via **96**, the only stereoisomer formed, 94%, Scheme 28).[235] In acyclic

Scheme 28[a]

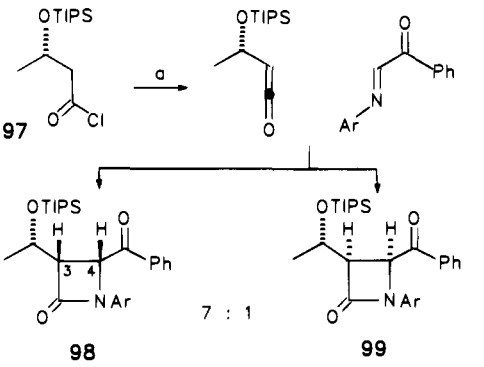


[a] (a) PhCHO, Me_2AlCl, toluene.

examples this reaction gave high ee's in the presence of an additional nearby OTIPS group only (Scheme 28, bottom).[346]

OTIPS as a stereodirecting group made possible two valuable syntheses of β-lactams: The first is a ketene–imine cycloaddition (Staudinger reaction, Scheme 29). While such reactions often lead to mixtures of *cis*- and *trans*-β-lactams, the TIPS ether **97** of (*S*)-3-hydroxybutyric acid chloride when treated with $^{i}Pr_2EtN$ in DMF at −40 to −20 °C in the

Scheme 29[a]

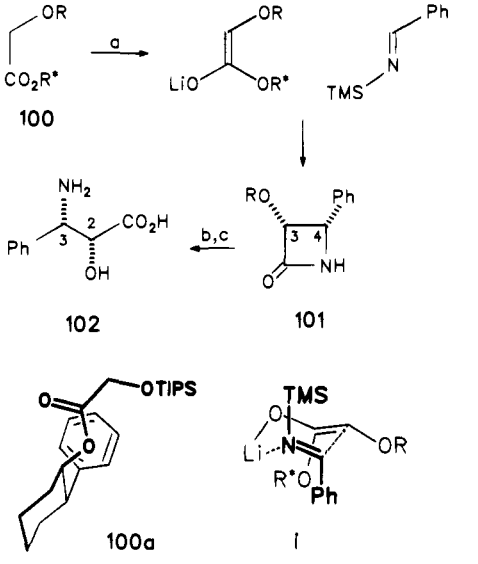


[a] (a) $^{i}Pr_2NEt$, DMF.

presence of an α-ketoaldehyde *N*-arylimine affords two 3,4-*cis*-disubstituted azetidinones **98** and **99** exclusively in 90% yield and a ratio of 7:1. The major diastereomer has at position 3 the correct stereochemistry required for thienamycin, it was converted in a few routine steps into a known versatile carbapenem intermediate.[347] Other less bulky groups in place of TIPS resulted in lower stereoselectivity. The kinetics of the cycloaddition was studied by low-temperature FT-IR, it was concluded that a ketene is really involved, rather than direct acylation of the imine by the acid chloride.[348]

The second synthesis, reported by Ojima and Georg, employs a highly stereoselective cyclocondensation of the lithium enolate of a chiral ester and an imine (Scheme 30). This asymmetric synthesis using

Scheme 30[a]



[a] (a) LDA, THF. (b) $^{n}Bu_4NF$, THF. (c) 6 N HCl, reflux.

R	R*	yield, %	ee, %
TBDMS	(−)-*trans*-2-phenyl-1-cyclohexyl	90	76
TIPS	(−)-*trans*-2-phenyl-1-cyclohexyl	85	96

a chiral auxiliary provides, in consistently high yield and ee, access to the C(13) side chain of taxol and analogs as enantiopure compounds from achiral commodity chemicals, when the α-(triisopropylsilyl)-oxy acetate of (−)-*trans*-2-phenyl-1-cyclohexanol (**100a**) is used.[160,349] When TBDMS was used instead of TIPS, for several auxiliary groups R* either the yield or the ee was found to be low. To rationalize these

results, the cyclic transition state assembly i was postulated which results from attack of the imine to the less hindered (front) face of the enolate depicted (*E* enolate in the authors' convention, see also Scheme 67). The first formed *N*-lithiated β-amino ester then cyclizes to afford β-lactam **101** and recovered auxiliary alcohol.

It was found recently that a camphor-derived auxiliary can be used. In this case also, the TIPS ether gives higher ee than the TBDMS or TES analogs.[350]

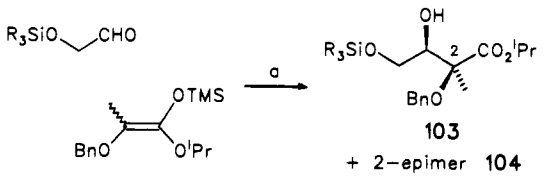
For an alternative β-lactam synthesis from a Ti ester enolate and an imine bearing a chiral auxiliary see ref 351.

The almost enantiopure (3*R*,4*S*)-azetidinone **101** is the cyclic form of the β-amino acid (2*R*,3*S*)-3-phenylisoserine **102**, the taxol side-chain acid. The open-chain amino acid can easily be esterified with the taxol core 13-alcohol, or alternatively, the β-lactam itself can be coupled to the same alcohol, but only after replacement of TIPS by a less demanding group, e.g. ethoxyethyl, TES, TBDMS (TIPS screens the neighboring carbonyl C atom).[352-354] This chemistry was used to prepare several analogs of the side chain, as well as other isoserines (e.g. norstatine) which may be useful as building blocks for inhibitors for enzymes such as renin or HIV-I protease.[159]

Just like an alcohol, a primary or secondary amine can attack the azetidinone **101**, leading under β-lactam opening to a dipeptide. In this case even the neighboring OTIPS is allowed.[355]

Mukaiyama has shown that α-[(triisopropylsilyl)-oxy]acetaldehyde is an ideal substrate for the Sn(II)-promoted enantioselective aldol addition with ketene acetals under the influence of a chiral enantiopure diamine (Scheme 31). Superior diastereoselectivity

Scheme 31[a]



[a] (a) $Sn(OTf)_2$, $^nBu_2Sn(OAc)_2$, (*S*)-1-methyl-2-[(1-naphthylamino)methyl]pyrrolidine, CH_2Cl_2, −78 °C.

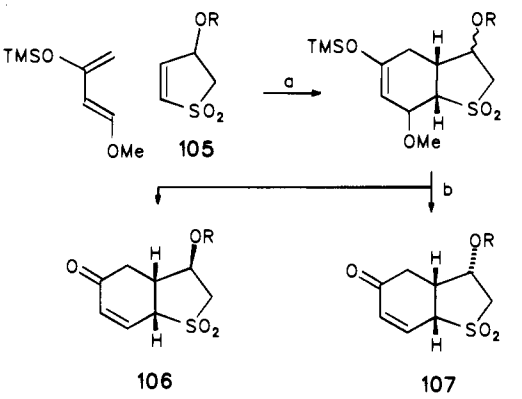
R_3Si	**103**/**104**	ee, % (**103**)
TBDMS	72/28	66
TBDPS	81/19	19
TIPS	91/9	90

(**103**:**104**) and enantioselectivity were achieved compared to the corresponding TBDMS or TBDPS ethers.[247]

Enantioselective epoxidation of alkenes and dienes catalyzed by an enantiopure (salen)Mn(III) complex results in higher ee's when the catalyst bears TIPS-oxy rather than ^{t}Bu groups in positions 5,5′. This agrees with earlier evidence that the stereoselectivity of this reaction profits from both bulky and electron-donating substituents.[356-359]

A case of stereoselectivity influenced by the mere steric effect of TIPS is the following: TIPS-oxy- and TBDPS-oxy-substituted dihydrothiophene-1,1-dioxides **105** as well as the corresponding benzyl ether were used as dienophiles in Diels–Alder reactions with Danishefsky's diene (Scheme 32) to provide

Scheme 32[a]



[a] (a) Heat. (b) Py·HOTs, heat.

R	**106** : **107**
Bn	1.2 1
TIPS	2.5 1

diastereomeric adducts **106**/**107** without any regioisomers.[32,187] The reaction is slightly more stereoselective for the TIPS than for the benzyl ether.

Similarly, the C=C bond in a 2-methylenebicyclo-[3.3.0]octan-1α-ol was hydrogenated over Pd to a 1:1 mixture of 2α- and 2β-methyl products, while the corresponding tertiary TIPS ether afforded the 2α-methyl product exclusively.[111]

If a reaction is more sensitive to electronic than steric effects of a silyl group, then triarylsilyl may be a better directing group than trialkylsilyl. An example is the Lewis acid promoted rearrangement of epoxy alcohols (or silyl ethers) to β-hydroxy (or silyloxy) carbonyl compounds studied by Yamamoto.[240,242]

6. Miscellaneous Uses of TIPS Ethers

Being large and apolar, the TIPS group is hydrophobic. This is very useful for physicochemical measurements of nucleosides, where derivatization of ribose and deoxyribose as TIPS ethers greatly enhances solubility in organic solvents, thus allowing molecular recognition phenomena to be studied by various physical methods. Thus, 2′-deoxy-3′,5′-bis-*O*-TIPS-cytidine and -guanosine are soluble in $CDCl_3$ at 20 °C in 0.5 M concentration.[360] The hydrogen-bond interaction G–C was studied by calorimetry,[361] ^{1}H-NMR,[299,361-363] and IR/Raman spectroscopy[360,364] on these TIPS derivatives, free of interfering deoxyribose hydroxyls. The transport of nucleosides and analogs through membranes enhanced by complementary base carriers was studied,[108] as was the recognition between guanosine and synthetic receptors.[300] The interaction between triisopropylsilylated nucleosides and porphyrins was studied by UV spectroscopy.[365]

The enhanced solubility of TIPS derivatives facilitated the synthesis of a [7]helicene[334,335] and made possible boronation of nucleosides by a boron exchange reaction in THF.[190] Boronated nucleosides are cytotoxic,[191,192] and seem promising for ^{10}B neutron capture cancer therapy.[190]

An $OSiR_3$ group can heavily influence a conformational equilibrium, see section II, ref 19. Another

such case, likewise not well understood, is that of a substituted benzothiazepinone (Diltiazem) measured recently.[366] While in this case the very bulky silyloxy groups such as TIPS-oxy and TBDPS-oxy prefer an equatorial position (to the same extent as does a methoxy), the slightly smaller TBDMS-oxy or the TMS-oxy group uniquely favor that conformer in which they are axial. A tentative rationalization (Si S attraction) was not backed by the experiments.

TIPS-oxy was used as a "stopper" group at both ends of a rotaxane axis.[230, 367-369]

In an attempt at understanding the high stereoselectivity of the catalytic OsO_4 Sharpless dihydroxylation using "dimeric" dihydroquinidine catalysts, Corey replaced the natural MeO group on such a catalyst's quinoline part by TIPSO.[85] The enantioselectivity (96% ee in the dihydroxylation of styrene with the OMe catalyst) dropped to 50% ee. This can be interpreted as a mechanical blocking of the styrene's access to the binding cleft by bulky TIPS-oxy.

The electrocyclic ring opening of ring B in the photochemical provitamin D_3 → previtamin D_3 conversion was found to be retarded by a bulky silyl group such as TIPS on a 1α-hydroxy group.[370] The effect was rationalized with the silyl group severely interfering with the C/D ring system in a tetraradicaloid transition state.

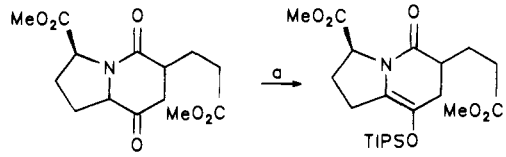
B. TIPS Enol Ethers

1. Formation

Aldehydes and ketones do not react with TIPS-Cl.[8] However, potassium ketone enolates (from the ketone by treatment with $KN(TMS)_2$[371]) or Li enolates (LDA[113,372]) provide the TIPS enol ethers. These are stable compounds that survive, e.g. an acidic aqueous workup and chromatography on silica.

Aldehydes and ketones react with TIPS-OTf in the presence of Et_3N (or DBU/DMAP[373]) in C_6H_6 to TIPS enol ethers.[8,374] The example in Scheme 33 (**108** → **109**) demonstrates the chemoselectivity of the method as well as an interesting regioselectivity.[375] The corresponding homologous 6-6-membered ring system, however, did not react under identical conditions, while with TBDMS-OTf it produced the opposite regioisomer along with an unexpected cyclized product.[376]

Scheme 33[a]

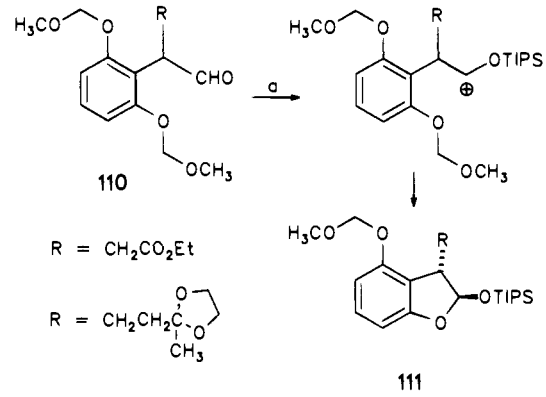


108 109

[a] (a) TIPS-OTf, NEt_3, C_6H_6.

Under these conditions the reaction may not involve an enolate, rather it may proceed via an addition-elimination sequence as indicated in **110** → **111** (Scheme 34), where an appropriately placed oxygen function in the molecule intervenes and induces a reaction path leading to a TIPS acetal.[180,377]

Scheme 34[a]



[a] (a) TIPS-OTf, NEt_3, THF, 0 °C.

Di-*tert*-butylpyridine in $CHCl_3$ was used as the base in TIPS enol ether formation,[273] and other solvents, such as ether or CH_2Cl_2, also work, leading to varying *E*/*Z* ratios.[378] Preformed Li enolates in THF[379,380] or K enolates in DME[381] likewise give TIPS enol ethers. Similarly, α,β-enones give TIPSO-dienes,[382-384] the ratio of regioisomers of which is solvent/base dependent.[384]

The primary product of a Michael addition to an α,β-enone can be trapped by TIPS-OTf resulting in a TIPS enol ether.[385]

The TIPS enol ether of a 1,3-diketone was prepared from the corresponding enol acetate[386] or enol pivalate.[373,387]

TIPS enol ethers of simple ketones were prepared regioselectively by hydrosilylation of α,β-enones using TIPS-H and a special Pt catalyst.[388]

A cyclic TIPS enol ether was prepared by Birch reduction of a TIPS aryl ether.[283]

A TIPS enol ether can be prepared by C=C bond formation from a TIPS ester and a reagent made from a 1,1-dibromoalkane, Zn, $TiCl_4$, and TMEDA in THF.[389] The reaction gives a better yield than the corresponding reaction with the TMS or TBDMS ester, the bulkiness of the TIPS group is reflected in that the selectivity for *Z* (*vs E*) enol ether formation known from alkyl or TMS enol ethers is lowered in case of the TIPS enol ether.

2. Inertness

Generally, TIPS enol ethers are inert under laboratory conditions. Thus a series of oxindoles exhibiting "hydrolytic lability" was routinely converted to the TIPS enol ethers for characterization.[390] A TIPS enol ether was used as a protected form of the ketone.[380]

TIPS enol ethers are not changed under the influence of DDQ,[375,391] DIBAL-H,[91,380,383] LAH,[30,392] $NaBH_4$,[30,391] Na/NH_3(liq),[392,393] Li/NH_3/EtOH,[283] LiDBB,[392] NaH,[371,374] LDA,[374,378] MeLi,[91] $TMSCH_2Li$ (by which TBDMS analogs are attacked),[394] NaSPh,[371] a Li acetylide,[30] several Lewis acids,[372] $AlCl_3$, −78 °C,[113] $TiCl_4$ at −20 °C,[236] $EtAlCl_2$,[112] $MeAlCl_2$,[236] Et_2AlCl,[112,236] Me_2AlCl,[395,396] Me_3Al,[112,392] and 0.01 equiv HOAc/3N $LiClO_4$ in ether.[397] Very electron rich TIPS enol ethers were, however, partially cleaved on treatment with some of these Lewis acids (room temperature, 1 h).[398]

TIPS enol ethers are inert against $Pd(OAc)_2$.[251-255]

PhIO/TMS-N_3 does not affect a TIPS enol ether grouping but effects unprecedented β-azidonation (see below).[396]

The TIPS enol ether of a 1,3-diketone survived treatment with MeMgBr or Me_2CuLi.[399]

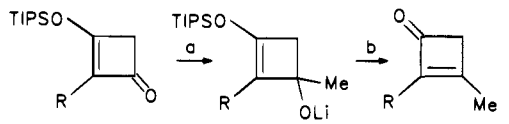
3. Desilylation

TIPS enol ethers can be cleaved to carbonyl compounds by mild acidic hydrolysis[30] (CF_3CO_2H, CH_2Cl_2, 5−10 min,[398] aqueous 1 M HCl,[234] HOAc/H_2O, 0 °C, 5 h[380]) or by treatment with HCl in EtOH/H_2O at 80 °C.[374,375] A TIPS enol ether which could not be cleaved by acid (under conditions that did cleave the corresponding TBDMS enol ether) was deprotected by CsF.[400] PCC in CH_2Cl_2 cleaves a TIPS enol ether to a ketone within 3 h at room temperature.[43] A β-acylamino TIPS enol ether was cleaved to the ketone on treatment with $TiCl_4$, Me_2AlCl, or BF_3·OEt_2.[392]

The reagent usually employed is $^nBu_4NF$ in THF at room temperature.[371] $^nBu_4NF$ in THF/HOAc at −78 °C for 30 min cleaved a TIPS enol ether to the ketone in the presence of a primary TIPS ether.[254] A cyclic, furanoid TIPS enol ether was cleaved to the ketone by iodide ion in DMF, this reaction did not work with a pyranoid TBDMS enol ether.[253]

The TIPS group is further often lost with regeneration of a carbonyl function, if a positive charge builds up on the former carbonyl C atom. This is generally the case when a TIPS enol ether is used as terminating group in a cationic cyclization, see below. Another example is given in Scheme 35.[91] (For comparison, TMS enol ethers are cleaved to the enolate by MeLi.)

Scheme 35[a]



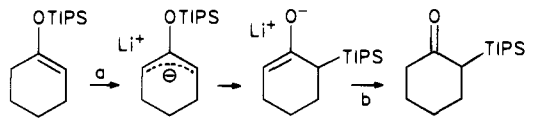
[a] (a) MeLi. (b) H_3O^+.

4. Reactions

For a general survey of silyl enol ether chemistry see the references.[401−403]

TIPS enol ethers when treated with $^nBuLi/KO^tBu$ in hexane rearrange to α-TIPS ketones by anionic 1,3 Si migration (e.g. **112** → **113**, Scheme 36).[379]

Scheme 36[a]



112 113

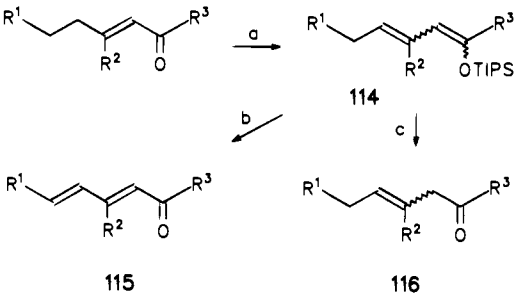
[a] (a) ^nBuLi, ^tBuOK, hexane, room temperature. (b) H_3O^+.

The C=C bond of a TIPS enol ether is as expected cleaved by O_3 to give a TIPS ester and a carbonyl component.[404]

An aldehyde was stereoselectively α-hydroxylated via Sharpless dihydroxylation of its silyl enol ethers.[373] The TIPS derivative provided higher ee (94%) than the TBDMS analog (78%).

A TIPS dienol ether, **114**, made from an α,β-enone, can be oxidized by $Pd(OAc)_2$ to the α,β;γ,δ-dienone **115** (Scheme 37).[382] Hydrolysis of **114** results in deconjugation (**116**).

Scheme 37[a]

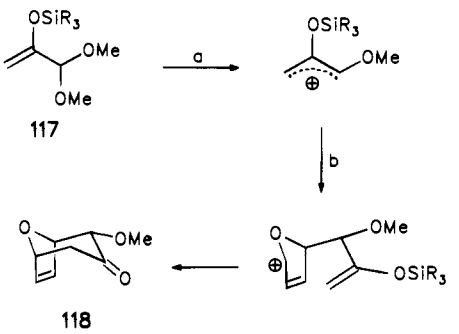


[a] (a) TIPS-OTf, Et_3N, CH_2Cl_2. (b) $Pd(OAc)_2$, K_2CO_3. (c) H_3O^+.

TIPS enol ethers are often used in C−C bond-forming reactions, especially in cyclizations.

Thus, silyl enol ethers of 1,1-dimethoxyacetone (**117**) were reacted with furans in the presence of a Lewis acid, to provide cycloaddition resulting in the 8-oxabicyclo[3.2.1]oct-6-ene system (**118**, Scheme 38).[372]

Scheme 38[a]



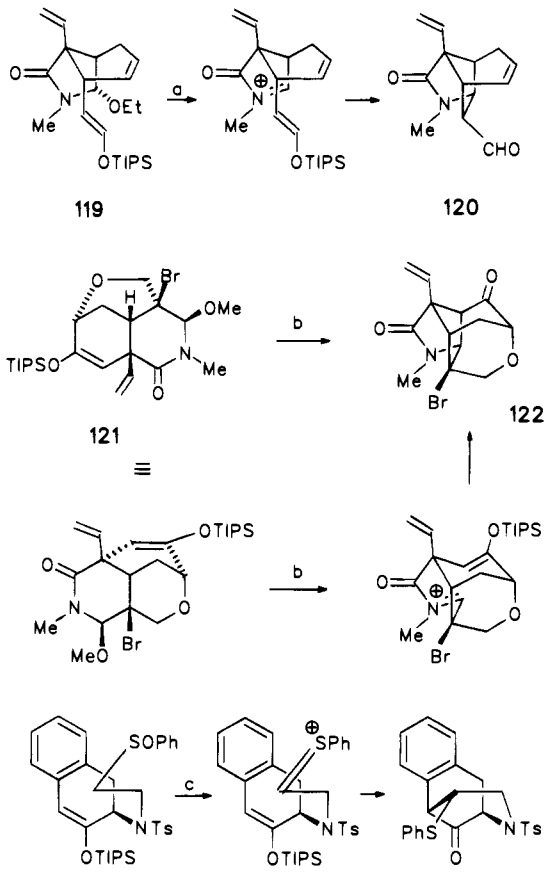
[a] (a) Lewis acid (TMS-OTf, $TiCl_4$, $SnCl_4$), CH_2Cl_2 or $MeNO_2$, −78 °C. (b) Furan. SiR_3 = TMS, TES, TBDMS, TIPS.

The shifting away of the enol ether double bond to form a new bond at the α-C results in buildup of positive charge on the former carbonyl C atom, whereby (unless the intermediate is trapped by a nucleophile or looses a proton) the silyl group is lost and the carbonyl function restored (e.g. **119** → **120**, **121** → **122**, **123** → **124**, Scheme 39).[371,378,405−407]

The cyclizations **125** → **126** and **127** → **128** shown in Scheme 40 were meant as model reactions for a projected synthesis of the taxane skeleton by formation of the central 8-membered ring, which after initial drawbacks[399] was achieved recently.[386,387]

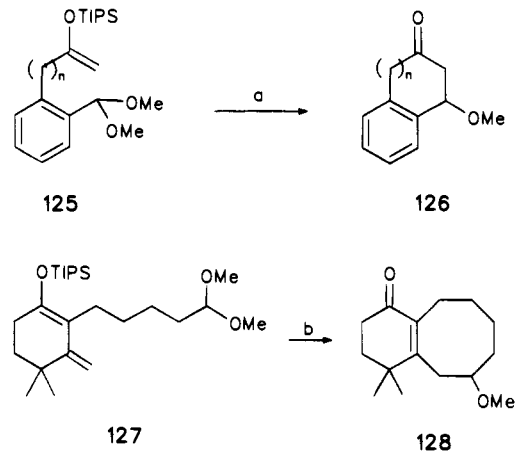
2-OTIPS-dienes **129** participate in Diels−Alder reactions with 2-oxo-3-butenoate esters **130a** to give adducts **131a** which can be transformed by ozonolysis and Paal−Knorr cyclization into 2,3,4-trisubstituted pyrroles **132**, as found in naturally occurring tetrapyrroles (Scheme 41).[404] This Diels−Alder reaction is cleaner and much more regioselective with TIPS-oxy dienes than with ethoxy-, TMS-oxy, or even TBDMS-oxy dienes. The regioselectivity was ascribed to steric congestion for R and TIPS-oxy in the transition state leading to the alternative "*meta*" Diels−Alder adduct. Alkoxy- or acyloxymethyl vinyl

Scheme 39[a]



[a] (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 20 °C, 5 min. (b) TFA, reflux, 15 min. (c) (1) $(F_3CCO)_2O$, 4-Me-2,6-di-tert-butylpyridine, CH_2Cl_2, 0 °C; (2) PhCl, 130 °C.

Scheme 40[a]



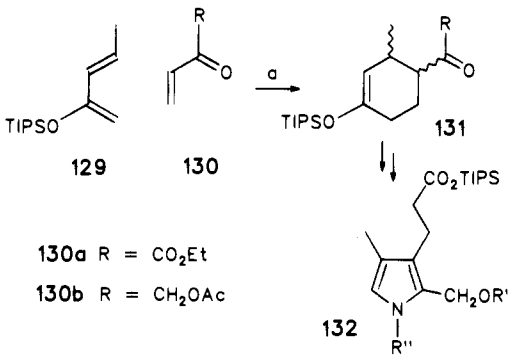
[a] (a) (1) 4 equiv of $TiCl_2(O^iPr)_2$, CH_2Cl_2, −78 °C; (2) H_2O. (b) (1) $TiCl_4$, CH_2Cl_2, −78 °C, 1 h; (2) H_2O.

ketones, e.g. **130b**, also work as dienophiles in such highly regioselective Diels–Alder reactions.[408]

2-TIPS-oxy dienes are more reactive in thermal as well as Lewis acid-catalyzed Diels–Alder reactions than the corresponding dienes without a silyloxy group.[236,383] The TIPS-oxy dienes are often more stable against Lewis acids than corresponding alkoxy dienes.[236]

1-(TIPS-oxy)cyclohexa-1,3-dienes, e.g. **133**, provide good yields of Diels–Alder adducts with acrylic

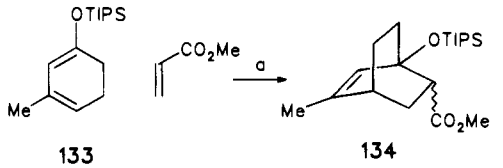
Scheme 41[a]



[a] (a) PhH, reflux.

esters, methyl vinyl ketone, acrolein, *etc.* in Lewis acid-catalyzed reactions (Scheme 42).[112,113]

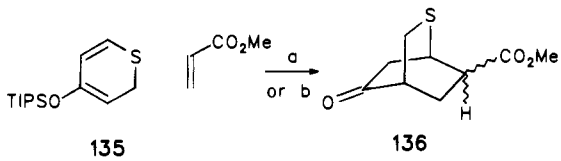
Scheme 42[a]



[a] (a) Et_2AlCl, $EtAlCl_2$, or $AlCl_3$, −78 °C, stereoisomer ratio *ca* 10:1, yield 85%.

Terminally *cis*-substituted dienes are often unreactive in Diels–Alder reactions. In order to overcome this limitation, electron-rich silyloxy-substituted 2*H*-thiopyrans (e.g. **135**) were employed in both thermal and Lewis acid-catalyzed Diels–Alder reactions with typical electron-poor dienophiles.[234,384,398,409] The bicyclic products such as **136** can be desulfurized, so that substituted 2*H*-thiopyrans may serve as equivalents for *cis*-substituted dienes (Scheme 43). An

Scheme 43[a]

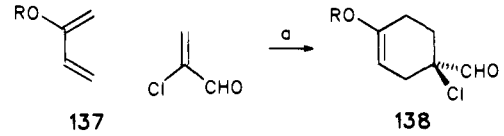


[a] (a) (1) PhMe, 120 °C, 6 days; (2) H_3O^+, 56%, stereoisomer ratio 0.6:1. (b) (1) $EtAlCl_2$, CH_2Cl_2, room temperature; (2) H_3O^+, 79%, stereoisomer ratio 1.2:1.

intramolecular version of this Diels–Alder reaction is known.[410] Such reactions are of preparative value only if the silyl group is TIPS, since the TMS-oxy or TBDMS-oxy dienes are easily cleaved to 2*H*-thiopyranones in the reaction medium.[384] An TIPS-oxy substituent may reside in the terminal or in the internal position of the diene system, although the former is generally less reactive.

A striking effect of a TIPS *vs* a TBDMS group was found in a catalytic asymmetric Diels–Alder reaction (Scheme 44).[391] 2-[(*tert*-Butyldimethylsilyl)-oxy]-butadiene (**137**, R = TBDMS) reacts with 2-chloroacroleine in the presence of 10% of the enantiopure *N*-tosyl-*B*-*n*-butyloxazaborolidinone derived from tryptophan to provide the 1,4,4-trisubstituted cyclohexene **138** (R = TBDMS) in 50–70% ee, whereas use of 2-[(triisopropylsilyl)oxy]butadiene results in 94% ee.

Scheme 44[a]



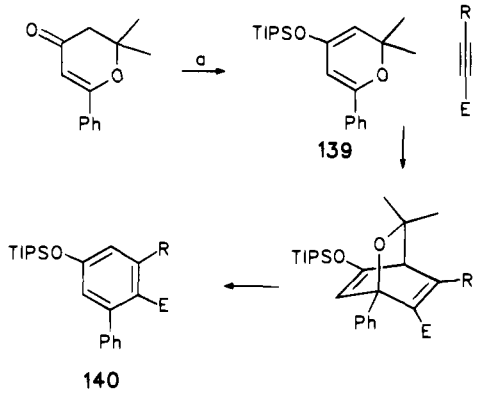
137 138

[a] (a) 10 mol % tryptophan derived *N*-tosyl-*B*-*n*-butyloxazaborolidinone, −78 °C, CH_2Cl_2.

R	ee, %
TBDMS or Me	50−70
TIPS	94

Heavily substituted 2,2-dimethyl-2*H*-pyrans with a 4-TIPS-oxy group **139** (made in situ from the corresponding 2,3-dihydro-4*H*-pyran-4-ones, di-*tert*-butyl-pyridine, and TIPS-OTf) react thermally with electron-poor acetylenes to provide, after loss of acetone from the intermediate 2-oxabicyclo[2.2.2]-octadiene, highly substituted TIPS-protected phenols **140** in good yields (Scheme 45).[273]

Scheme 45[a]



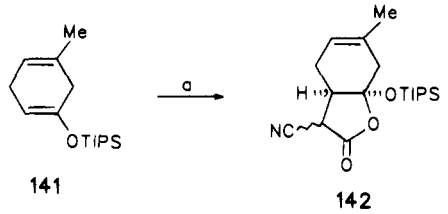
140

[a] (a) TIPS-OTf, di-*tert*-butylpyridine.

Intramolecular addition of a ketone Li enolate to a benzyne moiety did not occur, whereas the corresponding TIPS enol ether (a more nucleophilic enolate) added smoothly. Such a cyclization was the key step in Overman's synthesis of 3-acyl-3-alkyloxindoles.[374]

Cyanoacetic acid under the influence of $Mn_3O(OAc)_7$ can be annulated to a TIPS enol ether to provide an α-cyano-γ-lactone (e.g. **141** → **142**, Scheme 46).[283] TBDMS enol ethers had previously been

Scheme 46[a]



141 142

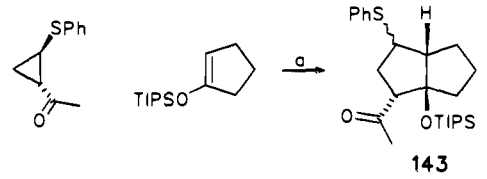
[a] (a) NC-CH_2CO_2H, $Mn_3O(OAc)_7$, KOAc, room temperature, 15 h.

found not to be useful in such reactions. This particular reaction is the first step in Corey's synthesis of paeoniflorin.

TIPS enol ethers containing an olefinic group were cyclized by electrochemical oxidation.[411,412]

TIPS (and TBDPS) enol ethers react with 1-acetyl-2-(phenylthio)cyclopropane under the influence of Me_2AlCl in a [3 + 2] cycloaddition to produce heavily substituted cyclopentanes **143** in a highly regio- and stereocontrolled manner (Scheme 47).[395] This reac-

Scheme 47[a]



143

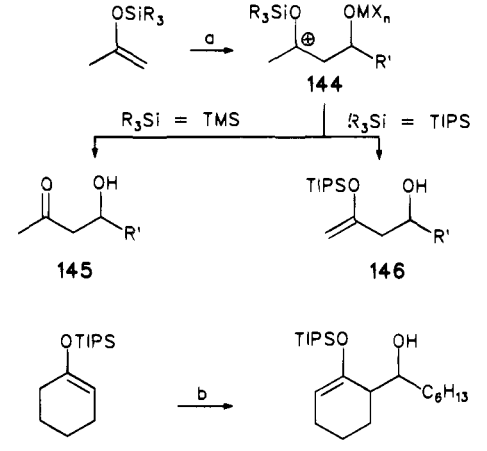
[a] (a) Me_2AlCl, CH_2Cl_2, 89%, major isomer:sum of other isomers = 93:7.

tion is not possible for the corresponding TMS compounds, with TBDMS it is less stereoselective.

TIPS enol ethers were α- or α′-perfluoroalkylated by treatment with a perfluoroalkyl iodide, a base, and Et_3B, the same reaction with TMS enol ethers gives the perfluoroalkylated ketones as byproducts.[413,414] The authors favor a radical addition/elimination mechanism.

The reaction of TMS enol ethers with aldehydes under the influence of strong Lewis acids affords aldols **145** (Scheme 48). Presumably, the initially

Scheme 48[a]

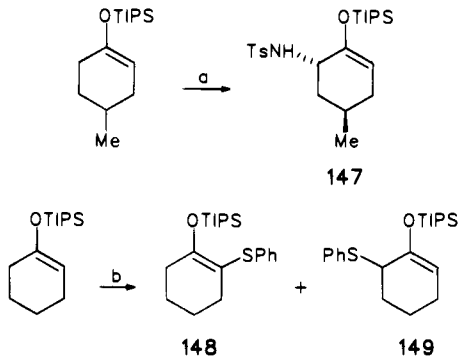


[a] (a) R′CHO, MX_n. (b) $C_6H_{13}CHO$, Me_2AlCl, CH_2Cl_2, −78 °C, 92%.

formed adduct **144** undergoes desilylation generating TMS-Cl. By contrast, the corresponding aldol adducts from bulky TIPS (or TBDPS) enol ethers undergo proton loss affording product enol ethers **146**.[415]

TIPS enol ethers of ketones react with many electrophiles in novel trialkylsilyl enol ether chemistry reported by Magnus: $(TsN)_2Se$ in CH_2Cl_2 at room temperature gives α′-tosylamino TIPS enol ethers **147** which are versatile intermediates,[393] while the corresponding TMS enol ethers give unstable products in low yields[30,371] or the products of desilylation (Scheme 49).[416] The NHTs group prefers an

Scheme 49[a]



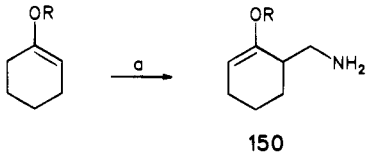
[a] (a) $(TsN)_2Se$, CH_2Cl_2, room temperature. (b) $(PhS)_2$, chloramine-T, 0 °C.

axial conformation unless a destabilizing 1,3 diaxial interaction interferes.[30]

The TIPS enol ether of cyclohexanone when treated with the adduct of diphenyl disulfide and chloramine-T gave a 1:1 mixture of α- and α′-phenylthio TIPS enol ethers **148/149** in 86% yield. The corresponding TMS ether was expected to be desilylated *in situ* and thus to avoid this regioisomerism. In fact α-(phenylthio)cyclohexanone was obtained in 70% yield by this reaction under mild, neutral conditions. The reaction is general for TMS enol ethers of ketones, the Se analogous reaction also works.[417]

α-Aminomethylation of silyl enol ethers (primary amino group) was achieved by reaction with the adduct of TMS-CH_2N_3 and $AlCl_3$, a formaldimine equivalent (→ **150**, Scheme 50). For the TBDMS enol

Scheme 50[a]



[a] (a) TMS-CH_2N_3, $AlCl_3$.

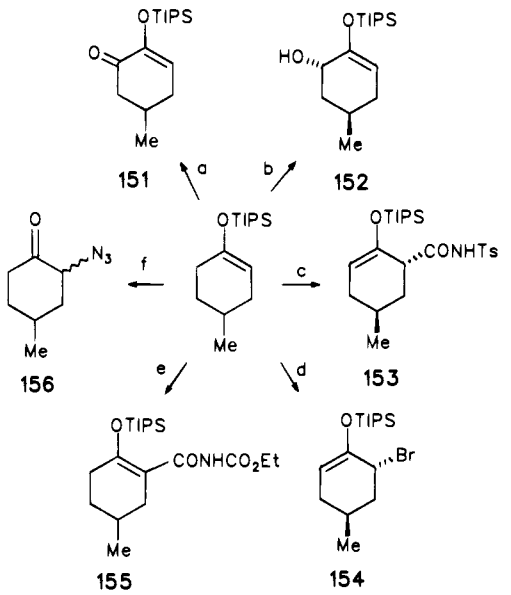
R	yield, %
TBDMS	56
TIPS	93

ether of cyclohexanone the yield was far lower than for the TIPS analog.[418] From TMS enol ethers similarly the corresponding β-amino ketones can be obtained in moderate yields. The α′-aminomethyl TIPS enol ethers in Scheme 50 can be condensed with an aldehyde and then cyclized to provide access to bicyclic 4-piperidones.[419]

TIPS enol ethers are oxidized by SeO_2 to α′-keto TIPS enol ethers **151**,[393,420] by H_2O_2/cat. SeO_2 to α′-hydroxy TIPS enol ethers **152**, by TsNCO to α′-tosylaminocarbonyl TIPS enol ethers **153**, by NBS to α′-bromo TIPS enol ethers **154**, by EtOOC-NCO to α-substitution products **155** (Scheme 51).[393] α-Azido ketones **156** are obtained by treatment of TIPS enol ethers with excess NaN_3/ceric ammonium nitrate in CH_3CN.[421] At least in the latter reaction the corresponding TMS enol ether cannot be employed due to rapid desilylation.

$^nBu_4NNO_3$ in CF_3CO_2H transforms TIPS enol ethers into α′-nitro TIPS enol ethers.[422]

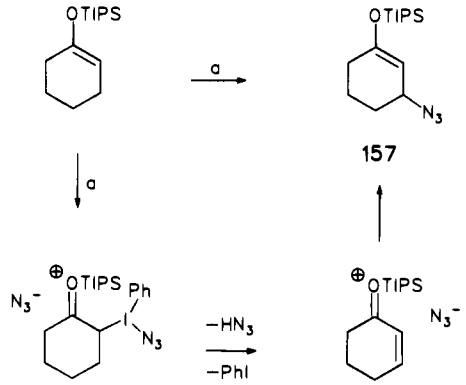
Scheme 51[a]



[a] (a) SeO_2, DMF. (b) H_2O_2/cat. SeO_2. (c) TsNCO, room temperature. (d) NBS, room temperature. (e) OCN-CO_2Et, 40 °C. (f) NaN_3/ceric ammonium nitrate, MeCN, −20 °C.

The unprecedented direct β-functionalization of a TIPS enol ether can be effected by reaction with PhIO and 2 equiv of TMS-N_3: β-azido TIPS enol ethers such as **157** are obtained in excellent yield (Scheme 52).[423] The active reagent is thought to be $PhI(N_3)_2$,

Scheme 52[a]



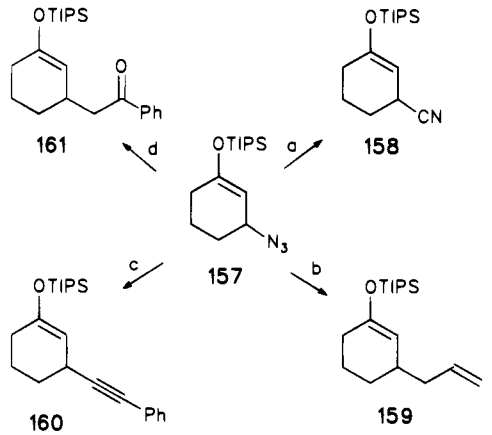
[a] (a) PhIO, 2 equiv of TMS-N_3, −15 °C, CH_2Cl_2, few minutes, 84%.

which adds to the educt giving an α-iodinized intermediate which eliminates PhI and HN_3 to yield an α,β-unsaturated oxonium ion ("enonium ion"). This adds azide ion in 1,4 fashion to give the observed product.

The enonium ion can be regenerated from the β-azido adduct **157** by treatment with a Lewis acid, it can be trapped by several C-nucleophiles to produce adducts with a β-C−C bond (**158**−**161**, Scheme 53).[416] The corresponding TMS enol ethers are not effective in this unusual substitution reaction.

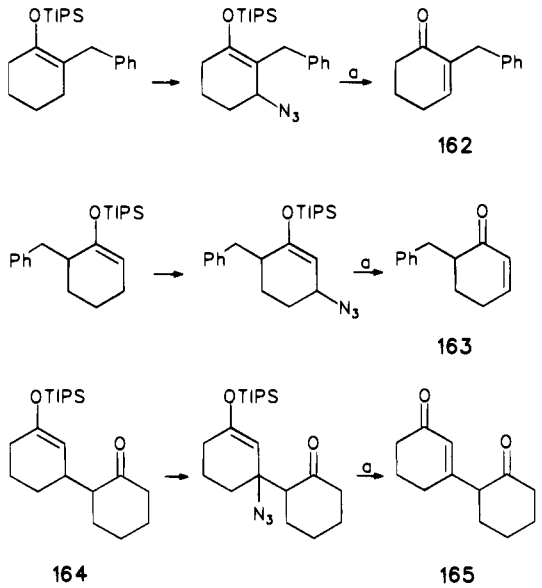
β-Azido TIPS enol ethers when treated with $^nBu_4$-NF in THF are transformed to α,β-enones (e.g. **162**, Scheme 54).[424] Since the former can be obtained regioselectively from ketones, this is a method for regioselectively preparing α,β-unsaturated ketones from ketones (**162** and **163**). This sequence of reactions works even if as a β-substituent on the TIPS

Scheme 53[a]



[a] (a) Et_2AlCN, THF, reflux. (b) Allyl-Sn^nBu_3, Me_2AlCl. (c) PhCCH, ^{n}BuLi, Me_2AlCl. (d) $H_2C{=}C(OTMS)Ph$, Me_2AlCl.

Scheme 54[a]

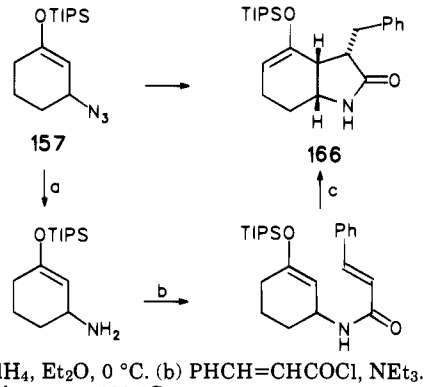


[a] (a) $^nBu_4NF$, THF.

enol ether a ketone is present (**164**, obtained as above using cyclohexanone TMS enol ether as the carbon nucleophile[416]), in this way a mixed ketone–enone **165** was prepared. This chemistry was recently reviewed.[425]

β-Azido TIPS enol ethers such as **157** are valuable intermediates, they allow annulation of 5-membered lactam rings onto the original ketone (product **166**)

Scheme 55[a]



[a] (a) $LiAlH_4$, Et_2O, 0 °C. (b) PHCH=CHCOCl, NEt_3. (c) Me_3Al, 1,2-dichlorobenzene, 180 °C.

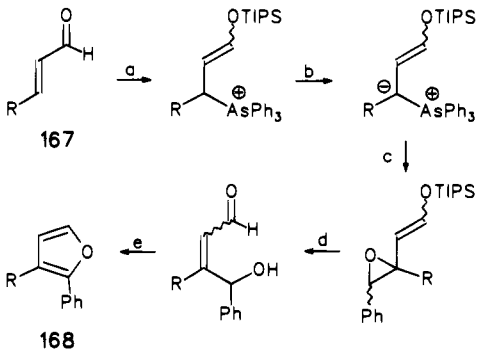
by the three-step sequence shown in Scheme 55.[392] A [2 + 2] cycloaddition mechanism was postulated to explain the observed stereochemistry.

The reaction of a TIPS enol ether with PhIO/TMS-N_3 is not observed in the presence of a tertiary amine, which is more reactive to this reagent combination.[396]

It may be of interest to note that the idea to use TIPS enol ethers for β-functionalization of ketones occurred to Corey in 1981, but that the present author, at that time a postdoc with Corey, was not able to transform this vision into reality using several oxidants.[43] Independently, Magnus had the same idea, and elegantly succeeded in its execution.

From an α,β-unsaturated aldehyde **167** (Scheme 56), Ph_3As, and TIPS-OTf in THF at −78 °C an

Scheme 56[a]



[a] (a) Ph_3As, TIPS-OTf, THF, −78 °C. (b) $KN(TMS)_2$. (c) PhCHO. (d) $^nBu_4NF$. (e) 10% aqueous HCl.

arsonio TIPS enol ether can be prepared, and treatment with $KN(TMS)_2$ then forms an ylide. This reacts with an aldehyde resulting in CC bond formation to give a [(triisopropylsilyl)oxy]vinyl epoxide which can be cyclized into a substituted furan **168**. Silyl enol ethers other than TIPS do not work in this sequence, since decomposition instead of ylide formation occurs on treatment of TMS or TES arsonio silyl enol ethers with base.[426]

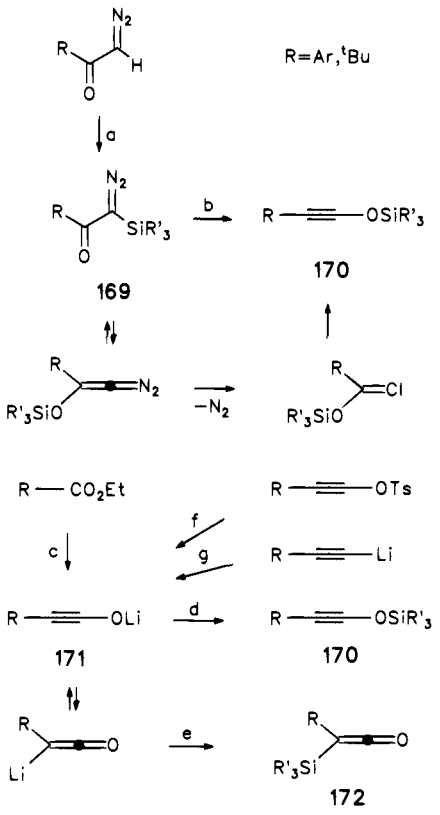
C. TIPS Ynol Ethers

(Silyloxy)alkynes **170** (Scheme 57) are isolable derivatives of the elusive 1-alkyn-1-ols. They owe their very existence to the protective effect of bulky silyl groups, such as TIPS or, to a lesser amount, TBDMS. TIPS and TBDMS ynol ethers survive chromatography on silica and distillation, in contrast to the TES derivatives.

TIPS ynol ethers were first obtained by Maas in 1985, when α-TIPS-α-diazomethyl aryl ketones **169** (R = aryl) were warmed in benzene.[427] Arylalkylidene carbenes are probably intermediates. This method of preparation is limited to aryl- and *tert*-butylalkynol silyl ethers.[268]

A straightforward general one-pot preparation of silyl ynol ethers from simple esters was found by Kowalski. The carbon chain of an ester is elongated using a reagent made from dibromomethane and a base, the lithium ynolate formed (**171**) is silylated with TIPS-Cl at −78 °C.[428] If TMS-Cl is used instead at a temperature as high as 0 °C, a TMS ketene **172** is formed. A lithium ynolate can alternatively be prepared by treatment of an alkynyl tosylate with MeLi[429] or by oxygenation of a lithium acetylide.[430]

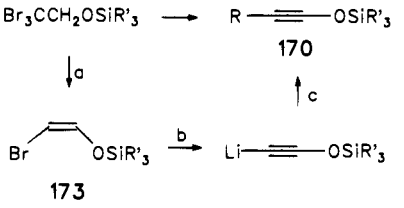
Scheme 57[a]



[a] (a) R'_3Si-OTf, $^iPr_2NEt$, Et_2O, 0 °C. (b) PhH, from room temperature to reflux. (c) CH_2Br_2, LiTMP, ^nBuLi. (d) (1) R'_3Si-Cl,THF/hexane, −78 °C; (2) pentane, H_2O, −78 °C. (e) (1) R'_3Si-Cl, THF/hexane, from −78 °C to room temperature; (2) H_2O. (f) 2 equiv of MeLi, THF, −20 °C. (g) LiOO^{t}Bu, from −70 to −20 °C.

A third method of preparation, well-suited for compounds with small substituents on the other side of the triple bond (**170**, R = H,CH_3), was developed by Danheiser (Scheme 58). A silyl ether of 2,2,2-

Scheme 58[a]



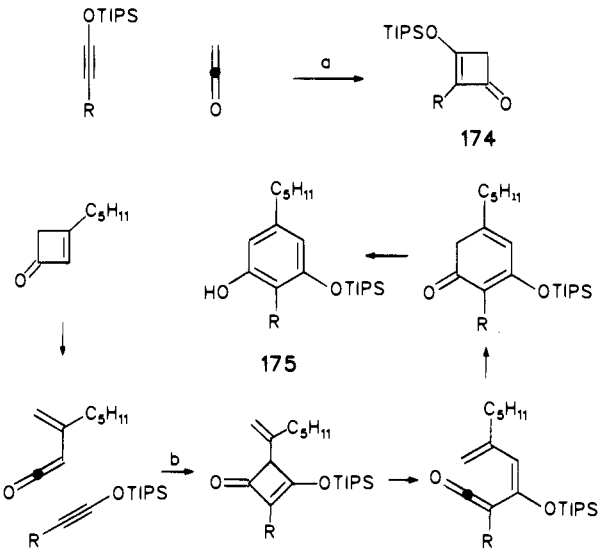
[a] (a) (1) 2 equiv of ^nBuLi; (2) H_2O. (b) 2 equiv of LDA, THF, 0 °C. (c) EtOH (for R = H) or MeI (for R = Me).

tribromoethanol is treated with 2 equiv of ^nBuLi to afford after hydrolysis the (*Z*)-silyl enol ether of 2-bromoacetaldehyde **173**. This on LDA treatment is converted to a lithium (silyloxy)acetylide which is then protonated or alkylated.[213] A very demanding trialkylsilyl group such as $^tBu_2MeSi$ is even better in these reactions than TIPS.

TIPS ynol ethers are rapidly converted to acids or esters on treatment with H_2O or alcohols[427] or on chromatographic workup.[431] In contrast to TIPS enol ethers, the silyl atom in TIPS ynol ethers is easily attacked by MeLi, to regenerate the Li ynolate.[428,429]

TIPS ynol ethers are outstanding ketenophiles. They react with ketene to provide 3-[(triisopropylsilyl)oxy]cyclobut-2-enones (**174**), and on heating with cyclobutenones they regioselectively form mono-TIPS protected resorcinols **175** by [2 + 2] addition to a vinyl ketene which forms from the cyclobutenone, followed by a cascade of electrocyclic steps (Scheme 59).[91,213]

Scheme 59[a]

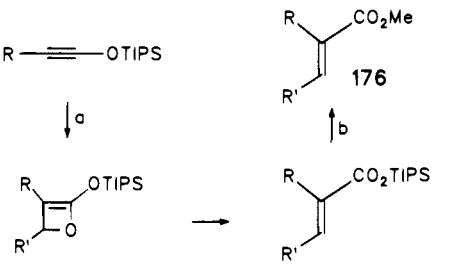


[a] (a) CH_2Cl_2, 0 °C. (b) PhH or PhMe, heat.

This reaction was exploited very elegantly by Danheiser (the vinyl ketene is now formed by photochemical Wolff rearrangement from a vinyl or aryl α-diazoalkyl ketone) for syntheses of several mono- and polycyclic phenols,[432] and of phenolic natural products, such as maesanin,[281] aegyptinones,[433] and components of the Chinese Dan Shen drug.[233,434]

TIPS ynol ethers in CH_2Cl_2 at −78 °C under $TiCl_4$ catalysis add in a [2 + 2] fashion to aldehydes, the oxetenes formed decay to TIPS esters of substituted acrylic acids (exclusively *E*), which in the presence of MeOH are transformed into the corresponding methyl esters **176** (Scheme 60).[435]

Scheme 60[a]

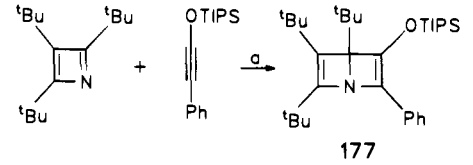


[a] (a) R'CHO, CH_2Cl_2, $TiCl_4$, −78 °C. (b) MeOH, CH_2Cl_2, $TiCl_4$, from −78 °C to room temperature.

A TIPS ynol ether as a moderately electron-rich alkyne undergoes [2 + 2]-cycloaddition to a protected azacyclobutadiene to regioselectively provide access to the Dewar pyridine **177** (Scheme 61).[436]

A special class of TIPS ethers of triply bonded carbon are metal [(triisopropylsilyl)oxy]carbyne complexes which arose from the work of Lippard.[437] The TIPS group allowed some insight into the process of CC bond formation between CO ligands complexed in *cis* configuration around a metal. Reduction of the biscarbonyl complex $[(dmpe)_2TaCl(CO)_2]$ with sodium amalgam results in an anion $[(dmpe)_2Ta(CO)_2]^-$

Scheme 61[a]



177

[a] (a) Pentane, room temperature.

which is attacked at a carbonyl oxygen when silylated with TIPS-Cl to give the carbyne complex [(dmpe)$_2$(OC)Ta≡COTIPS] (dmpe = $Me_2PCH_2CH_2PMe_2$). This latter complex when treated with TMS-Cl is again O-silylated, and interestingly under CC bond formation the acetylene complex [(dmpe)$_2$ClTa·TMSOC≡COTIPS] is formed.[31,438] Up to now, no attempts at liberating the bis(silyloxy)acetylene were undertaken.

D. TIPS Esters

TIPS esters are formed from an acid and TIPS-Cl (DMF, imidazole, 60 °C, 48 h[439] or THF, Et_3N, room temperature, 1 h[440]) or from an acid and TIPS-OTf (benzene, Et_3N, room temperature, 10 min[43]). A carboxylate can be silylated with TIPS-Cl at −78 °C.[407] TIPS esters are isolated without difficulty, they can be chromatographed on silica without loss.[43] For comparison, TMS or even TBDMS esters could not be isolated without excessive hydrolysis.[441] Mono-TIPS-monoalkyl esters of maleic acid were prepared from maleic anhydride, TIPS-Cl, an alcohol, and Et_3N.[442,443] TIPS methacrylate is obtained from the acid and TIPS-H in the presence of H_2PtCl_6 and hydroquinone.[444] Phosphinic acid TIPS esters were obtained from the corresponding Li phosphinate and TIPS-OTf at −78 °C.[445]

TIPS esters are formed in the Ireland−Claisen rearrangement of TIPS ketene acetals of esters of allylic alcohols,[446−450] from TIPS enol ethers and ozone,[404] and from TIPS ynol ethers and aldehydes.[435]

A TIPS ester was found stable to NH_3 and NaClO in EtOH/H_2O, it was saponified by dilute aqueous NaOH.[440] TIPS esters were cleaved to the acid by KF·2H_2O in HMPA,[450] or by $^nBu_4NF$.[446] A TIPS ester is reduced to the primary alcohol by LAH.[441,447] TIPS esters, like TBDMS esters, but more slowly, are transformed into acyl bromides by Ph_3PBr_2.[270] For the conversions TIPS ester → elongated TIPS enol ether[389] and TIPS ester → methyl ester[435] see above.

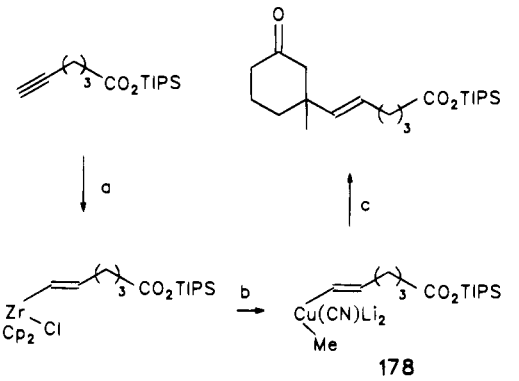
TIPS carboxylates are inert under hydrozirconation conditions and survive treatment with MeLi and Lipshutz cuprates.[250,451,452]

Unsaturated TIPS esters participate in halolactonization reactions to give halolactone products with concomitant loss of the TIPS moiety.[449]

In an α,β-unsaturated TIPS ester, the TIPS group completely protected the C=C double bond against Michael addition of an alkyl cuprate.[453] Such an effect was not seen in the corresponding TBDPS or TBDMS esters, which, moreover, were attacked at the carbonyl group.

An alkyl ester function generally is too electrophilic to be compatible with a strong nucleophile (e.g. RLi) in the same molecule. At the same time, an alkyl ester tends to complex a Lewis acidic center intra- or intermolecularly. Both these properties are very much attenuated in a TIPS ester. Therefore a higher order lithium organocuprate containing a TIPS ester function **178** (Scheme 62) can be formed by trans-

Scheme 62[a]



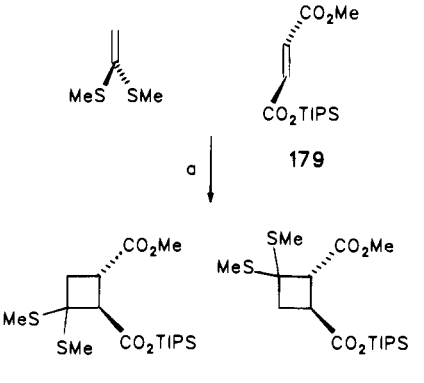
178

[a] (a) $Cp_2Zr(H)Cl$, THF, room temperature. (b) $Me_2Cu(CN)Li_2$, THF, −78 °C. (c) 3-Methylcyclohex-2-enone, THF, −78 °C.

metalation from the corresponding vinylzirconate, and adds to an α,β-enone in high yield.[451] This reaction does not work with the corresponding TBDMS ester.

In an intramolecular concurrence situation, in TIPS methyl fumarate **179**, the lower tendency of the TIPS ester group to complex the bulky Lewis acid MAD is reflected in regioselective [2 + 2] adduct formation with ketene acetals or dithioacetals (Scheme 63).[454]

Scheme 63[a]



82 : 18

[a] (a) MAD = MeAl(O-2,6-$^tBu_2C_6H_2$-4-Me)$_2$, PhMe.

A phosphinic acid TIPS ester gives the phosphinic acid chloride on treatment with oxalyl chloride.[445]

E. TIPS Ketene Acetals

TIPS ketene acetals are formed from Li ester enolates and TIPS-Cl. The Li ester enolate is prepared from the ester and LDA at −78 °C either in pure THF (→ mostly *Z* Li enolate, silylation gives (*E*)-silylketene acetal, reversal in substituent CIP priority) or in THF/HMPA (→ mostly *E* Li enolate to give (*Z*)-silylketene acetal).[448,450,455] TIPS ketene acetals survive aqueous workup and distillation (demonstrated for the TIPS ketene acetal of ethyl butyrate,[43] see also the purification of TMS and TBDMS ketene acetals[456a]).

Similarly, cyclic TIPS ketene acetals are formed from lactones, $LiN(TMS)_2$ and TIPS-OTf (a small

amount of α-TIPS lactone was also formed) in THF as predominantly the *E* isomers, or in THF/HMPA to give mostly *Z* isomers.[446] Lactones can be directly transformed into TIPS ketene acetals by treatment with TIPS-OTf and Et_3N (room temperature, 2 min) in C_6H_6, toluene or $CHCl_3$,[447] or in C_6H_6 at reflux.[449] The lactone enolate, if at all an intermediate under these conditions, is rapidly trapped by the highly reactive TIPS-OTf. If the enolate is generated using LDA and then reacted with the less reactive TBDMS-Cl, it has enough time to undergo side reactions.[449]

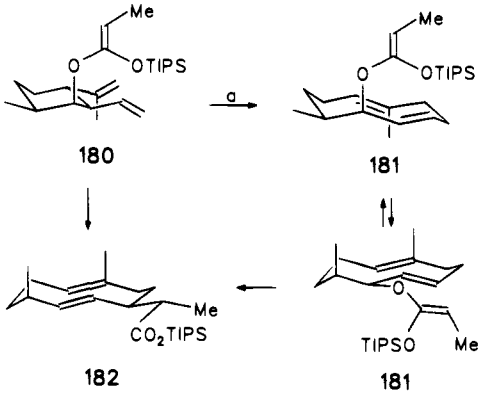
For the chemistry of silylketene acetals see ref 402.

A lactone was α-hydroxylated via Sharpless dihydroxylation of its silylketene acetals (TIPS or TBDMS), but ee's were low.[457]

Silylketene acetals of esters of allylic alcohols are substrates for the Ireland–Claisen rearrangement, a highly stereospecific reaction giving often at moderate temperature (room temperature to 70 °C) the silyl esters of γ,δ-unsaturated acids containing a new CC bond (the α,β-bond).[458] This reaction, although working on TMS- or TBDMS-ketene acetals,[204,206,458,459] was found to suffer from concurrent 1,3 O→C Si migration in the case of a TBDMS-ketene acetal.[459] This side reaction[456b] did not occur with the TIPS-ketene acetal,[450] and consequently the Claisen rearrangement of TIPS-ketene acetals has become popular for the synthesis of complex natural products, in particular those containing a medium-sized ring otherwise not easily accessible.

Thus, germacrane sesquiterpenes (+)-dihydrocostunolide and dihydroreynosine (10-membered rings) can be obtained by tandem Cope–Claisen rearrangement of TIPS-ketene acetal **180** derived from a 2,3-divinylcyclohexyl ester (Scheme 64).[448,450] The irreversible Claisen rearrangement **181** → **182** drives the unfavorable Cope rearrangement equilibrium **180** ⇄ **181** to completion.

Scheme 64[a]



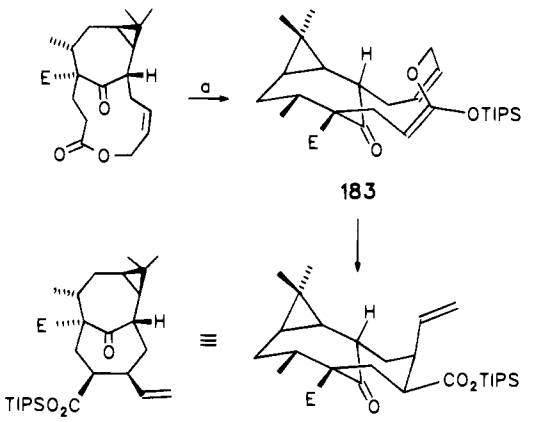
[a] (a) Dodecane, 200 °C, 140 min.

Similarly, the strained bridged 10-membered carbocyclic ring of ingenol (*trans* ring fusion) was constructed from a bridged 14-membered lactone by Claisen rearrangement of the cyclic TIPS ketene acetal **183** (Scheme 65).[449,460]

Stereocontrolled rearrangement of cyclic TIPS ketene acetals to $\Delta^{4,5}$-pipecolic acid esters **184** occurred at room temperature (Scheme 66).[447,461]

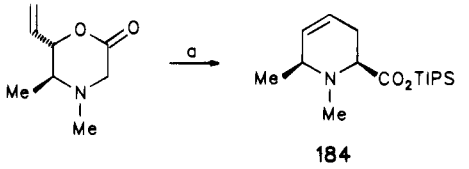
Carbocyclic enediyne rings of 10 and 11 members were obtained from corresponding 14- and 15-membered TIPS-ketene acetals derived from lactones in stereospecific low-temperature rearrangements.[446]

Scheme 65[a]



[a] (a) TIPS-OTf, NEt_3, PhH, reflux.

Scheme 66[a]



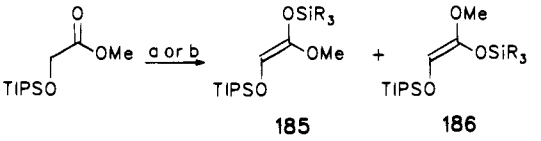
[a] (a) TIPS-OTf, NEt_3, $CDCl_3$, room temperature, 6 h.

The Ireland–Claisen rearrangement is of course most powerful if the configuration of the silyl ketene acetal can be controlled. This was in fact achieved in the following acyclic examples.

Allyl esters of fluoroacetic acid were Ireland–Claisen rearranged simply by treatment with Et_3N and TIPS-OTf below −60 °C, and then 3 days at room temperature. The TIPS-ketene acetal is formed under these conditions as predominantly the *Z*-isomer, resulting in a 8:1 mixture of product acids. Use of less bulky silyl groups gave lower stereoselectivity.[462]

Silylketene acetals **185** and **186** of hydroxyacetic acid esters (Scheme 67) can be formed in either *E* or *Z* configuration depending on conditions in a manner similar to those for simple esters, provided the OH is protected by a bulky silyl group such as TBDMS, TBDPS, or TIPS (compare Scheme 30).[463] The corresponding allyl esters are of demonstrated value for stereocontrolled Ireland–Claisen rearrangements.

Scheme 67[a]



[a] (a) LiTMP, TMS-Cl, THF/hexane, from −100 °C to room temperature. (b) (1) $LiN(TMS)_2$, THF/hexane/HMPA, −100 °C; (2) TBDMS-Cl, from −100 °C to room temperature; (3) aqueous $NaHCO_3$.

conditions	185 : 186		SiR_3
a	>99	1	TMS
b	3	97	TBDMS

Chlorocarbene and methylchlorocarbene add to TIPS ketene acetals in a weakly stereoselective manner, and after heating chain-elongated α,β-

unsaturated esters were obtained, formed by rearrangement of the intermediate chlorocyclopropanone acetals.[455]

α,β-Unsaturated esters (or amides) form the corresponding conjugated TIPS ketene acetals of β,γ-unsaturated esters or amides **114** (R^3 = O-alkyl or NR'R'') when treated with TIPS-OTf and Et_3N (Scheme 37).[464] These can be oxidized by $Pd(OAc)_2$ to α,β:γ,δ-dienoic acid esters or amides **115** (R^3 as above).[382] This does not work with TMS- or TBDMS-ketene acetals. The silyl dienyl ethers **114** are α- and γ-nucleophiles, reacting with a proton at the α-position under formation of β,γ-unsaturated esters **116**, or with an intramolecular Michael acceptor at the γ-position.

A thiol ester, *S-tert*-butylthiobutyrate, was lithiated (lithium isopropyl cyclohexylamide in THF at −78 °C) and treated with TIPS-OTf to provide the corresponding silylketene thioacetal as a single stereoisomer.[43] In presence of HMPA predominantly the other stereoisomer was formed. These *O*-TIPS-ketene thioacetals survive aqueous workup and chromatography on silica.

V. *N*-TIPS Compounds

A. *N*-TIPS Amines and Anilines

Formation of *N*-TIPS amines or anilines by silylation usually requires prior conversion of the amine to the lithium amide. Thus amines were lithiated by ^{n}BuLi in benzene and then silylated with TIPS-Cl (in the presence of TMEDA for hindered amines such as ^{t}BuNH$_2$).[465] Anilines were lithiated with ^{n}BuLi in Et_2O and then silylated with TIPS-Br.[52]

Similarly, TIPS-NH_2 was obtained from TIPS-Cl and liquid NH_3 in the presence[466] or absence of KNH_2.[467]

Aqueous workup was avoided in order to isolate *N*-TIPS amines and anilines. Generally, the N−Si bond in *N*-silyl amines is labile so that *N*-silyl amines can act as silylating agents. Thus the N−TIPS bond in heterocyclic *N*-TIPS amines was found to be easily cleaved by water (e.g. in wet Et_2O at room temperature).[431] TIPS-NH_2 reacts with water and MeOH to give TIPS-OH and MeO-TIPS, respectively, whereas the corresponding reactions of ^{t}Bu$_3$Si-NH_2 do not occur.[466,468]

When compounds containing both OH and NH_2 or NH groups (e.g nucleosides) are treated with a silylating agent in the presence of a base, N−Si compounds along with silyl ethers are often not obtained. In several cases this may be due to aqueous workup,[114,300] but without such a workup the result seems to be the same.[53,108,208] Similarly, ethanolamine and 4-amino-1-butanol are claimed to be cleanly O-silylated when treated with substoichiometric amounts of TIPS-Cl in CH_2Cl_2 without a base, followed by aqueous workup.[115]

The Li salt of ^{t}BuNHTIPS was formed using ^{n}BuLi (Et_2O, room temperature),[465] that of TIPS-NH_2 using ^{n}BuLi in hexanes.[467] The TIPS group in *N*-TIPS-amines is inert to ^{t}BuOCl in CH_2Cl_2, *N*-Cl-*N*-TIPS amines are cleanly formed with this reagent.[465]

Of several *N*-SiR_3 anilines the TIPS compound is slowest in solvolysis (MeOH/KOH/H_2O) as expected, the TBDMS, TES, ^{i}PrMe$_2$Si, and Et$_2$MeSi derivatives are more reactive in this order.[52]

Similar to an O-TIPS, a N(Me)-TIPS on an arene tricarbonyl complex directs lithiation/substitution to the *meta* position.[308]

Desilylation is achieved as usual with fluorides. In *N*,o-bis(TIPS)anilines the *N*-silyl group was selectively cleaved in presence of the aryl-TIPS (or a vinyl-TIPS) by treatment with KF in MeOH (reflux, 3 h).[469]

The *N*-TIPS derivative of a secondary amine is dehydrosilylated by the reagent combination PhIO/TMS-N_3 to give an imine.[396]

Aminyl radicals ^{t}Bu(R$_3$Si)N$^\bullet$ were generated (e.g. by photolysis of the *N*-Cl-amine) and observed using ESR spectroscopy.[465] These are π-radicals, the *N*-TIPS radical has the highest lifetime among those included in this study (SiR_3 = TMS, TES, TBDMS, TIPS).

A valuable protective group for primary amines is TBDPS.[470] The TBDPS derivatives of primary amines are reported to be more stable toward hydrolysis and chromatography than *N*-TIPS and much more so than *N*-TBDMS amines. They are inert to bases, alkylating and acylating agents and Swern oxidation. They are cleaved by 80% HOAc or py·HF.

B. *N*-TIPS Amides and Lactams

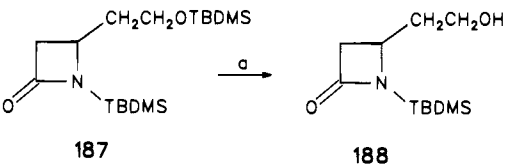
Primary amides were N-lithiated by ^{n}BuLi at −78 to 0 °C in THF and then silylated with TIPS-Cl or TBDMS-Cl at room temperature overnight. The *N*-TIPS and *N*-TBDMS amides survived flash chromatography, while the corresponding *N*-TMS compound could not be purified.[471]

From an *N*-TIPS amide the *N*-lithio-*N*-TIPS amide can be cleanly formed by ^{n}BuLi treatment at −78 °C. The corresponding *N*-TBDMS compound is partially desilylated under these conditions.[471]

Lactams can be triisopropylsilylated by simultaneous treatment with DBU and TIPS-OTf in MeCN.[472]

A *N*-TBDMS- or *N*-TIPS-β-lactam was found surprisingly inert toward aqueous HCl in MeOH, that is toward conditions which cleave TBDMS ethers. Thus the bis(TBDMS) compound **187** (Scheme 68) is

Scheme 68[a]



187 188

[a] (a) 0.5 N aqueous HCl, MeOH, 0 °C, 30 min.

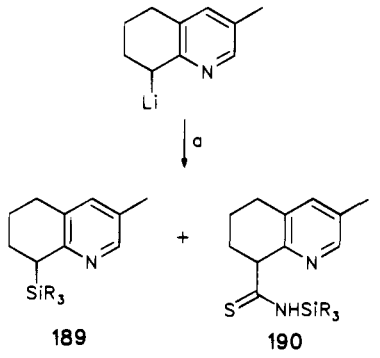
reported to afford after 30 min at 0 °C the N-silylated β-lactam **188** in quantitative yield.[473]

A phthalimide moiety could be selectively N-triisopropylsilylated in the presence of two indole units (^{i}Pr$_2$EtN, TIPS-OTf, diglyme, DMF, room temperature, 7 days).[474] The *N*-TIPS-phthalimide survived treatment with H_2NR/HCHO in HOAc at 65 °C, or with LDA or NaH. It was deprotected using HF·pyridine or ^{n}Bu$_4$NF or NaOAc in DMSO/H_2O at 65 °C.

A *N*-TIPS thioamide is reported to be stable toward NH_4Cl solution and to be slowly hydrolyzed to the thioamide by HCl solution.[475]

N-Silyl isothiocyanates (silyl pseudohalogenides, obtained from ammonium thiocyanate and silyl chlorides) can be attacked by an organolithium at Si or at C, resulting in silylation or thioamidation of RLi, respectively (Scheme 69).[475] It was found that while

Scheme 69[a]



189 190

[a] (a) (1) R_3Si-NCS; (2) H_2O.

R_3Si	189	190
TMS	sole product	–
TBDMS	–	sole product, 50% yield
TIPS	–	sole product, 85% yield

TMS isothiocyanate undergoes the first kind of reaction (→**189**), for the TIPS analog nucleophilic attack at Si is impossible, and the *N*-TIPS thioamide **190** is obtained. Since the N–Li precursor of **190** still has an acidic H atom (benzylic and allylic), transmetalation and quenching occurs if a reactive trapping agent is present, such as the isothiocyanate of a less bulky silyl group (TBDMS), limiting the yield of thioamidation product to 50%. The TIPS reagent in contrast does not react with the secondary metalation product, therefore the yield of **190** in this case is 85% (100% based on not recovered starting material).

C. *N*-TIPS Pyrroles, Indoles, and Other N-Heterocycles

The most important use N-TIPS has found is in *N*-TIPS-pyrroles and -indoles, where the TIPS group simultaneously protects the heteroatom and the neighboring atoms 2 and 5 (pyrroles) or 2 and 7 (indoles, "lateral protection") (Figure 1[476]).

N-TIPS-pyrroles and -indoles were obtained by sequential deprotonation and silylation, e.g. (1) LiN(TMS)$_2$, (2) TIPS-OTf;[477,478] (1) K in THF, (2) TIPS-Cl;[264] (1) ^{n}BuLi/THF, (2) TIPS-Cl;[476,479,480] (1) NaH/DMF, (2) TIPS-Cl.[476] Alternatively, simultaneous treatment with a base and a silylating agent is used, e.g. NaH and TIPS-OTf in DMF,[481] KH and TIPS-OTf in THF,[482] KH and TIPS-Cl in THF,[483] ^{t}BuOK and TIPS-Cl in DMF.[484]

^{i}Pr$_2$EtN is too weak a base, so that a phthalimide can be N-silylated in the presence of an indole moiety using this base.[474]

N-TIPS-pyrroles and -indoles survive an aqueous acidic workup (1 N HCl).[477,478,485]

Generally, *N*-TIPS-pyrroles are more persistent than the corresponding *N*-H-pyrroles[476,486] or *N*-TBDMS-pyrroles under laboratory conditions.[487]

The N-TIPS grouping is stable against BF_3·Et_2O,[477] $ZnCl_2$,[488] DDQ,[489] Dess–Martin periodinane,[477] Pd complexes,[479,485,490,491] H_2/Pd/C,[488] $NaBH_3CN$,[477] $NaBH_4$,[488] and Na naphthalenide.[485]

The silyl group in *N*-TIPS-pyrroles and -indoles is inert toward LDA,[492] Grignard reagents,[264] ^{n}BuLi,[477,493] ^{n}BuLi/TMEDA,[479,483,490] and ^{t}BuLi.[478,491,493] Heating for 24 h at 120 °C with R_FSO_2Cl and $RuCl_2(PPh_3)_3$ does not affect the N-TIPS group.[494] The N-TIPS group is unchanged under the influence of *N*-iodosuccinimide[491] and almost inert toward *N*-bromosuccinimide (conditions of halogenation of the arene).[486,487,495–497] However, side products brominated in the TIPS group were obtained on reaction with NBS in THF even at −78 °C.[264] This unwanted reaction can be suppressed by running the reaction in acetone.

N-TIPS-pyrroles and -indoles are desilylated by ^{n}Bu$_4$NF in THF at 0 °C, 5–10 min,[481,482,491,492] or in ether.[494] The N-TIPS group could be selectively removed in the presence of a primary TBDMS ether by this reagent.[498] *N*-TIPS-pyrroles can be desilylated by CsF in THF (40 °C, 4 h[493]) or in MeOH (room temperature, 16 h[499]). The same reagent is useful for a one-step conversion of *N*-TIPS to *N*-CO_2Me, by treatment with CsF and $ClCO_2Me$ in MeCN under ultrasound irradiation.[500] Desilylation of *N*-TIPS-pyrroles can be effected by treatment with saturated aqueous NH_4Cl,[495] or by CF_3CO_2H in acetic acid at room temperature (not at −35 °C).[501] Desilylation occurs under the influence of HCl in a reaction mixture,[502–504] on treatment with NaI in HMPA at

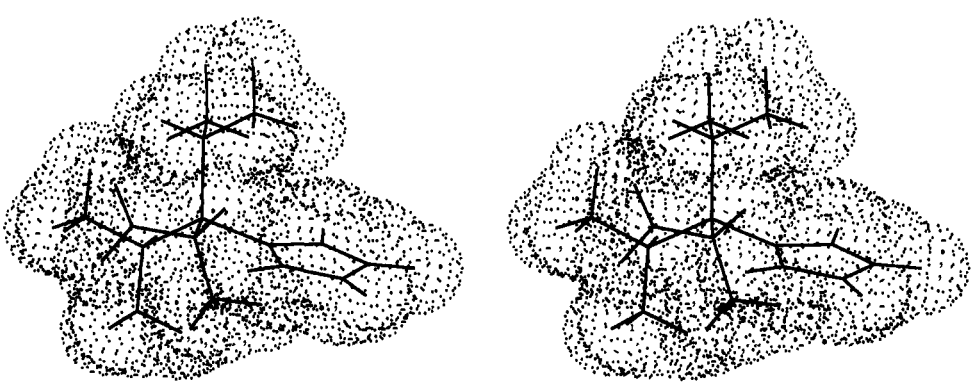
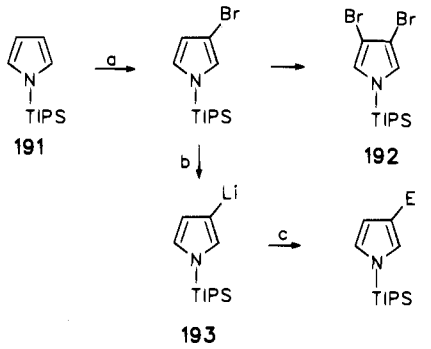


Figure 1. Stereopicture of *N*-(triisopropylsilyl)pyrrole. (Reprinted from ref 476, courtesy of Professor J. M. Muchowski. Copyright 1990 American Chemical Society.)

130 °C,[485] with a chloride in MeCN at 80 °C,[499] or on prolonged treatment with LiBr in THF at room temperature[505]

The reaction of *N*-TIPS-pyrrole **191** with NBS was studied extensively by the groups of Muchowski,[476,486,497] Kozikowski,[487,495] and others (Scheme 70).[264,496] The electrophilic substitution is directed

Scheme 70[a]



[a] (a) NBS, THF, −78 °C or acetone, reflux. (b) ^{n}BuLi, THF, −78 °C. (c) E-X.

to position 3, whereas the free pyrrole or compounds with smaller N-protecting groups such as TMS[476,486] or even TBDPS[487] invariably are substituted at position 2.[264,476,485,495,496,502,503] Dibromination in *N*-TIPS-pyrrole at −78 °C occurs very selectively at positions 3 and 4 (→**192**).[476]

Vilsmeier formylation in position 3 of *N*-TIPS-pyrrole was achieved[502−504] and several other electrophiles could be directly introduced (I^+, NO_2^+, RCO^+,[476] CF_3CO^+,[476,484] $^+COCO_2Et$, $^+SOC_6H_4Me$,[486] $^+CH_2NMe_2$,[499] succinoyl[488]). 3-Bromination of *N*-TIPS-indole was achieved using $pyH{\cdot}Br_3$.[485]

The products, and in particular lithiated *N*-TIPS-pyrroles such as **193** obtained by Hal/Li exchange,[264,476,487,491] made possible a host of synthetic applications (synthesis of verrucarin E,[497] heteroaryl C-glycosides,[506] 7-azabicyclo[2.2.1]heptanes,[500] 4-acylindoles,[481] fluorinated insecticidal pyrroles,[507] hapalindole Q,[485] lyngbyatoxin A analogs,[498,508] uroporphyrinogen-octanitriles[499]).

3-Bromo-*N*-TIPS-pyrrole can be cross-coupled with Grignard reagents under Pd(II) catalysis to produce 3-alkyl- or 3-aryl-*N*-TIPS-pyrroles.[509]

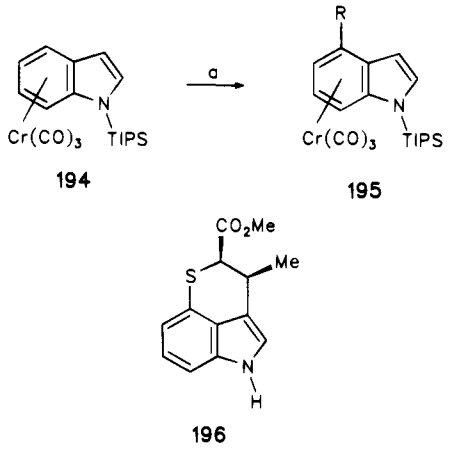
3-(Perfluoroalkyl)pyrrole was obtained by radical substitution in *N*-TIPS-pyrrole, while *N*-TMS-pyrrole gave mostly 2-substitution.[494]

3-Substituted *N*-TIPS-pyrroles are of interest as monomers for electrically conducting polymeric materials (electrode coatings).[484,493,496,510] In this connection pyrrole radical cations were studied by fast-scan cyclic voltammetry. It was found that a N-TIPS group enhances the lifetime of these radical cations (compared to the free pyrrole radical cations) by a factor of 8−13.[511]

Surprisingly, reaction of *N*-TIPS-pyrrole with the azo ester $H_2C{=}C(CO_2Et)N{=}NC_6H_3$-2,4-$(NO_2)_2$ resulted in a 2-substituted rather than a 3-substituted TIPS-pyrrole. This product was rationalized as resulting from a Diels−Alder reaction of the azoester acting as diene and the pyrrole as dienophile.[512]

In indoles *N*-TIPS protects positions 2 and 7 efficiently, as studied by Widdowson (Scheme 71).[479,490,492] Thus the tricarbonylchromium complex

Scheme 71[a]



[a] (a) (1) ^{n}BuLi, TMEDA, THF; (2) RX.

of *N*-TIPS-indole **194** was lithiated with ^{n}BuLi/TMEDA and then treated with electrophiles to provide 4-substituted products **195**. In particular, no 2- or 7-substituted products were found.[483] TIPS is more effective in this respect than TBDMS.[479] Transmetalation of the Li intermediates with $CuBr{\cdot}Me_2S$ is possible.[505] This chemistry was used for the synthesis of chuangxinmycin methyl ester **196**.[492]

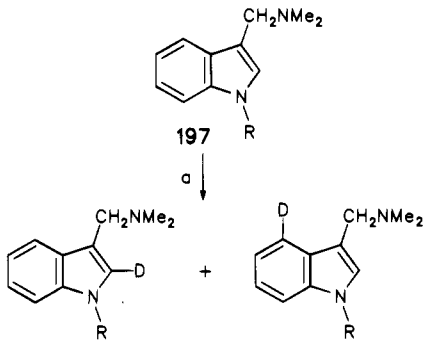
Similarly, addition of a nucleophile such as $LiCMe_2$-CN to the $Mn(CO)_3^+$ complex of *N*-TIPS-indole occurred in position 4 exclusively (position 4/position 7 ratio >10), while the corresponding *N*-Me and *N*-tosyl complexes gave a ratio of 2, *N*-TBDMS of 5.[513]

The TIPS group in *N*-TIPS-3-nitropyrrole does not completely prevent conjugate addition of a Grignard reagent in position 2, although the reaction proceeds less easily than in the corresponding thiophene.[489]

Similarly, N-TIPS does not prevent electrophilic 2-substitution in the pyrrole system, if this is an intramolecular reaction.[488]

Methyl-protected gramine (**197**, R = Me) is lithiated in position 2 (directed lithiation, Scheme 72).

Scheme 72[a]



[a] (a) (1) ^{t}BuLi, Et_2O, 1 h; (2) MeOD, −78 °C.

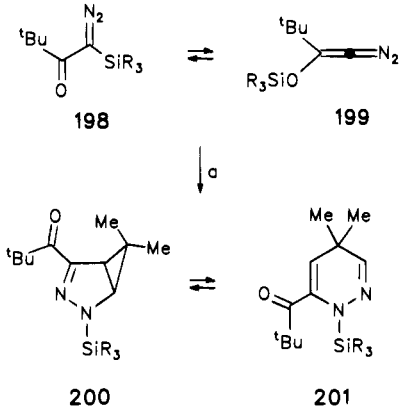
R	2-D-197	4-D-197
Me	93%	–
TIPS	–	88%

On the other hand, the N-TIPS analog is lithiated almost exclusively in position 4.[480]

The extremely electron-rich potentially antiaromatic *N,N'*-bis(TIPS)-1,4-dihydropyrazine can be prepared from pyrazine, K metal, and TIPS-Cl in THF.[36] TIPS shields the reactive N–Si bonds efficiently. This bis(silyl)dihydropyrazine is only slightly sensitive to oxidation by air, in contrast to the pyrophoric TMS analog. The dihydropyrazine ring is planar in the crystal.[36] The compound is reversibly one-electron oxidized in cyclic voltammetry. It can be oxidized by TCNE or TCNQ to produce long-lived cation radical/anion radical pairs which can easily be observed by ESR spectroscopy at room temperature. The analogs having TBDMS, TES, and TMS groups are less persistent.[514]

Acyl-TIPS-diazomethanes **198** thermally cycloadd to cyclopropenes to give mixtures of *N*-TIPS-homopyrazoles **200** and *N*-TIPS-1,4-dihydropyridazines **201**, probably via a diazo TIPS enol ether **199** (Scheme 73).[431] The products are in equilibrium via a 1,2

Scheme 73[a]



[a] (a) 3,3-Dimethylcyclopropene, Et_2O, 90 °C, pressure.

	equilibrium composition ($CDCl_3$, 35 °C)	
SiR_3	**200**	**201**
TBDMS	52	48
TBDPS	30	70
TIPS	>97	3

N→N silyl migration. Since in **201** there is a strong unfavorable interaction between the acyl and silyl groups, the equilibrium composition depends on the bulk of the substituents on Si. By this measure TBDMS and TBDPS were found less bulky than TIPS.

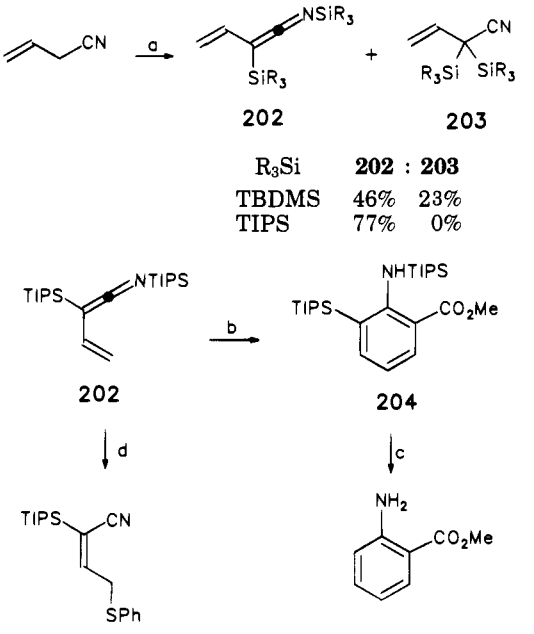
D. Miscellaneous *N*-TIPS Compounds

N-Silyl ketenimines including the TIPS derivative were prepared by silylation of the Li derivatives of nonenolizable ketenimines with R_3SiCl.[515] These compounds are easily hydrolyzed to the ketenimine, more slowly when the groups on Si are more bulky. From their electronic spectra (yellow oils or yellow solids) a bent structure for C=NSi was infered.

1,3-Bis(TIPS)carbodiimide, a pink oil, was obtained by triisopropylsilylation of calcium cyanamide with TIPS-F in HMPA,[47] by photorearrangement of 1,3-bis(TIPS)nitrilimine,[516,517] or by Sn/Si exchange (TIPS-Cl) in 1,3-bis(Me_3Sn)carbodiimide.[518]

N,α-Bis(TIPS)alkenylketenimines (**202**) were easily obtained by bis-lithiation/bis-silylation of allyl cyanides using LDA and TIPS-Cl (Scheme 74).[469] In

Scheme 74[a]



[a] (a) (1) LDA; (2) R_3Si-Cl. (b) HC≡C–CO_2Me, 150 °C, 4 h. (c) (1) KF, MeOH, reflux; (2) F_3CCO_2H, CCl_4, heat. (d) PhSCl.

contrast, use of TBDMS-Cl resulted in a mixture of this type of product and α,α-bis(TBDMS)allyl cyanide (**203**). This is as expected for silyl groups of varying bulk. The ketenimines are useful dienes for highly regioselective Diels–Alder reactions with acetylenic esters or α,β-unsaturated esters to give substituted anilines **204** or dihydroanilines, and with quinones to provide annulated anilines.[28,469,519]

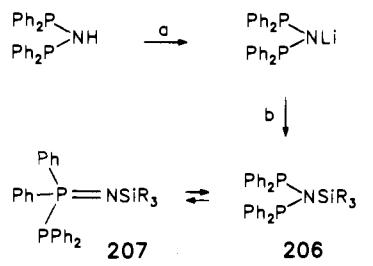
Unsubstituted *N*,α-bis(TIPS)vinylketenimine (**202**) adds PhSCl to provide the N-unsubstituted (*E*) substituted acrylonitrile **205**.[35]

The TIPS group was used to provide general stabilization for otherwise unstable classes of compounds. Thus the (*N*-TIPS-imino)phosphane Me_5C_5P=N-TIPS was obtained as a distillable liquid by elimination of HCl from Me_5C_5PCl–NHTIPS by LiN(TMS)$_2$.[467] The Me_5C_5 could be exchanged by reaction of the iminophosphane with 2,4,6-tri-*tert*-butylphenyl-lithium to give the corresponding tri-*tert*-butylphenyl iminophosphane without affecting the N=P bond.

When the Li salt of $(Ph_2P)_2NH$ is treated with TMS-Cl or TES-Cl, normal silylation to the silylamine $(Ph_2P)_2$N-TMS or -TES **206** is observed (Scheme 75). The bulky TIPS-Cl, on the other hand, results in an equilibrium mixture of the *N*-TIPS-amine and the isomeric TIPS-N=P(Ph)$_2$-PPh_2 **207**, due to steric crowding in the former.[520]

The Li salt of TMS-CHN_2 **208** (R_3Si = TMS) reacts with TMS-Cl to produce the disubstituted diazomethane $(TMS)_2CN_2$ **209** (Scheme 76). Triisopropylsilylation of the Li salt of TIPS-CHN_2 **208** (R_3Si = TIPS), on the other hand, results in bis(TIPS)-nitrilimine (TIPS–C≡N^+–N^-–TIPS, **210**), a distillable liquid.[516,517,677] Distinction between the two types of structure is easily made using ^{14}N NMR spectroscopy.[521] Other *N*-TIPS-nitrilimines were pre-

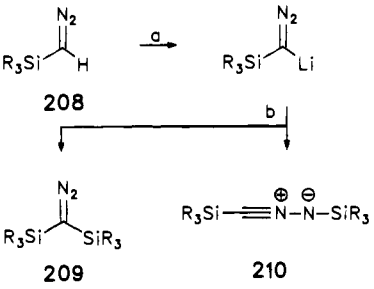
Scheme 75[a]



[a] (a) ^{n}BuLi, PhH/hexane. (b) R_3Si-Cl, THF.

SiR_3	206	: 207
TMS	sole product (80%)	–
TES	sole product	–
TIPS	mixture of products	

Scheme 76[a]



[a] (a) BuLi, DB-18-C-6,THF/hexane, −90 °C. (b) R_3Si-Cl.

R_3Si	209	: 210
TMS	sole product (46%)	–
TIPS	–	80%

pared similarly.[522] Bis(TIPS)nitrilimine and a *C*-TIPS-*N*-germylnitrilimine can be prepared from $(Me_3Sn)_2CN_2$ and TIPS-Cl[523] and from $(Me_3Sn)CN_2$(TIPS), respectively.[524] The 1,3-dipolar nitrilimines cycloadd to typical dipolarophiles to give 5-membered N-heterocycles.[525] Photolysis of nitrilimines gives the isomeric carbodiimides.[516,517] Thermally several nitrilimines rearrange to the more stable diazo isomers, but those bearing TIPS on N do not. The chemistry of nitrilimines was recently reviewed.[526,677]

VI. C-TIPS Compounds

A. TIPS Alkanes

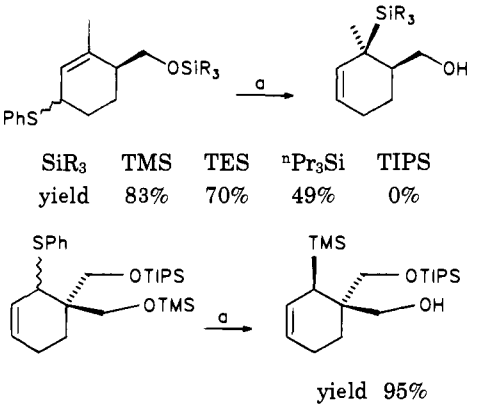
^{n}BuLi as expected is silylated by TIPS-Cl.[527] However, organolithiums bearing Li at an unactivated saturated carbon atom are often not available by deprotonation due to low acidity. Corresponding silanes can be prepared if the organometallic is made by another route, e.g. by reductive cleavage of a C−S bond[528] or by Sn/Li exchange.[529] Triisopropylsilylation on carbon occurs by intramolecular O→C Si migration in these examples.

TIPS alkanes are inert toward *m*-CPBA and PCC oxidation.[530]

Dichlorocarbene inserts into the Si−H bond in TIPS-H to give TIPS-$CHCl_2$.[48] Such silyl dihalogenomethanes are useful C_1 building blocks, they can be obtained alternatively by metalation and silylation of dihalomethanes.[531]

Desulfurization/Si migration (and desulfurization/silylation) routes similar to the above were used for preparation of allylsilanes from allyl phenyl sulfides bearing a silyloxy group, but TIPS did not migrate in contrast to all other R_3Si studied (Scheme 77).[201]

Scheme 77[a]



SiR_3	TMS	TES	$^n Pr_3Si$	TIPS
yield	83%	70%	49%	0%

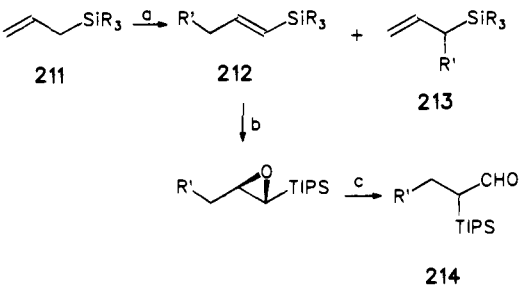
yield 95%

[a] (a) (1) LiDBB, THF, −78 °C; (2) H_2O.

Allyl-TIPS was obtained from allyl-MgCl and TIPS-OT[532] or TIPS-Cl.[533] The allyl α/γ-substitution problem was addressed using TIPS.

Allyl-TIPS **211** (SiR_3 = TIPS, Scheme 78) was

Scheme 78[a]



[a] (a) (1) ^{n}BuLi, TMEDA, hexane; (2) R'-I, −80 °C. (b) *m*-CPBA. (c) Silica gel, PhMe, reflux.

SiR_3	R'	212 : 213	
TMS	^{n}Pr	2	1
TIPS	^{n}Pr	17.4	1
TIPS	^{n}Bu	99	1

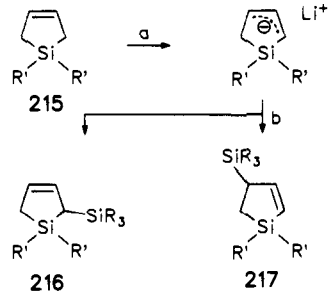
metalated by ^{n}BuLi/TMEDA, treatment then with alkyl halides gave the (*E*)-γ-products **212** with high selectivity (γ/α ≥ 17), which is better than the corresponding reactions with allyl-TMS **211** (SiR_3 = TMS).[532] The products **212** were epoxidized, and the α-TIPS epoxides rearranged to α-TIPS aldehydes **214**.

Allyl-TIPS (like a simple alkene) could be ω-nitrated by treatment with $NaNO_2$, $Ce(NH_4)_2(NO_3)_6$ and HOAc in $CHCl_3$, presumably by addition of $NO_2^{\bullet}$, followed by oxidation and loss of a proton.[534]

An allylic silyl group was introduced into a silacyclopentene **215** by lithiation (^{t}BuLi) and treatment with a silyl triflate or chloride (Scheme 79). The γ/α-selectivity of the reaction is generally low for many but the smallest electrophiles and does not depend on the electrophile's size in a consistent manner.[535]

Silyl groups of varying size were used as tools to shed some light on the mechanism of the diastereoselective addition of allylboronates to α-methylbutyraldehyde (Scheme 80).[536] Thus from allylsilanes by lithiation and borylation the (*E*)-γ-silyl-substituted allylboronates **218** were prepared with R_3Si = TMS, TES, TIPS. No α-substitution was found. In their

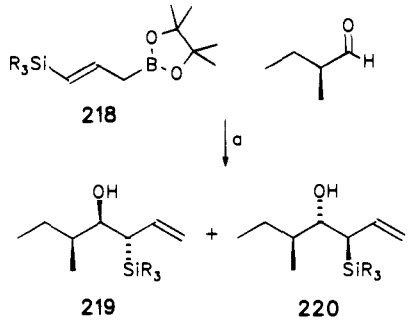
Scheme 79[a]



[a] R' = C_6H_4-4-^{t}Bu. (a) ^{t}BuLi,THF/HMPA, −78 °C. (b) R_3Si-X.

R_3Si	X	216 : 217	
TMS	OTf	1.3	1
TIPS	OTf	1	1.3
TMS	Cl	1	1.2
TIPS	Cl	1.4	1

Scheme 80[a]



[a] (a) Room temperature, 3−4 days.

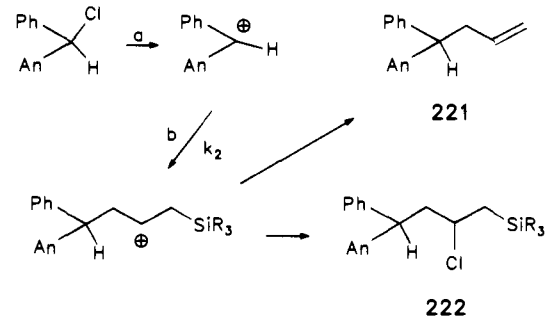
SiR_3	219 : 220	
TMS	73	27
TES	74	26
TIPS	72	28
(^{t}Bu)	75	25
(Me)	77	23

reactions with α-methylbutyraldehyde, surprisingly, the size of the silyl group was found to have no effect on the diastereoselectivity. This result was rationalized using force field calculations of the cyclic transition state: Even a (*E*)-γ-Me group on the boronate sufficiently interacts with the ethyl group in the aldehyde to disfavor certain transition state conformations to the point that these do no longer contribute significantly to the overall diastereoselectivity. A larger group then has no further effect.

The efficiency of the photoreaction of allylsilanes with 1,4-dicyanobenzene to produce 4-allylbenzonitriles drops off in the series allyl-TMS (Φ = 0.223), allyl-TES (0.180), allyl-TBDMS (0.055), allyl-TIPS (0.040).[537] The reaction is thought to procede via a free allyl radical which is formed from an allylsilane radical cation and a nucleophile. The trend in the quantum yields thus reflects the difficulty of attack of a nucleophile to Si in bulky silanes.

The chemistry of allylsilanes is dominated by their reaction with electrophiles to give allyl compounds with loss of the silyl group from a carbenium intermediate.[402,538] The nucleophilicity of allylsilanes (various silyl groups) was measured in their reaction with a diarylcarbenium ion (Scheme 81).[533,539] While TMS- and TES-allylsilanes gave the "substitution products" **221**, TBDMS- and TIPS-allylsilanes gave

Scheme 81[a]



[a] An = 4-MeO-C_6H_4. (a) BCl_3,CH_2Cl_2, −78 °C. (b) Allyl-SiR_3, −78 °C.

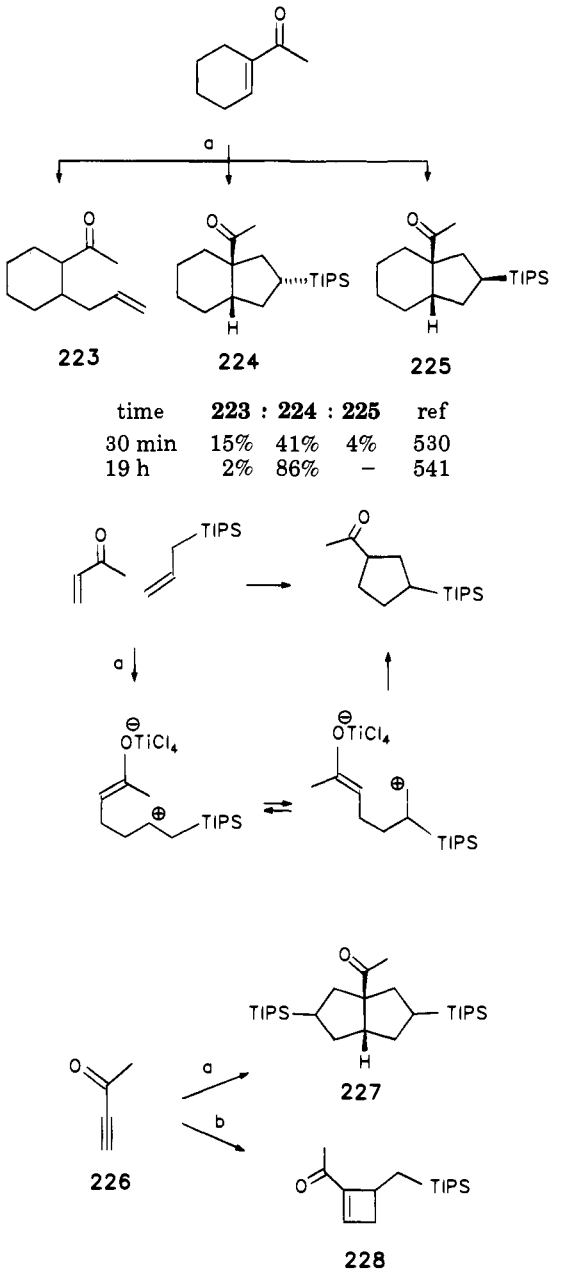
SiR_3	221 : 222		rel k_2
TMS	100	0	187
TES	100	0	313
TPS	60	40	3.21
TBDMS	0	100	204
TIPS	0	100	439

"addition products" **222**, due to hindered attack of the nucleophile Cl^- at Si in the latter cases. The rate-determining step is, however, the reaction between carbenium ion and allylsilane, and a good straight line was obtained in a plot of log k_2 *vs* the sum of Taft's inductive substituent constants σ_I for the three groups on Si. This was interpreted to indicate that the reactivity (nucleophilicity of allylsilanes) is determined mostly by the polar effect of the Si groups. However, the same data were interpreted in terms of both polar and steric effects by a different research group,[17] and it was concluded that the θ values (cone angles) derived previously for PR_3 are a good measure for the steric effect of $-SiR_3$ as well.

The reaction of allyl-TMS with α,β-enones in the presence of Lewis acidic chlorides is known to result in conjugate allylation (→ **223**, Scheme 82, Sakurai reaction), which includes a nucleophilic attack at Si. Silicon-containing byproducts of such reactions originally assigned (silylmethyl)cyclobutane structures are in fact silylcyclopentanes.[540] These byproducts can be made synthetically useful major products simply by changing from allyl-TMS to allyl-TIPS, since TIPS is less easily attacked by nucleophilic Cl^- as required for the Sakurai reaction.

Thus, allyl-TIPS reacts with α,β-enones under the influence of $TiCl_4$ to provide access to cyclopentanes **224/225** in high yield and stereoselectivity (Scheme 82).[530,541,542] The reaction is thought to proceed by Michael addition, cationic 1,2-silyl shift, and cyclization. A cyclic transition state model was proposed, in which the silyl shift proceeds via a siliranium ion (pentavalent Si).[540] This reaction works in the TBDMS, TBDPS, TPS, ^{i}Pr$_2$PhSi, and (best) TIPS series. The requisite allylsilanes can be obtained by metalation using ^{n}BuLi/KOtBu, e.g. from (*Z*)- and (*E*)-2-butene.[542] This annulation method is valuable for the synthesis of condensed and spirocyclic ring systems containing two contiguous quaternary carbon centers.[543] If an ynone starting material such as **226** is used, the reaction proceeds twice forming a 1-acetyl-3,7-bis(TIPS)bicyclo[3.3.0]octane (**227**) as a mixture of three diastereomers.[544] The reaction course is, however, highly dependent on the nature of the Lewis acid. Thus **226** and allyl-TIPS in the presence of ZnI_2

Scheme 82[a]



[a] (a) Allyl-TIPS, $TiCl_4$, CH_2Cl_2, −25 °C. (b) Allyl-TIPS, ZnI_2, CH_2Cl_2.

provide mostly 1-acetyl-4-(TIPS-methyl)cyclobutene (**228**).[545]

α,β-Unsaturated esters and α,β-unsaturated lactams undergo the same reaction, providing both silylcyclopentanes and (silylmethyl)cyclobutanes depending on the temperature.[546,547] The 5-membered ring products seem to be the thermodynamically more stable.

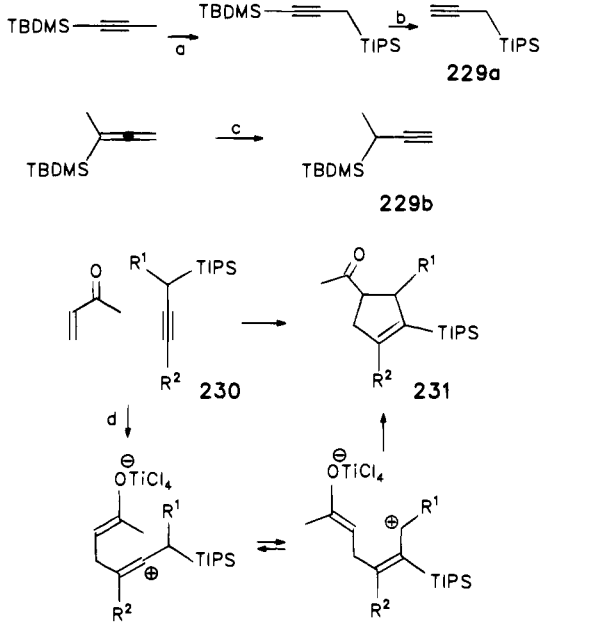
If the electrophile attacked by allyl-TIPS is a benzylic cation, then a 5- or 6-membered ring annulation results.[548]

In an intramolecular version of this reaction principle an open-chain acetal complexed to a Lewis acid was used as the electrophile, resulting in 6- or 7-ring formation. Interestingly different stereoselectivities in the cyclization step depending on TMS or TIPS were observed, although in the final step the silyl group is lost in this reaction.[549]

For a similar reaction of vinylsilanes see the section on TIPS alkenes.[550]

Propargylsilanes **229** can be obtained from alkynes by silylation of the propargylic lithium derivatives or by isomerization of allenylsilanes (Scheme 83).[9,530]

Scheme 83[a]



[a] (a) (1) ^{t}BuLi,THF, −78 °C, 2 h; (2) TIPS-Cl. (b) $AgNO_3$, KCN, H_2O/EtOH. (c) 1.5 equiv of ^{n}BuLi, Et_2O. (d) $TiCl_4$, CH_2Cl_2, −78 °C.

The chemistry of propargylsilanes has been reviewed.[538]

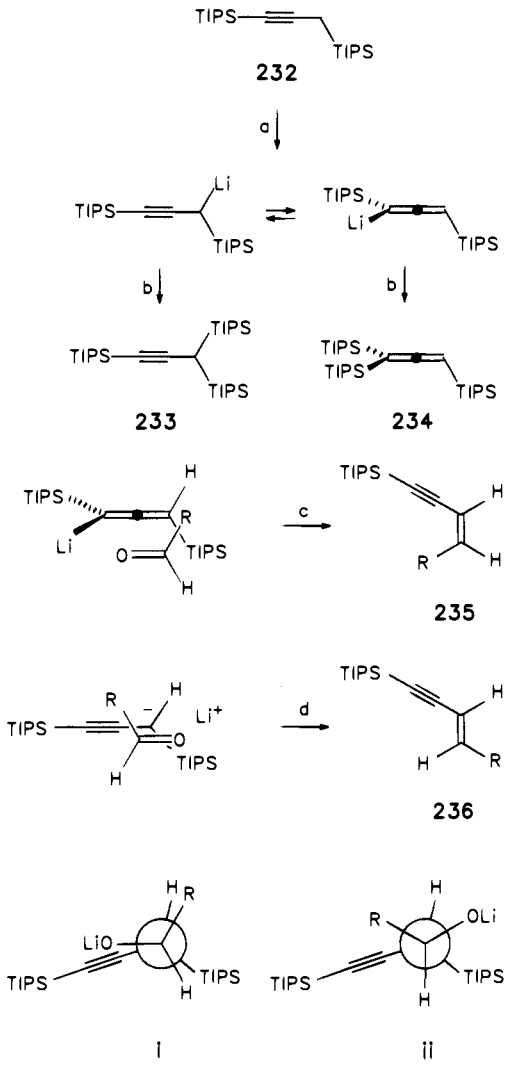
Propargyl-TIPS compounds **230** react with α,β-enones in the presence of Lewis acids ($TiCl_4$) to provide cyclopentenes **231** in a reaction similar to the above.[530]

The Li derivative of 1,3-bis(TIPS)propyne (**232**, Scheme 84) in THF is an equilibrating mixture of propargylic and allenic species. Thus on quenching with TIPS-OTf a mixture of tris(TIPS)propyne (**233**) and tris(TIPS)allene (**234**) (1:8) was obtained.[43] However, in its Peterson reaction with aldehydes it behaves like a propargylic anion to produce enynes **235/236**.[9] The propargylic TIPS is an important stereodirecting control element. Thus either *Z*- or *E*-enynes can be obtained at will, depending on the reaction conditions (in THF **235** via i, in THF/HMPA **236** via ii, Scheme 84). Replacement of this group by e.g. TBDMS or TMS results in reagents of lower stereoselectivity. The method was employed by Overman in the syntheses of gephyrotoxin and laurenyne.[551,552] The TIPS group on the acetylenic carbon is essentially a protective group, it can be replaced by TMS without loss of stereoselectivity.[553,554] The use of **232** and similar reagents was reviewed recently,[272] as was the chemistry of silylated dienes and enynes.[555]

Benzylsilanes are obtained by silylation of benzyllithium or benzylmagnesium halides.

Benzylsilanes can be obtained from dicyanostyrene and disilanes in a photoinduced electron transfer reaction. Interestingly, if the disilane is unsymmetric, e.g. TMS-TIPS, the more bulky silyl group is

Scheme 84[a]



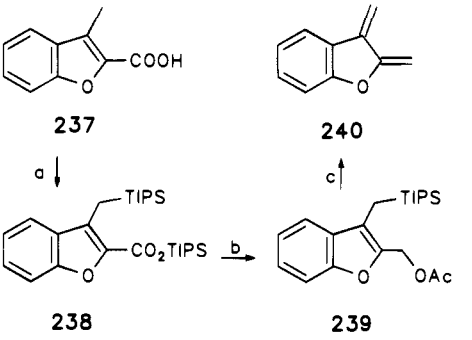
[a] (a) ^{n}BuLi, THF, −20 °C. (b) TIPS-OTf, −78 °C. (c) THF. (d) THF/HMPA.

incorporated (e.g. 30:1 preference for TIPS over TMS). This can be understood in terms of attack of a nucleophile at the disilane cation radical, liberating the more bulky silyl radical.[556]

A series of benzylsilanes was one electron oxidized in MeCN, and the decay of the resulting benzylsilane radical cation was observed by laser flash photolysis.[557] The rate data obtained were rationalized by assuming attack of a nucleophile (solvent MeCN or an added alcohol) on the Si atom in the radical cation resulting in C−Si cleavage. The lifetime of the TIPS-substituted radical cation was found to be *ca.* 1000 times longer than that of the TMS compound. The corresponding TES radical cation possesed a lifetime intermediate between these two albeit closer to the TMS value. Similar conclusions were drawn from a study of benzylsilane oxidation by $K_5[Co^{III}W_{12}O_{40}]$ in $AcOH/H_2O$.[558] While for the TMS compound the electron transfer is rate determining, for the TIPS compound the desilylation step is slowest.

A valuable diene, benzofuran-2,3-xylylene **240**, was obtained by fluoride induced 1,4-elimination from the corresponding benzylic TIPS compound **239** (Scheme 85).[441] Compound **239** was obtained by lithiation (LDA) and silylation (TIPS-Cl) of 3-methylbenzofuran-2-carboxylic acid **237** followed by reduction and acetylation. The intermediate bis(TIPS) compound **238** is isolable, whereas the TMS and TBDMS analogs were easily hydrolyzed.

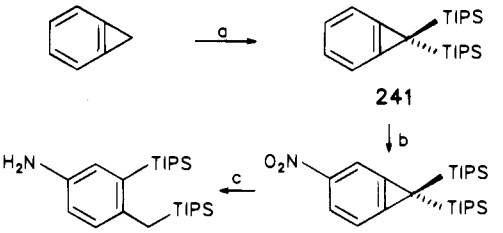
Scheme 85[a]



[a] (a) (1) LDA,THF; (2) TIPS-Cl. (b) (1) $LiAlH_4$,Et_2O; (2) Ac_2O, DMAP,CH_2Cl_2. (c) $^{n}Bu_4NF$, THF/MeCN.

A cyclopropabenzene **241** bearing two geminal TIPS groups on the apical cyclopropene C was synthesized from cyclopropabenzene by double lithiation/silylation (Scheme 86).[559,560] The cyclopropene

Scheme 86[a]



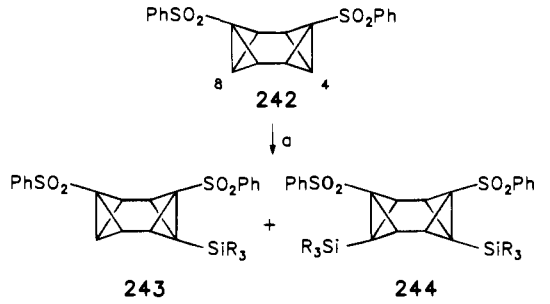
[a] (a) (1) ^{n}BuLi; (2) TIPS-Cl; (3) repeat. (b) 67% HNO_3. (c) Zn/NaOH.

ring in this compound is extremely inaccessible for a reagent, e.g. unlike that in cyclopropabenzene it does not open under the influence of electrophiles or acids. Therefore **241** is stable and behaves like a typical arene giving substitution reactions in the 6-membered ring, e.g. with 67% HNO_3 at position 3. The 3-nitro derivative behaves as a nitroarene. However, by Zn in NaOH the 3-membered ring is reductively opened, with concomitant migration of one TIPS group.

Cyclopropyl-TIPS can be obtained by Si migration to a cyclopropyllithium made by destannylation.[529]

(*Z*)-3,7-Bis(phenylsulfonyl)octabisvalene **242** can be lithiated at the 4 and 8 positions, subsequent silylation gives the 1-silylbicyclo[1.1.0]butanes **243** and **244** even for SiR_3 = TIPS (Scheme 87).[561]

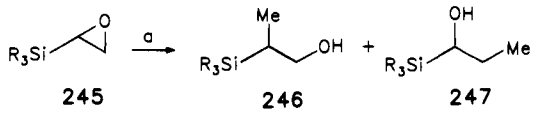
Scheme 87[a]



[a] (a) (1) ^{n}BuLi; (2) R_3Si-Cl or R_3Si-OTf.

The regioselectivity of the opening of α-silyl epoxides **245** by organocopper reagents is strongly influenced, as expected, by the size of the silyl group, as well as by reagent and conditions. Thus while TMS epoxides react cleanly at the α-C (→ **246**, Scheme 88), TIPS-oxirane reacts with $Me_2CuLi{\cdot}BF_3$

Scheme 88[a]



245 **246** **247**

[a] (a) $Me_2CuLi{\cdot}BF_3$, Et_2O.

R_3Si	**246** : **247**	
TES	76	24
TBDMS	34	66
TIPS	0	100

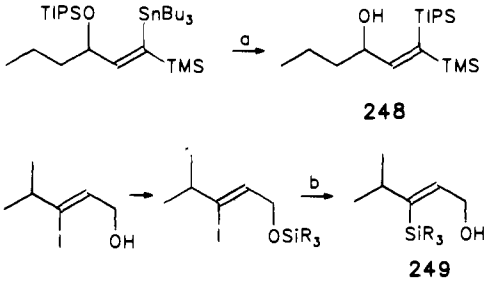
in ether at the β-C exclusively (→ **247**).[562] Both types of products can thus be obtained selectively. They are valuable precursors for stereodefined alkenes (oxidation, addition of an organometallic, and Peterson elimination), and for acylsilanes (oxidation of **247**), respectively.

B. TIPS Alkenes

Vinyllithium was silylated by TIPS-Cl, whereas vinylmagnesium bromide did not react.[527]

The intramolecular TIPS transfer to an organolithium works well for vinyllithiums generated from the corresponding stannane[529] or by Hal/Li exchange in vinyl iodides (Scheme 89).[563] By these methods

Scheme 89[a]



248 **249**

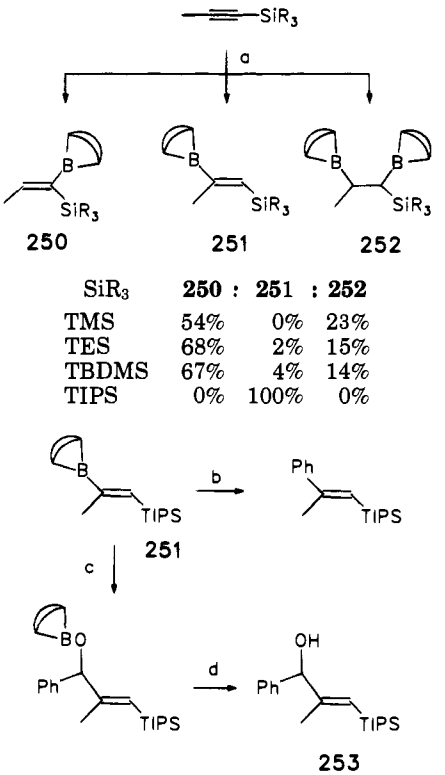
[a] (a) MeLi,THF. (b) (1) ^{t}BuLi, THF; (2) H_2O.

γ-TIPS-allyl alcohols such as **248**/**249** were obtained.

Vinyl-TIPS was regioselectively hydroborated by 9-BBN to produce, after oxidation, 2-TIPS-ethanol.[527] The 1-isomer was prepared from 1-TIPS-1-methoxyethene by acid hydrolysis and reduction.

Vinyl-TIPS compounds can be prepared from TIPS-acetylenes by addition of a reagent across the triple bond. 1-TIPS-propyne is hydroborated by 9-BBN to the (*Z*)-2-boryl-1-propenylsilane **251** (SiR_3 = TIPS) in excellent regio- and stereoselectivity, no regioisomer **250** or bisadduct **252** is formed (Scheme 90).[564] The TMS, TES, and TBDMS analogs preferentially lead to **250** along with some **252**. The boryl group in **251** (SiR_3 = TIPS) is cleanly replaced by an aryl or vinyl group (retention of configuration) by the Suzuki reaction (aryl bromide, cat. $Pd(PPh_3)_4$, OH^-).[565] The same borane reacts with an aromatic aldehyde to provide the secondary γ-TIPS allylic alcohol **253** after removal of the boryl group.[566]

Scheme 90[a]



250 **251** **252**

SiR_3	**250** :	**251** :	**252**
TMS	54%	0%	23%
TES	68%	2%	15%
TBDMS	67%	4%	14%
TIPS	0%	100%	0%

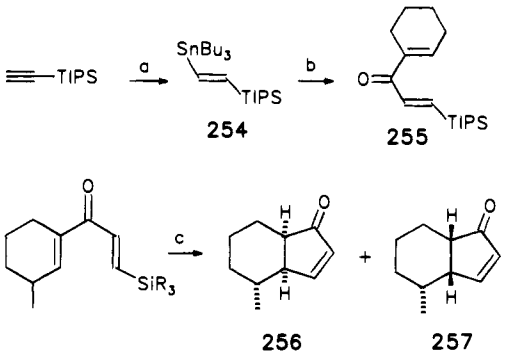
253

[a] (a) 9-BBN, 90 °C, 1 h. (b) PhBr, catalyst $Pd(PPh_3)_4$, NaOH, THF. (c) PhCHO, 110 °C. (d) H_2N-C_2H_4-OH.

In hydroboration of 1-silyl-3-phosphoramidopropynes likewise, a TIPS group in contrast to a TMS directs the boron away from itself.[567]

^{n}Bu$_3$SnH adds to TIPS-acetylene to give 1-stannyl-2-TIPS-ethene **254** (Scheme 91).[568] Sn/Li exchange

Scheme 91[a]



254 **255** **256** **257**

[a] (a) ^{n}Bu$_3$SnH, AIBN, 120 °C. (b) (1) ^{n}BuLi, THF, −78 °C; (2) cyclohexene-1-carbaldehyde; (3) NiO_2, Et_2O. (c) $FeCl_3$ ("98%"), CH_2Cl_2.

SiR_3	**256** : **257**	
TMS	78	22
TIPS	90	10

produces the corresponding TIPS-vinyllithium which can be 1,2-added to an α,β-unsaturated aldehyde to provide after oxidation a β-TIPS divinyl ketone **255**. This is the substrate for the Si-directed Nazarov cyclization (cyclopentenone annulation, → **256**/**257**).[568,569]

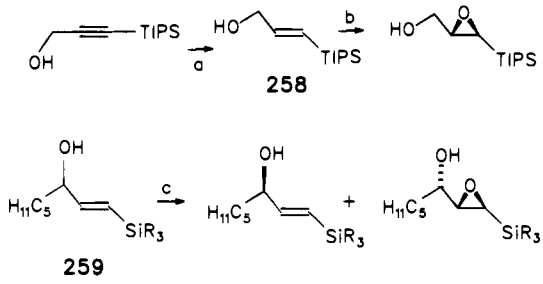
Partial hydrogenation of a TIPS-alkyne results in a TIPS-alkene.

TIPS-vinyllithium was added to a chiral hydrazone with excellent diastereoselectivity.[570]

Cyclopropyl ketones were obtained from the reaction of a silylselenylethene and an α,β-unsaturated ketone under Lewis acid influence, resulting in a Si-stabilized carbenium ion which subsequently cyclizes. In the case of the TIPS derivative, cyclization is prevented by steric bulk.[550]

A primary γ-TIPS-allyl alcohol, **258**, was epoxidized under Sharpless conditions in ≥ 98% ee (Scheme 92).[532] Racemic secondary γ-TIPS-allyl-alcohol **259**

Scheme 92[a]



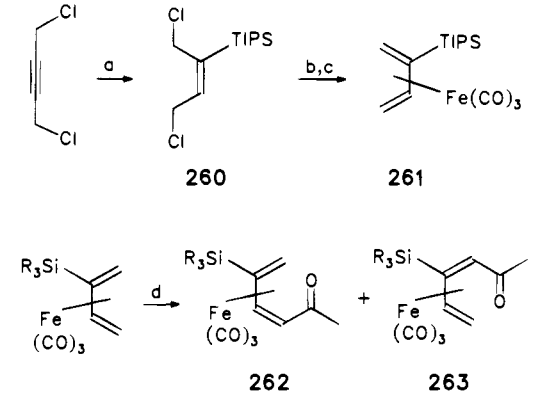
[a] (a) $LiAlH_4$,THF. (b) Sharpless epoxidation using (L)-(+)-DET. (c) ^tBuOOH, $Ti(O^iPr)_2DIPT$.

SiR_3	k_{fast}/k_{slow}
TMS	700
TIPS	300

when subjected to Sharpless epoxidation showed a less efficient kinetic resolution than the TMS analog, though the k_{rel} values for both are excellent.[571]

TIPS-alkenes can be obtained by hydrosilylation of a C≡C bond. Thus hydrosilylation of 1,4-dichloro-2-butyne (TIPS-H, H_2PtCl_6) gave the vinylsilane **260**, which was transformed into a 2-TIPS diene by dechlorination and further into the corresponding Fe-$(CO)_3$ complex **261** (Scheme 93).[64] This was Friedel–

Scheme 93[a]



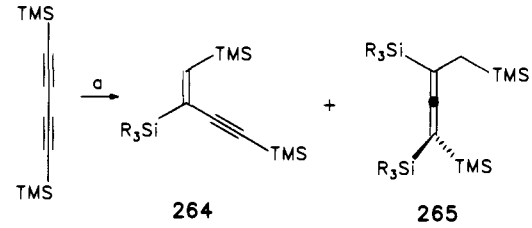
[a] (a) TIPS-H, H_2PtCl_6. (b) Zn, EtOH. (c) $Fe_2(CO)_9$, PhH, 50 °C. (d) CH_3COCl, $AlCl_3$, CH_2Cl_2.

R_3Si	**262**	: **263**
TES	6	1
TIPS	sole product	–

Crafts acylated in excellent yield, regio- and stereoselectivity (regioselectivity far better than for the corresponding TES compound). A second acylation, possible for the TES complex after *Z*/*E* isomerization, is completely suppressed by TIPS. The second acylation is, however, possible after reduction of the ketone to the hydrocarbon.[63]

Hydrosilylation of 1,4-bis(TMS)-1,3-butadiyne by TIPS-H/H_2PtCl_6 stops after one triple bond has reacted, to selectively provide (*E*)-2-TIPS-1,4-bis-(TMS)but-1-en-3-yne **264** (R_3Si = TIPS, Scheme 94).

Scheme 94[a]



[a] (a) 3–4 equiv of R_3Si-H, 0.2 mol % H_2PtCl_6.

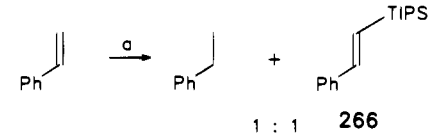
R_3Si	temp, °C	time, h	**264** : **265**
TMS	100	2	40%[†] 46%
TES	80	0.5	0% 100%
TIPS	90	8	92% 0%

[†] Reagent TMS-H was consumed by formation of $(TMS)_2$.

Further reaction is prevented probably by steric crowding, in that a complex of **264** (R_3Si = TIPS) and Pt cannot form, or cannot add a second TIPS-H. Smaller silyl groups do give bisadducts **265**.[61,62]

(*E*)-β-TIPS-styrene (**266**) was unexpectedly obtained as the only Si-containing product on attempted hydrotriisopropylsilylation of styrene, while use of TES-H produced the expected silylphenylethanes (Scheme 95).[57,58] $^tBu_3SiH$ did not react.

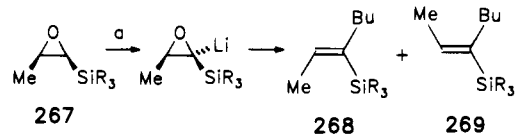
Scheme 95[a]



[a] (a) TIPS-H, 0.1 mol % $RhCl(PPh_3)_3$, 100 °C.

Vinylsilanes containing a new CC bond are obtained from *cis*-epoxysilanes **267** by a reductive alkylation effected by excess RLi. The product stereochemistry is completely reversed in going from TES (*Z*-selective, → **268**) to TIPS (*E*-selective, → **269**, Scheme 96).[572] The process is thought to proceed via

Scheme 96[a]



[a] (a) 4 equiv of ^nBuLi, 1,2-dimethoxyethane.

SiR_3	**268** : **269**
TES	92 8
TIPS	1 99

deprotonation a to Si, α-elimination, addition of RLi, and elimination of Li_2O. In an intermediate, rotation around the central CC bond can occur, and will do so if this results in relief of strain between a bulky silyl and the originally *cis*-alkyl group. The TIPS compound gives high yields consistently, whereas the smaller silyl groups in a side reaction are attacked at Si (TMS by ^nBuLi, TES by MeLi).

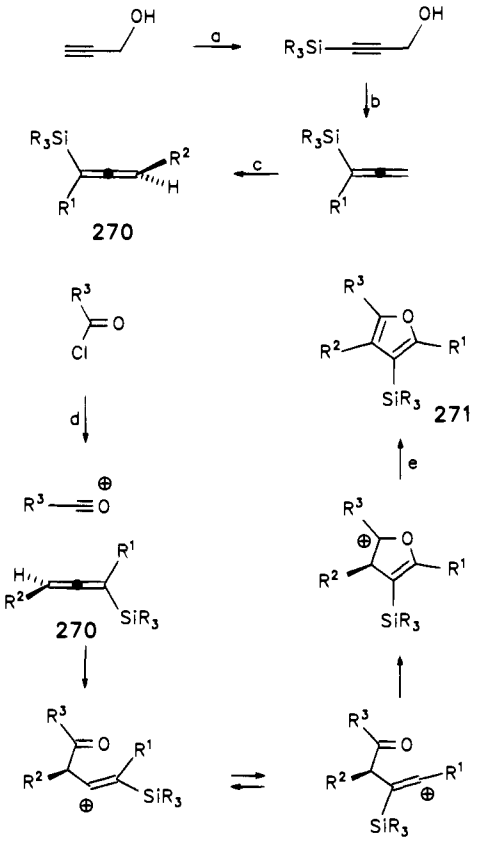
Vinylsilanes (and allylsilanes) were subjected to the Sharpless asymmetric dihydroxylation. The ee values of the product α-silyl vicinal diols varied considerably, in most cases being disappointingly low, and TIPS compounds gave lower ee's than TMS or TES analogs.[573] α-Silyl diols can be transformed into acetonides under acid catalysis for the TIPS, but not for the TMS case.

Silylated α-*exo*-methylene β-lactones can be prepared by a hydrosilylation/ cyclocarbonylation from a propargyl alcohol, CO, a silane, a tertiary amine, and $Rh_4(CO)_{12}$. The TIPS compound is formed less efficiently than the TBDMS or TES analogs.[574]

For *N*,α-bis(TIPS)vinylketenimine **202** see Scheme 74.

Allenylsilanes are starting materials in a useful synthesis of furans **271** developped by Danheiser (Scheme 97).[575] He prepared 1-mono- and 1,3-disub-

Scheme 97[a]



[a] (a) (1) 2 equiv of EtMgBr, THF; (2) 1 equiv of R_3Si-Cl; (3) H_2O. (b) (1) MeMgCl, THF; (2) MsCl; (3) R^1MgCl, CuBr, LiBr, THF. (c) (1) ^{n}BuLi, THF; (2) R^2X. (d) $AlCl_3$, CH_2Cl_2, −20 °C. (e) Et_3N.

stituted 1-allenylsilanes (e.g. **270**) by C-silylation of propargyl alcohol, followed by mesylation, replacement by R^1-MgCl, and lithiation/alkylation using R^2-X. An 1-allenylsilane **270** containing TIPS or TBDMS adds to an acylium ion (obtained from an acid chloride and $AlCl_3$) at its position 3 (regiodirecting effect of the Si group). The Si then migrates to the positive charge at the central C atom, leaving behind a positive charge at the former 1-position, which forms a bond to the oxygen, resulting in cyclization.

This sequence does not work for R_3Si = TMS due to desilylation reactions, and if the allene's position 3 is unsubstituted (R^2 = H), TIPS is better than TBDMS, probably since TIPS shields the then free position 4 in the furan more efficiently. The TIPS group is cleaved from the furan by pyridinium poly(hydrogen fluoride).

C. TIPS Alkynes

TIPS is a good protective group for acetylenes. TIPS acetylenes were prepared from the Li salt of the alkyne and TIPS-OTf[9,576,577] or TIPS-Cl,[578] or from the alkynylmagnesium bromide and TIPS-Cl.[564,568]

The bis(bromomagnesio) derivative of propargyl alcohol reacts with 1 equiv TIPS-Cl under C-silylation to $TIPSC{\equiv}CCH_2OH$.[575] A TMS alkyne can be converted to the TIPS alkyne by successive treatment with MeLi and TIPS-OTf,[576] while the reverse is impossible, since C≡CTIPS does not react with MeLi.[579]

The bromozinc derivative of an acetylene, RC≡CZnBr, reacts slowly if at all with R_3Si-OTf in ether/THF at −40 °C.[385]

The relative rates of cleavage of PhC≡CTMS, PhC≡CTES, PhC≡CTIPS by aqueous methanolic alkali are 277:1:0.00074.[580] Of C≡CTMS, C≡CTES and C≡CTIPS only C≡CTMS is cleaved by 1 N NaOH in MeOH/THF 1/1 within a few minutes. C≡CTES also is cleaved by the same reagent after longer reaction or by K_2CO_3 in MeOH/THF 1/1, C≡CTIPS is unaffected by both these reagents.[581]

C≡CTIPS survives treatment with CF_3CO_2H/H_2O, K_2CO_3/MeOH, or MeLi,[579] or NaH,[582] whereby C≡CTMS is cleaved.[576,583-585] It survives short treatment with HF in $MeCN/CHCl_3$ (room temperature, 1 h, whereby O-TBDMS is cleaved), while it is cleaved by the same reagent during 24 h.[586]

C≡CTIPS further survives Swern oxidation,[586] ^{n}BuLi,[9,375,586] DIBA-H, PDC, $CBr_4/PPh_3/Zn$, *B*-bromocatecholborane,[587] and PPh_3.[23,586]

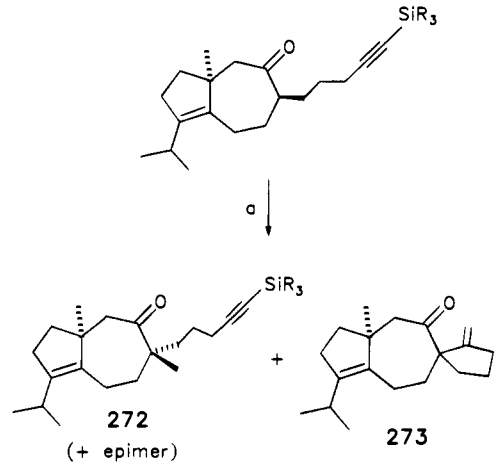
C≡CTBDMS is cleaved by KOH in THF/H_2O,[576] or by $AgNO_3$/KCN,[530] but like C≡CTIPS it survives H_2SO_4/CH_2Cl_2.[576]

Cleavage of TIPS from an acetylene by $^n Bu_4NF$ in THF is usually rapid (2 min at room temperature),[588] though a counterexample is known.[586] In a hexakis(TIPS-ethynyl) compound stepwise desilylation could be followed spectroscopically.[37] Although this deprotection is very reliable, some cases of target sensitivity to the conditions are known, resulting in decomposition.[589-591]

TIPS is generally superior to TMS as an acetylene protecting group, in that TMS being more easily cleaved can lead to side products derived from the free acetylene, such as the ene reaction product **273** instead of the expected alkylation product **272** in Scheme 98.[582,588,592,593]

The superiority of TIPS over TMS as acetylene protecting group was used in the synthesis of spectacular isolable polyynes by Vollhardt,[37,594] Tobe (1,10-bis(TIPS)decapentayne[595]), and Diederich.[23,38,576,581,584,587,589,590,596-600] TIPS-substituted polyynes are easily handled in solution, in contrast to their TMS or unsubstituted counterparts, in that the TIPS groups at the same time protect the C≡C bonds and enhance the solubility in common organic solvents. In the crystalline state the TIPS groups form an inert matrix, in which the C≡C bonds are embed-

Scheme 98[a]



[a] (a) NaH, MeI, DME.

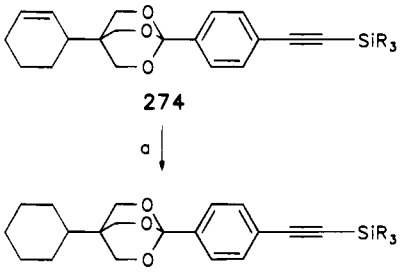
SiR_3	272 :	273
TMS	–	sole product
TIPS	60%	–

ded and thus prevented from polymerization, see e.g. Figure 7 in Diederich's recent review.[601]

TIPSC≡CBr is a useful reagent in such syntheses.[576,594,595] The differentially protected *cis*-enediyne TMSC≡CCH=CHC≡CTIPS was shown to be a useful building block for enediyne antibiotics.[583]

Shielding of a C≡C triple bond by TIPS is much more efficient than by TMS. Thus hydrogenation of the disubstituted olefinic C=C bond in **274** (SiR_3 = TIPS) was observed as the almost exclusive process, whereas the TMS analog was hydrogenated nonselectively at the C=C and C≡C bonds (Scheme 99).[602]

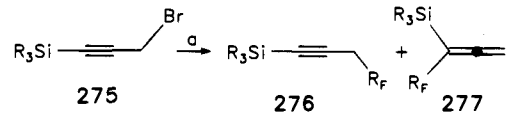
Scheme 99[a]



[a] (a) H_2, 5% Pt/C, EtOAc, NEt_3, 5.5 h.

While silylpropargyl bromide **275** (R_3Si = TMS) was attacked by R_FCu (R_F = C_6F_{13}) both at the propargylic site and at the silyl-bearing acetylenic C to give a mixture of products **276/277**, the corresponding TIPS compound **275** (R_3Si = TIPS) underwent attack at the propargylic site exclusively (Scheme 100).[603]

Scheme 100[a]

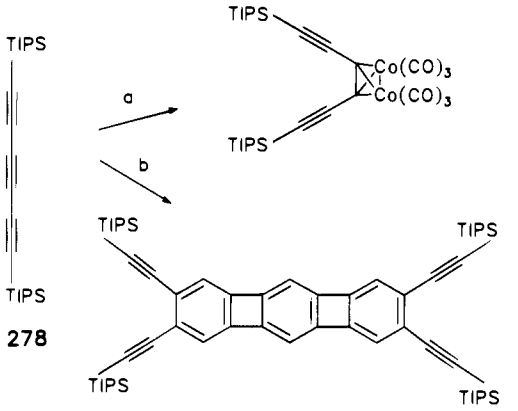


[a] R_F = C_6F_{13}. (a) R_FCu, DMSO.

R_3Si	276 :	277
TMS	1	1
TIPS	1	0

While a C≡CTMS group easily reacts with $Co_2(CO)_8$,[604] 1,6-bis(TIPS)hexa-1,3,5-triyne (**278**) both reacts with $Co_2(CO)_8$ and cycloadds 1,2,4,5-tetraethynylbenzene at the central rather than at the two terminal C≡C bonds (Scheme 101).[589,594,598] Tetra-

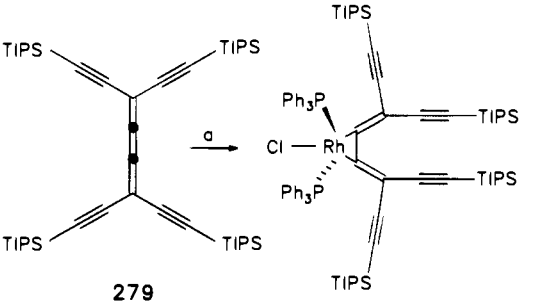
Scheme 101[a]



[a] (a) $Co_2(CO)_8$, *n*-hexane, 25 °C, 12 h. (b) 1,2,4,5-Tetraethynylbenzene, $CpCo(CO)_2$, DMF, toluene, reflux, *hν*.

(TIPS-ethynyl)buta-1,2,3-triene (**279**) complexes Rh at the central butatriene bond rather than at one of the four acetylenic bonds (Scheme 102).[23]

Scheme 102[a]



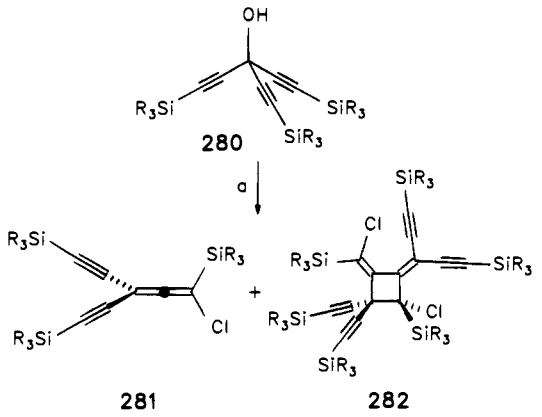
[a] (a) $Rh(PPh_3)_3Cl$, CH_2Cl_2, 20 °C.

The bis(TMS) derivative of diethynyl ketone tosylhydrazone cyclizes to a pyrazole, whereas the TIPS analog even on prolonged refluxing in toluene does not.[590]

However, shielding of a C≡C triple bond by TIPS is not absolute. Thus chloride ion can attack the chloro sulfite from TIPS-propargylic alcohol **280** (SiR_3 = TIPS, Scheme 103) to afford 1-TIPS-1-chloroallene **281** (SiR_3 = TIPS) as a stable compound. The corresponding TMS-allene **281** (SiR_3 = TMS) could not be isolated due to rapid dimerization to **282** (SiR_3 = TMS).[605]

While a C≡CTMS is hydroborated by $^cHx_2BH$ selectively (B binds to the external, Si-bearing C), C≡CTIPS reacts nonselectively with the same reagent.[579,606] However, 9-BBN adds to C≡CTIPS highly regio- and stereoselectively (B binds to the internal C, Scheme 90).[564,565] Hydrostannylation is also possible (see the section on TIPS alkenes).[568] *C*-TIPS-propargyl alcohol was reduced to allyl alcohol **283** by LAH (Scheme 104).[532] Semihydrogenation of a TIPSC≡C bond to a *trans*-double bond seems to be feasible also by hydromagnesiation using ^{i}BuMgBr/catalytic $(C_5H_5)_2TiCl_2$.[571]

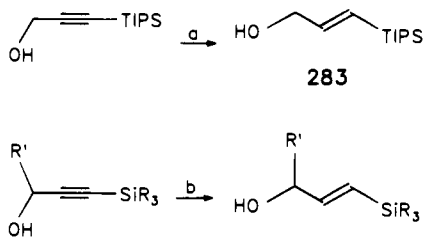
Scheme 103[a]



[a] (a) $SOCl_2$, CH_2Cl_2, −78 °C, 20 min.

R_3Si	281 : 282	
TMS	–	76%
TIPS	86%	–

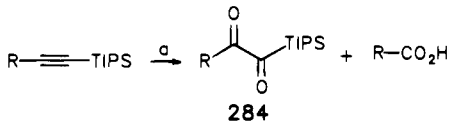
Scheme 104[a]



[a] (a) (1) $LiAlH_4$, THF; (2) H_3O^+. (b) (1) ^{i}BuMgBr, $(C_5H_5)_2TiCl_2$; (2) H_3O^+.

A TIPSC≡C bond is oxidized by $RuO_2/NaIO_4$ in $CCl_4/CH_3CN/H_2O$ to provide a mixture of the carboxylic acid shorter by one C and of an α-keto acyl TIPS compound **284** (TIPS α-diketone, Scheme 105).[591,607]

Scheme 105[a]

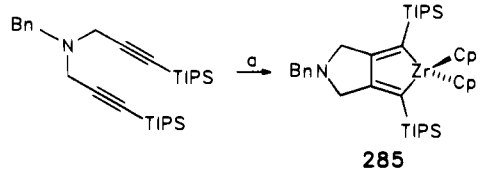


[a] (a) RuO_2, $NaIO_4$, CCl_4, MeCN, H_2O, room temperature.

Surprisingly, in the Co-catalyzed [2 + 2 + 2]-cycloaddition of silyl-protected propiolic acids to an ω-alkynenitrile the bulk of SiR_3 was found to be of little consequence.[608]

Two C≡CTIPS moieties can react with a $ZrCp_2$ unit with bonds formed between Zr and the terminal acetylene carbons (**285**, Scheme 106).[609]

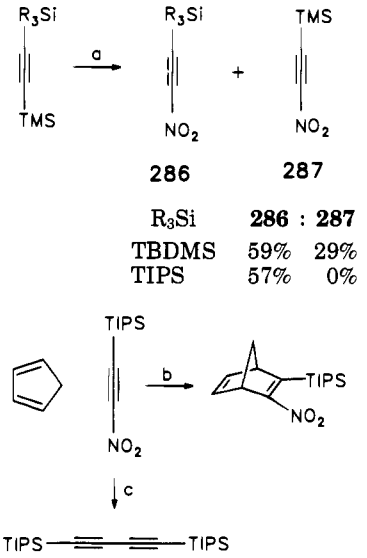
Scheme 106[a]



[a] (a) ^{n}BuLi, Cp_2ZrCl_2, THF, room temperature, 2 h.

1-TIPS-2-nitroacetylene (**286**, R_3Si = TIPS) was synthesized from nitronium hexafluorophosphate and TMSC≡CTIPS exclusively, probably by selective desilylation of a cyclic nitronium ion intermediate. The TBDMS compound reacted less regioselectively (Scheme 107).[610] **286** (R_3Si = TIPS) is a stable

Scheme 107[a]

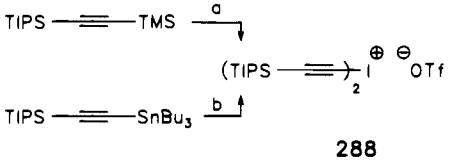


[a] (a) NO_2^+ PF_6^-, MeCN, room temperature. (b) CCl_4, room temperature, 3 days. (c) 200 °C.

compound out of the intrinsically very sensitive class of nitroacetylenes. 1-TBDMS-2-nitroacetylene is much less stable than the TIPS compound, 1-TMS- (**287**) even less. The stabilization is due to TIPS blocking the access of nucleophiles to C-1 and presumably to inductive electron donation from TIPS. Thermolysis of TIPS-nitroacetylene resulted in 1,4-bis(TIPS)-butadiyne. The 1-silyl-2-nitroacetylenes (**286**) are valuable dienophiles and dipolarophiles.[611]

The dialkynyliodonium triflate $(TIPSC{\equiv}C)_2I^+$ OTf^- (**288**) can be prepared by the routes shown in Scheme 108. In contrast to its TMS analog it is a stable

Scheme 108[a]



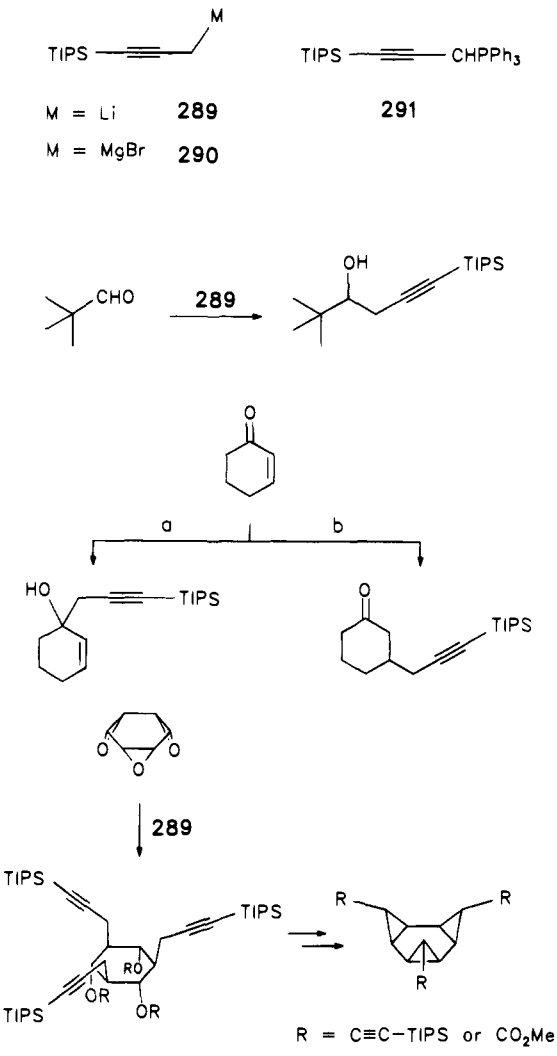
[a] (a) OI^+ ^-OTf, CH_2Cl_2, from −78 °C to room temperature. (b) $(NC)_2I^+$ ^-OTf, from −40 to +20 °C.

compound.[612,613] There is a clear difference between the two compounds in their thermal stability and reactivity toward O_2, H_2O, and nucleophiles.

TIPS-propynyllithium (**289**) is a useful nucleophilic reagent for elongation of carbon chains by a functionalized C_3 unit, even in situations where TMS-propynyllithium fails (Scheme 109).[9,614-617] In most cases the TIPS reagent behaves as a decent propargylic anion, avoiding problems of propargyl/allenyl isomerism. In Scheme 109 a few example reactions are given. The use of this and similar reagents was recently reviewed.[607]

The corresponding triisopropylsilylated Grignard reagent **290** has the same merit and was routinely used in synthesis.[145,238,579,606,618-624] When reacted with allylic substrates, it usually gives clean S_N2 (not

Scheme 109[a]



[a] (a) **289**, THF. (b) **289**, THF/HMPA 3/1.

S_N2') reaction.[238,622,623] The corresponding Wittig reagent **291** has also been used.[625,626]

The protected acetylide $^-C{\equiv}CTIPS$ was used as a monodentate ligand for hemine-like Fe^{III} complexes.[627]

D. TIPS Arenes

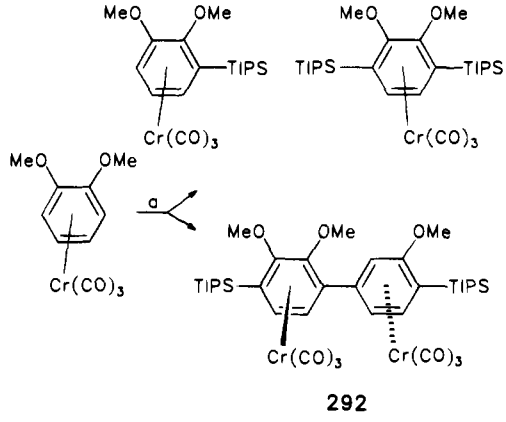
Substituted phenyllithiums were silylated using TIPS-H,[39] TIPS-Cl,[628] or TIPS-F.[46] The desilylation rates in acid were measured. TIPS arenes are *ca.* 20 times less reactive than the corresponding TMS arenes in such solvolyses.[46] TIPS can be removed from a benzene ring by the action of CF_3CO_2H.[469]

$Cr(CO)_3$ complexes of methoxybenzenes were mono- and dilithiated and silylated using TIPS-Cl to give mono- and di-TIPS derivatives as well as an interesting disilylated biphenyl **292** devoid of one methoxy group (Scheme 110).[27,629]

TIPS-benzene was obtained by metalation of benzene (^{n}BuLi/^{t}BuOK, then TIPS-Cl). Metalation of this compound under similar conditions and treatment with electrophiles gave predominantly *para* along with some *meta* substitution.[630] TMS-benzene in contrast is metalated at the methyl groups.

Benzene was Friedel–Crafts silylated using TIPS-Cl/$AlCl_3$/^{i}Pr$_2$NEt in low yield (TIPS arenes are easily

Scheme 110[a]

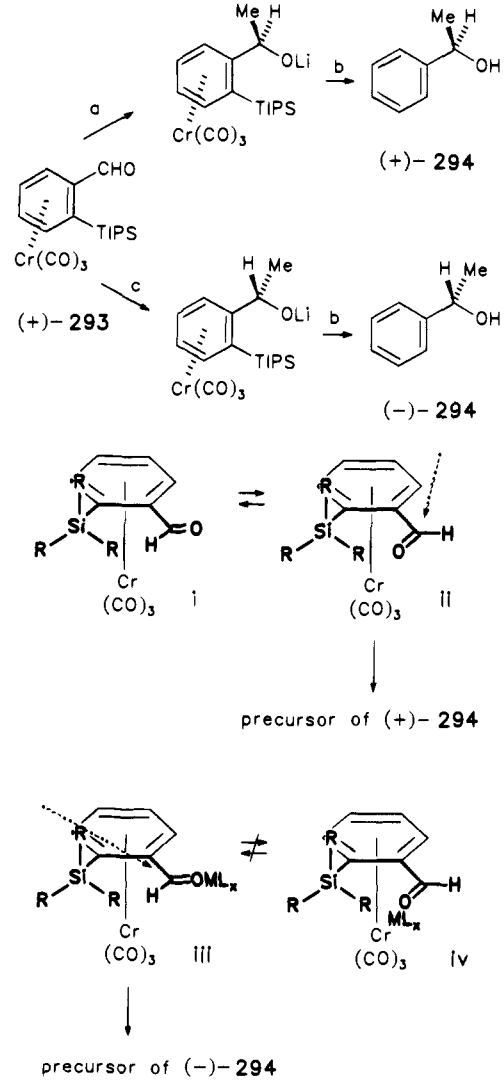


[a] (a) (1) ^{n}BuLi, THF, −78 °C; (2) TIPS-Cl.

desilylated by acid).[631] Similar results were obtained for ferrocene.[632]

The stereochemistry of the addition of "Me$^-$" to (o-TIPS-benzaldehyde)chromium(0) tricarbonyl complex **293** is directed by TIPS (Scheme 111). From the

Scheme 111[a]



[a] (a) MeLi, THF, −78 °C. (b) (1) ^{i}PrOH; (2) ^{n}Bu$_4$NF,CH_2Cl_2; (3) O_2, *hν*, Et_2O. (c) (1) $MgBr_2{\cdot}OEt_2$,Et_2O; (2) MeMgI.

enantiomerically pure starting material by addition

of an organometallic, desilylation ($^nBu_4NF$) and decomplexation, chiral 1-phenylethanol **294** was obtained in 100% ee.[633] Both product enantiomers are available from each starting enantiomer depending on the absence or presence of a Lewis acid, as shown in Scheme 111.

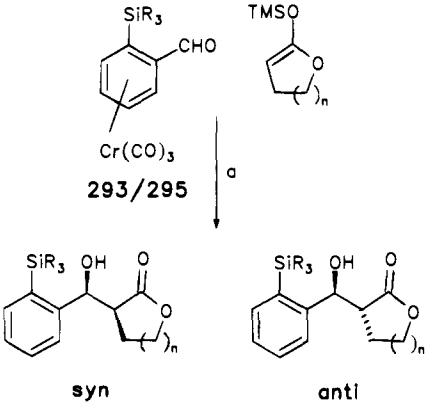
The results can be understood in terms of the reactant conformations **i**–**iv** depicted in Scheme 111, bottom. Without a Lewis acid there is a rapid equilibrium between **i** and **ii**. In both the carbonyl carbon is screened from below by the $Cr(CO)_3$ group. The top face of C=O is unreactive in **i** due to TIPS, while it is accessible in **ii**, resulting in (+)-**294**. For a **293**-ML_x adduct, on the other hand, conformation **iv** is unattainable due to steric crowding with TIPS, therefore the nucleophile has to enter via the hindered trajectory shown in **iii** resulting in slow formation of (−)-**294**.

Enantiopure **293** was obtained by resolution of (±)-**293** (via the L-valinol imine) which in turn was made by lithiation (^{n}BuLi) and silylation (TIPS-Cl) of the ethyleneacetal of the benzaldehyde Cr complex. The acetal group was hydrolyzed to aldehyde without affecting the arene-TIPS by treatment with aqueous HCl in THF (room temperature, 6 days).

While the above is certainly not a preparative method for enantiopure 1-phenylethanol, it does allow us to observe the action of TIPS quite clearly. As expected, TMS was less efficient.[634]

When the same *ortho*-TIPS benzaldehyde Cr(0) complex **293** was reacted with cyclic silyl ketene acetals in a $BF_3{\cdot}OEt_2$ mediated aldol reaction, a higher stereoselectivity was observed than for the TMS analog **295** in the case of the 5-membered ring ketene acetal only (Scheme 112).[635] Using the corresponding free o-silylbenzaldehydes (no $Cr(CO)_3$), no stereoselectivity was obtained for SiR_3 = TMS, some moderate selectivity was achieved for TIPS with all three cyclic silyl ketene acetals tried.

Scheme 112[a]

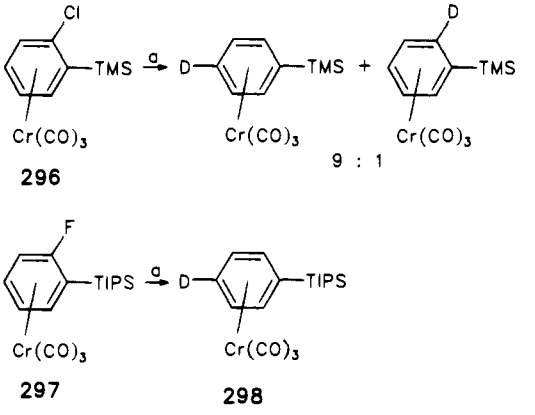


[a] (a) (1) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C; (2) CAN, MeOH, −20 °C.

SiR_3	*n*	*syn* : *anti*	
TMS	1	66	34
TIPS	1	85	15
TMS	2	87	13
TIPS	2	83	17
TMS	3	90	10
TIPS	3	67	33

TIPS on a benzene ring directs nucleophilic substitution away from itself, more efficiently so than does TMS. Thus while (2-chloro-TMS-benzene)chromium(0) tricarbonyl (**296**) and $LiEt_3BD$ produced a 9:1 mixture of 4-deuterio and 2-deuterio-TMS-benzene complexes, (2-fluoro-TIPS-benzene)chromium(0) tricarbonyl **297** gave 4-deuterio-TIPS-benzene complex **298** exclusively (*"tele-meta"* substitution, Scheme 113).[636] The mechanism of this unexpected reaction course is not yet understood.

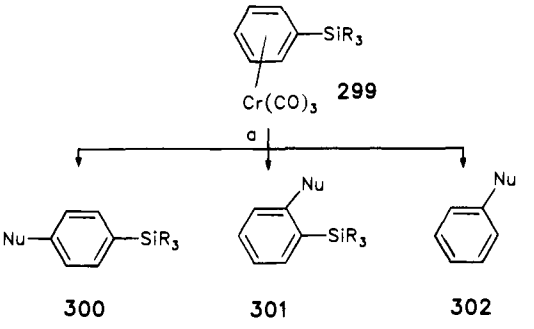
Scheme 113[a]



[a] (a) (1) $LiEt_3BD$, THF, 78 °C, 1 h; (2) H^+.

Tricarbonylchromium complexes of silylbenzenes even without further substitution are amenable to substitution by a nucleophile. Thus reaction of **299** (SiR_3 = TMS) with 2-lithio-1,3-dithiane afforded a mixture of *para*- and (mostly) *ortho*-dithianyl-TMS-benzene (**300/301**) together with desilylation product **302** after decomplexation, whereas the TIPS analog **299** (SiR_3 = TIPS) cleanly provided the *para* substitution product **300** (Scheme 114).[637] Several organonolithium compounds (carbon nucleophiles, e.g. ^{n}BuLi, ^{s}BuLi, allyllithium, vinyllithium) reacted similarly. Less clean reactions were observed for PhLi (deprotonation of substrate) and for TBDMSC≡CLi, which as a "slim" nucleophile was able to attack the Si atom even in TIPS, forming TBDMSC≡CTIPS and the Cr(CO)$_3$ complex of PhLi.

Scheme 114[a]

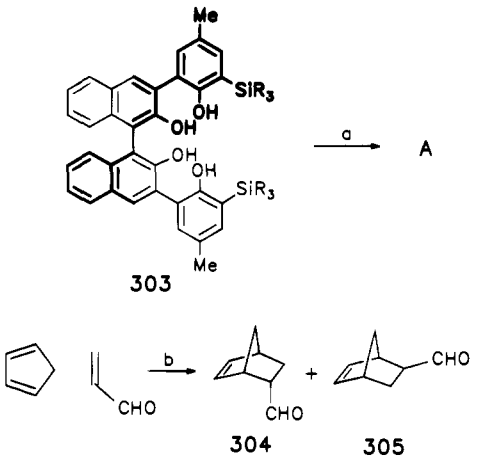


[a] Nu = 1,3-dithian-2-yl. (a) (1) 2-Lithio-1,3-dithiane, THF/HMPA, −78 °C, 3 h. (2) I_2.

SiR_3	**300** :	**301** :	**302**
TMS	16%	42%	23%
TIPS	95%	trace	0%

Silylphenols were used as substituents on an enantiopure binaphthol core providing a chiral surrounding for a Ti central atom and thus catalysts for asymmetric Diels–Alder reactions (Scheme 115).[638] While the TIPS compound **303** (SiR_3 = TIPS) gave

Scheme 115[a]



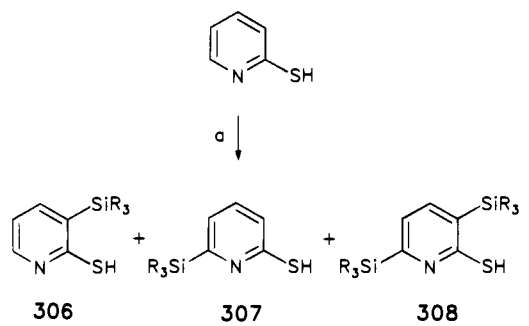
[a] (a) $Ti(O^iPr)_4$, CH_2Cl_2, azeotropic removal of ^iPrOH. (b) 10 mol % **A**, CH_2Cl_2, −78 °C, 3.5 h.

SiR_3	**304**	**305**	ee, % (conf, **304**)
TPS	88	12	88 (*S*)
TIPS	92	8	55 (*S*)

disappointingly low ee's, triarylsilyl groups resulted in ee's up to and above 90%.

2-Pyridinethiol was metalated with an excess LDA in the presence of silyl chlorides. Hindered silyl chlorides such as TBDMS-Cl and TIPS-Cl gave rise to 3,6-bis(silyl)pyridinethiols **308** and 6-monosilyl-2-pridinethiols **307**, while smaller silyl chlorides, e.g. TMS-Cl and TES-Cl, gave 3-monosubstitution only (**306**, Scheme 116).[639] No S-silylation was observed.

Scheme 116[a]



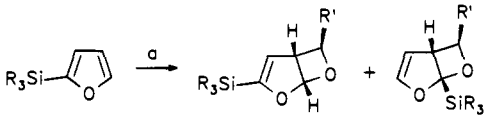
[a] (a) (1) LDA, R_3Si-Cl, THF; (2) H_2O.

SiR_3	LDA	**306**	**307**	**308**
TMS	excess	55%	–	–
TES	excess	45%	–	–
TIPS	excess	–	–	30%
TBDMS	excess	–	–	60%
TBDMS	2.5 equiv	–	30%	30%

Compound **306** could not be obtained for bulky SiR_3. No explanation was given. However, in a later publication the complexation of the 3-TIPS isomer **306** (SiR_3 = TIPS) with $[MoCl_4(CH_3CN)_2]$ is reported; no preparation is given.[640] The silylated pyridinethiols were used as ligands in Mo complexes in model studies for the N_2 reduction in Mo enzymes.

Furans were 2-triisopropylsilylated in the usual way via the 2-lithio derivative (^{t}BuLi/THF, −40 °C, then TIPS-OTf).[641,642] The TIPS group protected the adjacent furan double bond against hydrogenation (H_2/Rh) and the furan ring against oxidation (DDQ). In 2-TIPS-furan, photoaddition of aldehydes occurs mostly at the free double bond with high stereoselectivity and regioselectivity (→ **309/310**, Scheme 117).[643] TIPS is more efficient than TMS in this

Scheme 117[a]



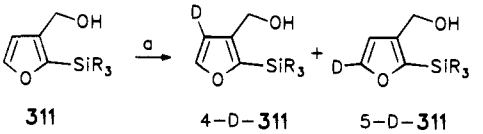
[a] (a) R'CHO, PhH, *hν*, K_2CO_3.

R_3Si	R'	**309**	**310**
TMS	Ph	2.5	1
TIPS	Ph	>20	1
TMS	Et	1.2	1
TIPS	Et	4.0	1

respect. The TIPS group was cleaved by ^{n}Bu$_4$NF[642,644] or by HF in THF/MeCN.[641]

A silyl group on C-2 of furan-3-methanol **311** was used to prevent complexation of ^{n}BuLi to the ring oxygen, thereby retarding C-5 metalation (Scheme 118). Lithiation could thus be directed to the 4-posi-

Scheme 118[a]



[a] (a) (1) 2.2 equiv of ^{n}BuLi, DME, −20 or 0 °C, 1 h; (2) MeOD, excess LiCl.

SiR_3	temp, °C	4-D-**311**	5-D-**311**
TMS	−20 or 0	100	0
TBDMS	−20 or 0	100	0
TIPS	−20	100	0
TIPS	0	75	25

tion rather than to the normal 5-position.[644]

2-TIPS-furan- and -thiophene-3-carboxylic acids were prepared from furan- and thiophene-3-carboxylic acid TIPS esters by anionic O→C Si migration.[439]

2-TIPS-furans survive MnO_2, OsO_4, catalytic amounts of H_2SO_4/py·HTs in CH_2Cl_2, LAH,[642] chromatography on neutral Al_2O_3 or silica buffered with Et_3N.[643]

3-TIPS-furans were synthesized by a [3 + 2] annulation, see Scheme 97.[575]

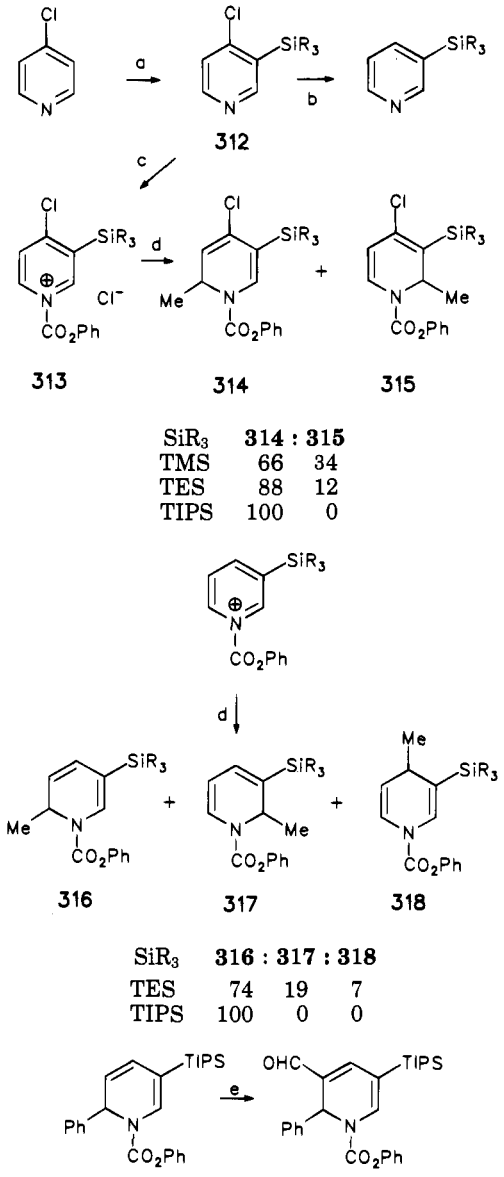
2-TIPS-thiophene was prepared from 2-thienyllithium and TIPS-Cl.[645]

5-TIPS-pyrrole-2-carbaldehyde was obtained by lithiation/silylation (TIPS-OTf) of the dimer of 6-(dimethylamino)-1-azafulvene[646] or by Br/Li exchange and silylation (TIPS-Cl) of 2-bromo-6-(dimethylamino)-1-azafulvene.[647] The 4-TIPS isomer was obtained similarly from the dimer of 3-bromo-6-(dimethylamino)-1-azafulvene.[648]

The directing power of TIPS was exploited most fruitfully by Comins in 3-TIPS-pyridinium salts and 5-TIPS-1,2-dihydropyridines, providing access to a range of alkaloids mostly in enantiomerically pure form, such as the indolizidines elaeokanin A and C,[649,650] septicine and tylophorine,[651] the quinolizidine alkaloids myrtine, lasubine I and subcosine I,[652] as well as porantheridine,[653] sedamine,[654] pumiliotoxin C,[655] and solenopsin A.[656]

Thus, 2- or 4-chloropyridine was lithiated/silylated in position 3 (LDA, TIPS-Cl, directed lithiation, Scheme 119).[649] The 4-chloro products **312** were converted into the *N*-phenoxycarbonyl pyridinium salts **313** and then treated with Grignard reagents to give, in the case of SiR_3 = TMS or TES, mixtures of two regioisomeric 1,2-dihydropyridines **314/315**. For R_3Si = TIPS the reaction is completely regioselective, providing the product of Grignard attack away from TIPS, **314**. Likewise, when position 4 is free, addition of Grignard reagents gives mixtures of the two 1,2-dihydropyridines **316/317** and the 1,4-dihydropyridine **318** for R_3Si = TES, whereas 3-TIPS protects both its neighbor positions 2 and 4 giving rise to the 5-TIPS-2-alkyl-1,2-dihydropyridine **316** exclusively. These products can be substituted by the Vilsmeier–Haack reagent at position 3 cleanly.

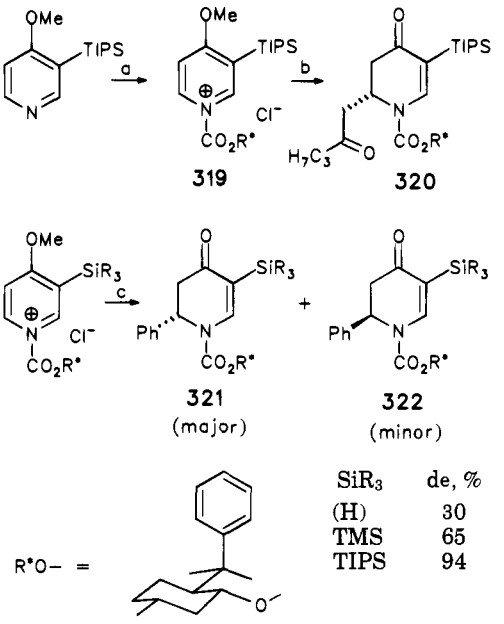
Scheme 119[a]



[a] (a) (1) LDA, THF, −78 °C; (2) R_3Si-Cl. (b) H_2,Pd/C. (c) PhOCOCl, THF, −78 °C. (d) MeMgCl, THF. (e) $POCl_3$, DMF, CH_2Cl_2.

In 1-(alkoxycarbonyl)-4-methoxypyridinium salts bearing a 3-TIPS group, **319** (Scheme 120), Grignard reagents or Zn enolates add to position 6 (away from TIPS) to produce 2,3-dihydro-4-pyridones **320–322** after acidic workup.[653,654,657]

Scheme 120[a]



[a] (a) R*OCOCl. (b) (1) 2-Pentanone, LDA, $ZnCl_2$, Et_2O/THF, −78 °C; (2) H_3O^+, diastereoselectivity 92%. (c) PhMgCl, PhMe/THF −78 °C; (2) H_3O^+.

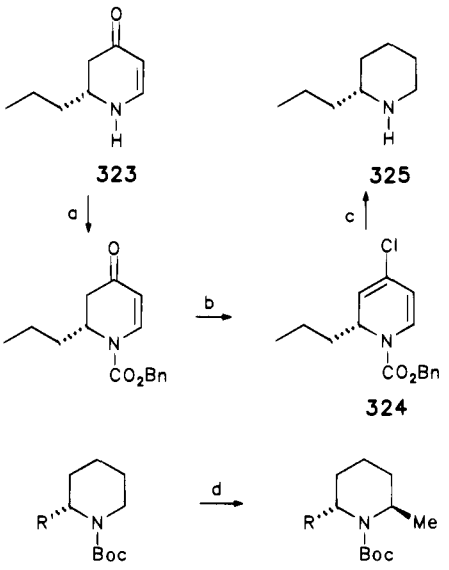
The true value of TIPS here, of course, is not in this regioselectivity, since in the absence of TIPS this problem would not exist. The value of TIPS is in its combined action with a chiral auxiliary group on N. Thus, if the substrate is chiral due to a chiral substituent on N, such as [(−)-(8-phenylmenthyl)-oxy]carbonyl or its nor analog (Scheme 120),[654,658] then the reaction becomes highly diastereoselective for SiR_3 = TIPS, not TMS. Probably TIPS as above screens the vicinal carbon atom, so that the nucleophile attacks the other carbon, on the side not blocked by the phenyl ring of the chiral auxiliary.[657,659] The auxiliary can be cleaved and recovered (NaOMe or Na_2CO_3 in MeOH), thus producing chiral 5-TIPS-2-alkyl-2,3-dihydro-4-pyridones in high ee. These were used in the syntheses mentioned above. Recently the method was expanded in that both a new more efficient chiral auxiliary[660] and a new position of attachment (4) were introduced.[661]

To obtain such products without the help of TIPS, one would expect a highly efficient C_2-symmetric chiral auxiliary on N to be required. However, a surprisingly simple solution was found by Streith, using no silyl group and a nonsymmetric chiral auxiliary on N which allowed site and face differentiation through precomplexation with a Grignard reagent.[662]

A TIPS group on a dihydropyridine survives treatment with NCS/Ph_3P and with several acylating agents.[649] The TIPS group can be removed from 5-TIPS-2-alkyl-1,2-dihydropyridines by HBr/HOAc in CH_2Cl_2,[649] from 5-TIPS-2-alkyl-2,3-dihydro-4-pyridones by oxalic acid in MeOH,[650,652] HBr/HOAc in CH_2Cl_2,[653] or HCl in THF.[654] The TIPS in 5-TIPS-2,3-dihydro-4-pyridones can be replaced by Br by treatment with py·HBr_3 in CH_2Cl_2.[651]

Enantiopure 2-alkyl-2,3-dihydro-4-pyridones such as **323** can be converted into enantiopure 4-chloro-1,2-dihydropyridines (e.g. **324**) by the action of $POCl_3$/DMF (Scheme 121).[663] The latter may be hydrogenated to enantiopure substituted piperidines. Using this chemistry (−)-coniine **325** was prepared. Enantiopure *N*-Boc-2-alkylpiperidines **326** can be lithiated and alkylated diastereoselectively *trans* in position 6 (→ **327**).[656] This made possible the synthesis of (−)-solenopsin A by the TIPS-methoxypyridinium route.

Scheme 121[a]



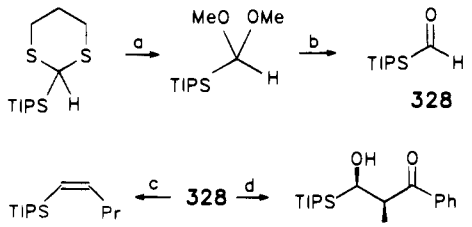
[a] (a) (1) ^{n}BuLi; (2) BnOCOCl. (b) $POCl_3$/DMF, $ClCHCCl_2$, room temperature. (c) H_2, Pt/C, Pd/C. (d) (1) ^{s}BuLi,TMEDA; (2) Me_2SO_4.

E. Acyl TIPS Compounds

For the synthesis and chemistry of acylsilanes see recent reviews.[402,664]

Formyl-TIPS (**328**) was synthesized from 2-TIPS-1,3-dithiane (Scheme 122)[665] or from TIPS-CH(Bt)-(Cb) (Bt = benzotriazolyl, Cb = carbazolyl).[666] It is a reasonably stable greenish-yellow liquid, except that it ignites spontaneously when exposed to air. Otherwise its chemistry resembles that of a typical bulky aldehyde (e.g. Wittig and aldol reactions).

Scheme 122[a]



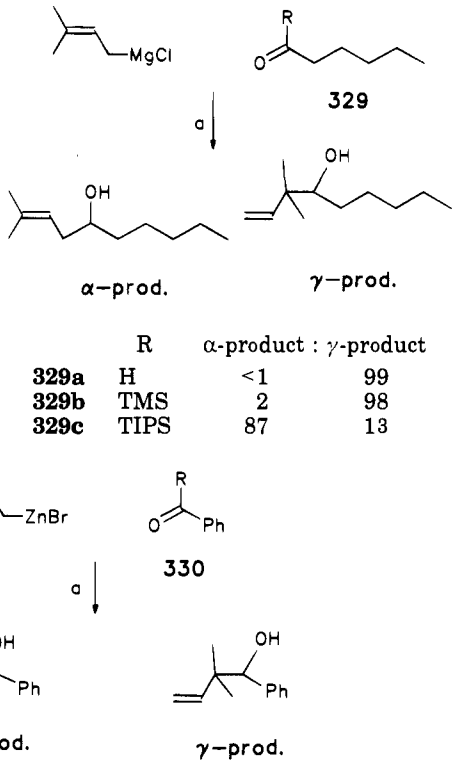
[a] (a) $HgCl_2$,HgO, MeOH. (b) $LiBF_4$, H_2O/MeCN. (c) Ph_3PCHPr, 98% *Z*. (d) (*Z*)-propiophenone Li enolate, >97% *syn*.

Acyl-TIPS compounds are usually prepared from the corresponding 2-alkyl-2-TIPS-1,3-dithianes.[667,668] Acetyl-TIPS was obtained by silylation of (1-methoxyvinyl)lithium, followed by hydrolysis.[527] Higher acyl-TIPS compounds were obtained by cuprate addition to the epoxide of vinyl-TIPS, followed by oxidation.[669]

Reduction of an acylsilane (BH_3·Me_2S) gave the corresponding α-silyl alcohol. The reduction can be made enantioselective by using chlorodiisopinocampheylborane as the reagent.[670]

The problem of regioselectivity (α/γ-attack) in the reaction of allylic and propargylic organometallics with aldehydes was addressed using the help of TIPS in the electrophile (Scheme 123). While an aldehyde **329a** or an acyl-TMS compound **329b** reacted with the dimethylallyl Grignard reagent to give predominantly γ-products, the acyl-TIPS compound **329c** gave predominantly the α-product, derived from attack of the organometallic's less sterically encumbered α-position.[667,668] Similar trends were found in the reaction of allyl-zinc reagents with benzoylsilanes **330**.

Scheme 123[a]



	R	α-product	γ-product
329a	H	<1	99
329b	TMS	2	98
329c	TIPS	87	13

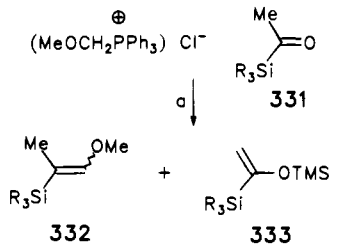
	R	α-product	γ-product
330b	TMS	90	10
330c	TIPS	>99	1

[a] (a) (1) Et_2O or THF, 0 °C, 10−60 min; (2) H_2O; (3) ^{n}Bu$_4$NF.

The low reactivity of the carbonyl C in acyl-TIPS may become a problem, in such a case acyl-TMS was a better choice.[671] The α-TMS homopropargylic alcohols resulting from addition of a propargyl metal reagent to an acyl-TMS can be desilylated by treatment with KO^{t}Bu (1,2 Brook rearrangement) in presence of a OTBDPS group.[671]

Protection of a carbonyl C by an adjacent TIPS group is also seen in the fact that acetyl-TIPS (**331c**) does not react with $MeOCHPPh_3$, in contrast to the corresponding TES or TMS compounds **331a,b** (Scheme 124).[672] Compound **331c** instead forms the enolate, which can be trapped as 1-[(trimethylsilyl)-oxy]-1-(triisopropylsilyl)ethene (**333c**).[672]

Scheme 124[a]



[a] (a) (1) ^{t}BuLi, THF, −90 °C; (2) **331**; (3) TMS-Cl.

	R_3Si	**332** :	**333**	**332***E*/*Z*
331a	TMS	81%	–	76/24
331b	TES	69%	30%	84/16
331c	TIPS	–	sole product	–

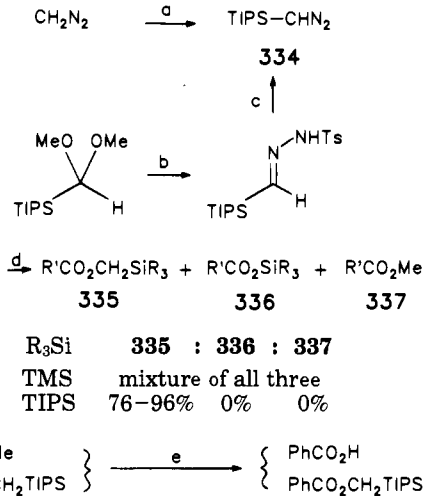
The low reactivity of the carbonyl C in an acyl-TIPS was used to advantage by Lipshutz. Thus, an acyl-TIPS did not react when treated with $Cp_2Zr(H)Cl$ (THF, room temperature, 30 min) or $Me_2Cu(CN)Li_2$ (THF, −78 °C), so that a C≡C bond contained in the molecule could be hydrozirconated, a mixed higher order cuprate could then be formed and added in a 1,4 manner to an α,β-enone. Treatment with ^{n}Bu$_4$NF then liberated the aldehyde.[250] A TES analog could not be used for this chemistry due to carbonyl reduction by the Zr hydride.

For TIPS α-diketones see Scheme 105.

F. TIPS–Diazo Compounds

Silylated diazomethanes can be prepared from silylmethylmagnesium chlorides using a diazo transfer reagent or by direct silylation of CH_2N_2 by a silyl triflate in presence of a base.[516,673] TIPS-CHN_2 **334** was prepared either by the latter method[516] or from the tosylhydrazone of formyl-TIPS using DBU (Scheme 125).[674] It is a distillable, easily handled

Scheme 125[a]



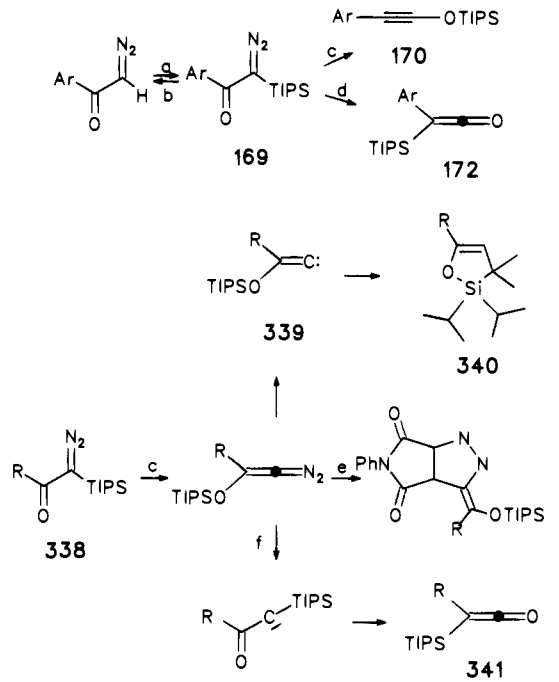
[a] (a) ^{i}Pr$_2$NEt, TIPS-OTf, Et_2O, −20 °C. (b) $TsNHNH_2$. (c) DBU, THF, room temperature. (d) R_3SiCHN_2, 100 °C. (e) Aqueous LiOH,THF, 25 °C, 3.5 h.

liquid, which can be used to cleanly prepare TIPS-methyl esters **335** (SiR_3 = TIPS) from acids. TMS-methyl esters **335** (SiR_3 = TMS) are formed as mixtures with TMS esters **336** (SiR_3 = TMS) and methyl esters **337**. TIPS-methyl esters are well-protected methyl esters. Thus, in a mixture of methyl benzoate and TIPS-methyl benzoate the former was completely hydrolyzed by aqueous LiOH/THF, while the latter was completely recovered.[674]

Silyl diazomethanes can be deprotonated, and a phosphorus substituent may be introduced using a phosphorus chloride. Thermolysis of the phosphanyl silyl diazomethanes gives phosphanyl silyl carbenes which are relatively stable, long-lived, isolable species, but do show the typical carbene behavior.[675,676]

Aryl and alkyl α-diazomethyl ketones are acidic enough to be deprotonated (^{i}Pr$_2$NEt) and silylated (R_3Si-OTf). The silyl (even the TIPS) compounds **169** are extremely easily protiodesilylated, e.g. by MeOH (Scheme 126, see also Scheme 57).[427] The aryl TIPS-

Scheme 126[a]



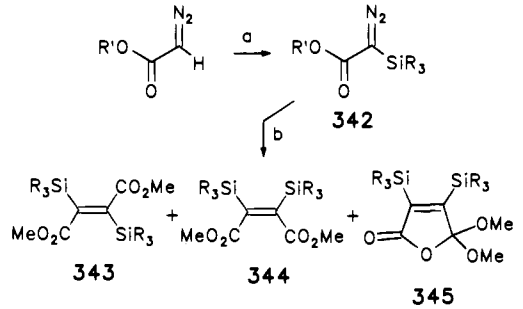
[a] (a) ^{i}Pr$_2$NEt, TIPS-OTf. (b) MeOH. (c) Heat. (d) *hν*. (e) *N*-Phenylmaleimide. (f) *hν* or Cu(I).

diazomethyl ketones can be thermally transformed into alkynyl TIPS ethers **170** (isolable and even distillable), or they can be photochemically rearranged into TIPS ketenes **172**.[267,427] Alkyl TIPS-diazomethyl ketones **338**, on the other hand, thermally rearrange to 1-oxa-2-sila-cyclopent-4-enes **340** in what is probably a carbene insertion into a CH bond of an alkyl residue on Si, occurring in an alkylidenecarbene **339**.[267] The alkylidenecarbenes are formed from the starting material by thermal 1,3 C→O Si migration followed by loss of N_2. The intermediate (silyloxy)diazoalkenes could be trapped by dipolarophiles.[268] Photochemically or under Cu^I catalysis alkyl TIPS-diazomethyl ketones **338** undergo Wolff rearrangement to TIPS ketenes **341**.[678]

α-Diazocarboxylic acid esters and α-diazophosphonic acid esters are C-silylated by the reagent combination R_3Si-OTf/^{i}Pr$_2$NEt, SiR_3 = TMS, TBDMS, TIPS (→ **342**, Scheme 127).[679] Transesterification to a silyl ester competes in the case of *tert*-butyl esters.

The Cu^I- and Rh^{II}- catalyzed decomposition of silyl diazoacetic acid esters was studied in some detail.[680] The TIPS derivative **342d** (R′ = Me, SiR_3 = TIPS),

Scheme 127[a]



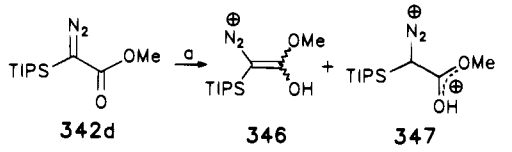
[a] (a) $^{i}Pr_2NEt$, R_3Si-OTf. (b) (R′ = Me) CuOTf, PhMe, room temperature.

	SiR_3	343 : 344 : 345		
342a	TMS	51%	8%	–
342b	TES	36%	–	36%
342c	TBDMS	40%	–	40%
342d	TIPS	–	–	31%

in contrast to all the others, was not decomposed by Rh catalysts. Under Cu^{I} triflate catalysis **342a–c** led to the expected fumaric and maleic acid esters **343/344**, together with a formal carbene dimer of the unusual structure **345**, which was the sole product from **342d**. A cycloaddition between the intermediate methoxy silyl ketene and the diazonium enolate of the starting material was proposed to account for this product.

Methyl α-TIPS-α-diazoacetate (**342d**, Scheme 128)

Scheme 128[a]



[a] (a) FSO_3H, SO_2.

was dissolved in superacids at low temperature, to give products of both O-protonation, **346**, and C,O-diprotonation, **347**. Since TIPS is not prone to be attacked by nucleophiles, and the medium (purified FSO_3H/SO_2) was not a good fluoride source, both these primary products were rather persistent and directly observable by NMR at −75 °C.[681]

G. Miscellaneous *C*-TIPS Compounds

For preparation and reactions of TIPS-CN see the references.[41,50,682–684]

α-TIPS ketones were prepared by anionic 1,3 O→C Si rearrangement from TIPS enol ethers.[379]

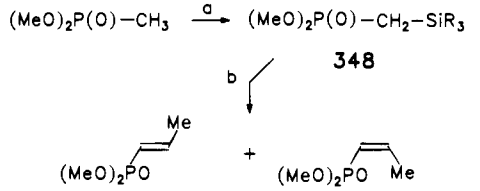
α-TIPS aldehydes were obtained by rearrangement of TIPS epoxides effected by treatment with silica gel in boiling toluene.[532] The TIPS epoxides were prepared from vinyl-TIPS and *m*-CPBA.[572]

α-TIPS carboxylic acid esters were prepared by thermal 1,3 O→C Si migration (200 °C) in TIPS ketene acetals obtained by O-silylation of esters,[456b] or by alcoholysis of TIPS ketenes which are formed on irradiation of α-TIPS α-diazomethyl ketones.[678]

An α-TIPS lactone was obtained on oxidation of a 2-TIPS furan by DDQ.[642]

In contrast to carboxylic acid esters, phosphonic acid esters are C-silylated by treatment with LDA and R_3Si-Cl (→ **348**, Scheme 129). Triisopropylsilylation could be effected in the case of methanephosphonic acid esters, but not for the higher homologs, which could be silylated by smaller R_3Si-Cl.[685,686] The Peterson reaction of α-silylmethanephosphonic acid esters with acetaldehyde is stereoselective for the TIPS derivative **348c** in contrast to the TES or TBDMS analogs **348a,b**.[685] A phosphinic acid ester allyl-P(Ph)(O)OR was likewise lithiated (LDA) and silylated (TIPS-OTf) on carbon.[445]

Scheme 129[a]



[a] (a) (1) LDA, THF, R_3Si-Cl. (b) (1) LDA, THF, CH_3CHO, from −80 °C to room temperature; (2) H_2O.

	R_3Si	*E* : *Z*	
348a	TES	50	50
348b	TBDMS	45	55
348c	TIPS	90	10

An α-thiophosphinoyl-α-TIPS-ketene was obtained from the reaction of a thiophosphinoyl ethoxyacetylene with TIPS-I.[687]

TIPS-acylcarbenes are postulated as intermediates on irradiation of α-TIPS α-diazomethyl ketones in benzene.[678] They rearrange to isolable α-TIPS-ketenes **341** (Scheme 126).

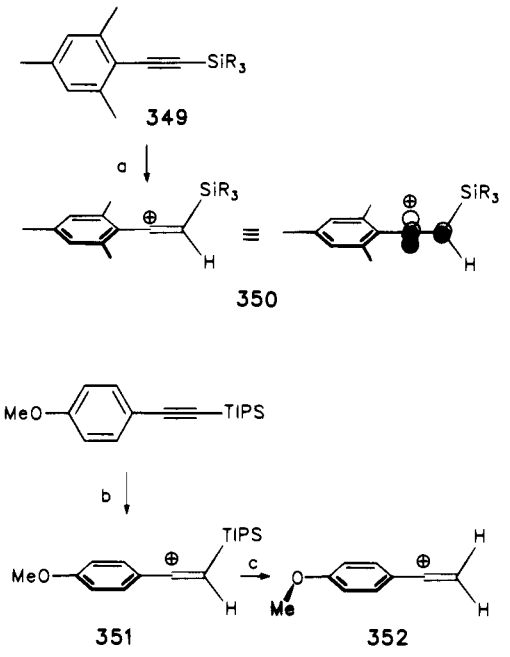
TIPS-phosphanylcarbenes were obtained as isolable compounds by thermolysis (25–35 °C) of the corresponding diazo compounds which were prepared from TIPS-diazomethane by lithiation and phosphanylation.[675,676] Interestingly, the behavior of the TMS- and the TIPS-phosphanylcarbene is essentially identical.

For β-Si-stabilized alkyl cations see Scheme 81.

TIPS served well in stabilizing otherwise elusive cations. Thus, persistent β-silyl stabilized α-aryl vinyl cations **350** were generated by protonation of 2-silyl-substituted 1-mesitylalkynes **349** with FSO_3H/SbF_5 in SO_2ClF/SO_2F_2 at −130 °C (Scheme 130). Their ^{13}C NMR spectra were interpreted in terms of β-Si hyperconjugation.[688] The TIPS-substituted species is more persistent than e.g. the TMS analog. Nevertheless, the TIPS-substituted *p*-anisyl vinyl cation **351**, prepared similarly at −130 °C, loses the silyl group at above −115 °C by attack of even the weak nucleophiles present in this superacidic solution.[578] The cleanly formed product is the 2-unsubstituted aryl vinyl cation **352**, in which rotation about the aryl-O bond is slow on the NMR time scale, giving rise to two signals for the *ortho* and two for the *meta* positions. This phenomenon was explained by the increased electron demand in cation **352** not stabilized by a SiR_3.

2-Adamantyl radicals bearing a silyl group at an α-carbon were prepared from *exo*-methyleneadamantane, TMS-H or TIPS-H, and di-*tert*-butyl peroxide under irradiation in cyclopropane.[60] Their ESR spectra were recorded, and the hyperfine splitting values were compared to theoretical ones.

Scheme 130[a]



[a] (a) FSO_3H, SbF_5, SO_2ClF, SO_2F_2, −130 °C. (b) FSO_3H, SbF_5, SO_2ClF, SO_2F_2, CD_2Cl_2, −130 °C. (c) −115 °C.

Trialkylsilyl radicals were added to C_{60}. In TMS-C_{60}• and even $^tBu_3Si$-C_{60}• rotation about the fullerene–Si bond is unhindered on the NMR time scale.[689] The same is true for TES-C_{60}• and TIPS-C_{60}•, in which however rotation about Si–C_{alkyl} is frozen at or sligthly above room temperature.

VII. Miscellaneous TIPS Compounds

Triisopropylsilyl mercaptan, TIPS-SH, was prepared from H_2S, ^{n}BuLi, and TIPS-Cl. Its potassium salt, TIPS-SK, is alkylated by primary or secondary R-X to provide alkyl TIPS sulfides which when desilylated ($^nBu_4NF$) and alkylated (R′-X) provide access to unsymmetrical sulfides RSR′.[690] TIPS-SK can be used to prepare vinyl and aryl sulfides by coupling with vinyl and aryl halides under Pd catalysis.

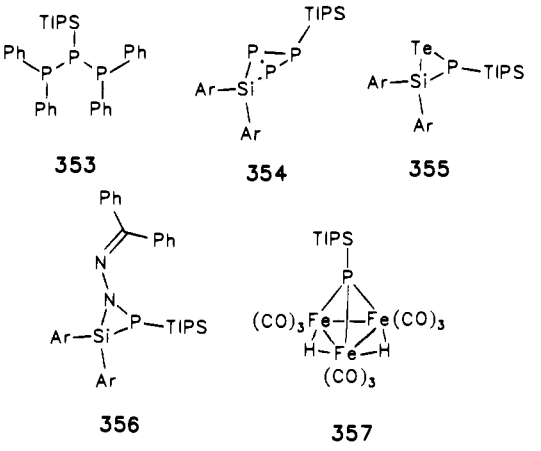
Na_2S was silylated using TIPS-I. The product, bis(TIPS) sulfide, was also obtained from the disilane $(TIPS)_2$ and SF_6.[49] The $^tBu_3Si$ analog which could not be obtained from $^tBu_3Si$-I was generated from H_2S and 1,3-bis($^tBu_3Si$)triazene.[691]

Allyl mercaptan was S-silylated by TIPS-OTf (benzene, Et_3N, 0 °C, 90%).[43] The product on metalation (^{s}BuLi) suffered rapid 1,2 S→C Si migration.

4-(TIPS)thio-substituted styrene was polymerized.[692,693]

TIPS on a P atom was used for kinetic stabilization of highly reactive systems such as a P_3 chain, **353**,[34] a 1,2,3-triphospha-4-silabicyclo[1.1.0]butane **354**,[694] a telluraphosphasilirane **355**,[24] an azaphosphasiliridine **356**,[695] or a Fe_3P cluster **357** (Scheme 131).[696] The latter TIPS compound is much more stable than the usual P-TMS compounds, e.g. it can be chromatographed. The silyl group is cleaved by $^nBu_4NF$ in CH_2Cl_2 or by unusual reagents such as $[(Ph_3P)_2N]Cl$, whereas $^nBu_4NF$ in THF deprotonates **357**. Further P-TIPS cleaving reactions with conservation or modification of the Fe_3P cluster were reported recently.[697,698]

Scheme 131[a]

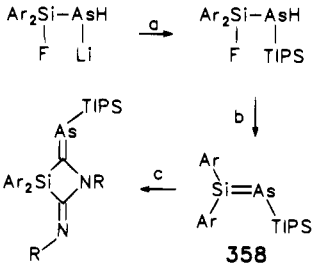


[a] Ar = 2,4,6-^{i}Pr$_3$-C_6H_2.

TIPS on an As atom is found in the As analog of **355**.[24]

A kinetically stable compound with a Si=As double bond ("arsasilene") was prepared, **358**, with a TIPS protecting group on the As introduced by silylation of a As–Li intermediate (Scheme 132).[24] Compound

Scheme 132[a]



[a] Ar = 2,4,6-^{i}Pr$_3$-C_6H_2. (a) TIPS-OTf. (b) (1) ^{n}BuLi, hexane/THF; (2) PhMe, 90 °C. (c) 2 RNC, −80 °C.

358 (or its phosphorus analog) reacts with isocyanides to form silaazacyclobutanes with an exocyclic =As-TIPS (or =P-TIPS) group.[699] With hexane-1,6-diisocyanide a macrocyclic "dimer" is formed.[700] Further reactions of **358** are reported in ref 701.

The silylarsane $TIPS-AsH_2$ was lithiated (^{t}BuLi) and reacted with ^{t}BuGeF$_3$ and ^{t}BuLi to give a crystalline $As_6Ge_2Li_6$ cluster which is completely surrounded by ^{t}Bu and TIPS groups via Ge–C and As–Si bonds.[702]

Disilenes stabilized by bulky silyl groups were prepared by reductive coupling of dibromosilanes (lithium naphthalene or Na), e.g. $(TIPS)_2SiBr_2$ → $(TIPS)_2Si{=}Si(TIPS)_2$. The product in the solid state is yellow; it shows no twisting of the Si=Si bond (dihedral angle TIPS–Si–Si–TIPS 0°), but the TIPS groups at Si(1) are tilted 10°, those at Si(2) 10° in the opposite direction out of the formal Si_6 plane. In solution the material is deep-red, probably due to twisting. The $(TBDMS)_4$ and $(^iPr_2MeSi)_4$ analogs have interestingly different properties.[703]

A Rh-TIPS bond was formed by irradiation in TIPS-H of $(\eta^5$-$C_5H_5)(Me_3P)Rh(\eta^2$-$C_6F_6)$ to result in $(\eta^5$-$C_5H_5)(Me_3P)Rh(TIPS)H$.[704]

Species which are claimed to come close to a free $^iPr_3Si^+$ (silylium or silicenium) ion were obtained in condensed phase from TIPS-H and hydride abstract-

ing reagents of the trityl type, using exotic extremely weakly coordinating anions. Their nature is controversially discussed.[705-708] $^{t}Bu_3SiH$ in contrast reacted sluggishly with the trityl salt resulting in a complex product mixture.[708,709]

$^{i}Pr_3Si^{\bullet}$ and $^{t}Bu_3Si^{\bullet}$ radicals were observed ESR spectroscopically,[710,711] as well as the corresponding radical cations $R_3SiH^{\bullet+}$.[712,713] For the role of $^{i}Pr_3Si^{\bullet}$ in the preparation of benzyl-TIPS see the section on TIPS alkanes.[556]

VIII. 1,n TIPS Migrations

TIPS, like other trialkylsilyl groups, can migrate between different nucleophilic sites in a molecule under anionic conditions even at −78 °C.[714] The reactions are assumed to involve nucleophilic attack at Si to produce a pentacoordinate Si intermediate or transition state. As can be expected for such a mechanism, TIPS is definitely less prone to the reaction than other less bulky R_3Si groups, e.g. TBDMS.[74,77,306,308,529,682,715] A nice demonstration of the differing migratory aptitudes of the various R_3Si groups is seen in inter- and intramolecular concurrence reactions.[201]

As a rule, these reactions are intramolecular rearrangements, as can be inferred from the observation that the migration termini have to be geometrically close to one another,[476] and as was amply demonstrated by crossover experiments.[202,379,439,528,538,563,716,717]

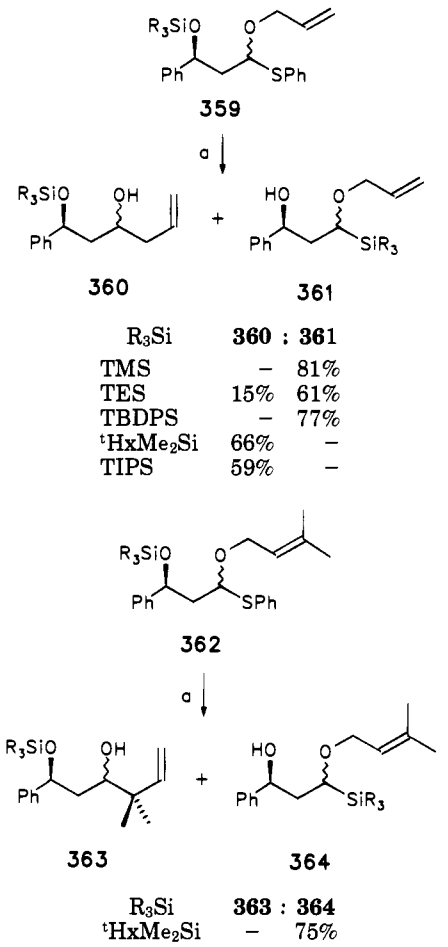
For TMS the reaction is often not observed since the Si in this group is open to attack by an external nucleophile (intermolecular attack), resulting in loss of TMS.[528,716,718]

Several such reactions are of considerable synthetic value for particular classes of silanes.

The composition of the product mixtures can be controlled both by the reactivity of the SiR_3 group (kinetic control) and by the relative stabilities of the anionic species under the given conditions (thermodynamic control). The counterion and the solvent can greatly influence the equilibrium. Thus Keay found a 1,4 O→C Si migration when silyl ethers of 3-(hydroxymethyl)furans or -thiophenes were treated with $^{n}BuLi$/THF/HMPA at −20 °C, but not in the absence of HMPA.[716] Exactly the reverse reaction was observed on treatment of the *C*-silyl alcohols with NaH in DMF or KH in THF, but not with RLi or RMgBr in THF.[202] Similarly, 1,4 O→C or 1,4 C→O Si migrations occurred depending on conditions (MeLi/THF or NaH/DMF).[529] For the C→O direction catalytic amounts of NaH are sufficient, since the carbanion produced by Si migration deprotonates the OH function in another alcohol molecule. TBDMS migrates 1,6 O→O in Na/liquid NH_3, but not in Li/liquid NH_3.[211] Interestingly, a 1,11 O→O Si migration was observed for $Et_2{}^{i}PrSi$, but not for TIPS.[74]

An interesting case of concurrence between 1,4 O→C Si migration and [2,3] Wittig rearrangement undergone by the same kind of organometallic species, made by reductive C-S cleavage in **359/362**, was observed by Brückner (Scheme 133). When the trialkylsilyl group was highly hindered (TIPS, $^{t}HxMe_2Si$), the Wittig rearrangement won (→ **360**), when on the other hand the Si was more susceptible to nucleophilic attack (TMS, TBDPS), or when the

Scheme 133[a]



[a] (a) (1) Li-naphth, THF, −78 °C; (2) H_2O.

Wittig rearrangement was slowed down by additional substitution in the allyl ether (**362**), then (even for $Me_2{}^{t}HxSi$) the Si migration was faster (→ **361,364**).[715]

Specifically, the following types of anionic 1,n Si migrations were observed for TIPS:

1,2 O→C: [α-(Silyloxy)alkyl]stannane → (α-hydroxyalkyl)silane;[717] TIPS allyl ether → 1-TIPS allyl alcohol, on reaction with 2 equiv of $^{s}BuLi$ in THF at −78 °C.[43] Similarly *1,2 S→C*: TIPS allyl sulfide → 1-TIPS allyl mercaptan (1.2 equiv of $^{s}BuLi$ in THF/HMPA at −78 °C).[43]

1,3 O→C: Aryl silyl ether → 2-silylphenol;[308,312,638] silyl enol ether → α-silyl ketone (the reverse reaction can be induced thermally[43]).[379]

1,4 O→C: γ-Silyloxyalkyl phenyl sulfide → (γ-hydroxyalkyl)silane;[528] 3-[(silyloxy)methyl]furan → 3-(hydroxymethyl)-2-silylfuran;[716] silyl ester of furan-3-carboxylic acid → 2-silylfuran-3-carboxylic acid;[439] (*Z*)-3-iodoallyl silyl ether → (*Z*)-3-silylallyl alcohol;[563] (*Z*)-3-stannylallyl silyl ether → (*Z*)-3-silylallyl alcohol;[529] *cis*-1-stannyl-2-[1-(silyloxy)alkyl]cyclopropane → *cis*-1-silyl-2-(1-hydroxyalkyl)cyclopropane;[529] secondary allyl silyl ether → β-silyl ketone.[79]

1,3 C→O: Li salt of 2,2-dibromo-2-silyl-1-phenylethanol → 2-lithio-2,2-dibromo-1-phenylethyl silyl ether.[531]

1,4 C→O: Tricarbonylchromium complex of o-silyl-1-phenylethanol → complex of 1-phenylethyl silyl ether;[633,634] 3-(hydroxymethyl)-2-silylfuran → 3-[(si-

lyloxy)methyl]furan;[202] (*Z*)-3-silylallyl alcohol → allyl silyl ether.[529]

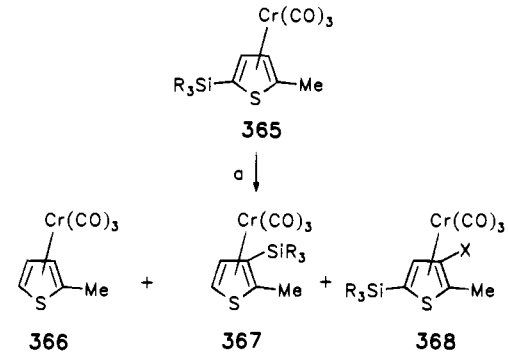
1,4 O→O: 1,2-Diol 1-TIPS-ether → 1,2-diol 2-TIPS ether (such reactions are common for TBDMS ethers[65,301]).[77,87] In triisopropylsilylated ribonucleosides no TIPS migrations between 2′-O and 3′-O were found in dry aprotic solvents,[70,296,302] except under severe conditions.[719]

1,3 C→N: α-Silylcyanohydrin → *N*-silyl enamine (1,4 O→N Si migration was found for some R_3Si, but not for TIPS).[682]

1,2 N→C: 2-Bromo-*N*-TIPS-pyrrole → 2-TIPS-pyrrole;[476] *N*-TIPS gramine → 2-TIPS-gramine.[480]

As an exception, *inter*molecular anionic Si migrations were observed in the (2-silyl-5-methylthiophene)-chromium(0) tricarbonyl complexes **365** on treatment with ^{t}BuLi (Scheme 134). The less hindered silyl

Scheme 134[a]



[a] (a) (1) ^{t}BuLi, THF, −78 °C, 3 h; (2) H^+.

R_3Si	**366** :	**367** :	**368** (X = H) :	**368** (X = SiR_3)
TMS	80%	–	–	–
TES	51%	27%	–	–
IPDMS	30%	59%	–	11%
TBDMS	–	–	90%[†]	–
TIPS	–	–	95%	–

[†] D_2O workup gave the same product with X = D, *ca.* 70%.

groups TMS, TES, and IPDMS are open to intermolecular attack by ^{t}BuLi, resulting in desilylation (→ **366**), and by the 4-Li derivative, resulting in 1,3 C→C Si migration (→ **367** and **368**). In contrast, the bulky TBDMS and TIPS groups cannot be attacked intermolecularly, and since intramolecular attack by the lone pair in position 4 is likewise impossible for geometric reasons, in these cases the 4-Li derivative is persistent, it can be trapped by an electrophile such as D_2O (→4-D-**365**).[645]

Cationic 1,2 C→C Si migrations (analogs of Wagner-Meerwein) are well known.[682,714] With silyl = TIPS such steps play a key role in Knölker's and Danheiser's syntheses of silylcyclopentenes and -cyclopentanes from propargyl- and allylsilanes[530,541-543] and of furans from allenylsilanes,[575] see also the section on allylsilanes.

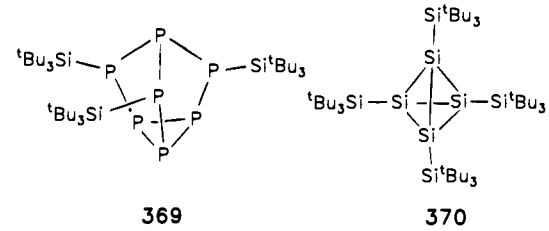
A 1,4 O→O TIPS migration is involved in a one-carbon ring expansion reaction of 1-[(triisopropylsilyl)oxy]cycloalkanecarboxaldehydes under the action of Lewis acids.[92]

Of course, thermal Si migrations are also known. For TIPS thermal 1,3 O→C and 1,3 C→O Si rearrangements were observed (*O*-silyl ketene acetal → α-silyl-acetic acid ester,[456b] α-diazo-α-silyl ketone → 1-diazo-2-(silyloxy)alkene[268,431]) as well as 1,3 N→O Si migrations (*N*-silylformanilide → *O*-silyl formimidate,[720] for smaller R_3Si the opposite direction was observed). Also known are the following: 1,2 N→N;[431] 1,2 N⇄C;[683] 1,2 P→C;[701] 1,2-O→C;[721] 1,5 O→N;[268] other O→N.[431]

IX. Other Bulky Silyl Groups

With TIPS being a useful group due to its bulkiness, resulting in durability and useful directing effects, even stronger effects can be expected for even bulkier silyl groups, e.g. tri-*tert*-butylsilyl, the logical completion of the series. This group, which is sometimes called "supersilyl",[722] has found two uses in chemistry: In elementorganic chemistry it serves as a stabilizing group allowing isolation of otherwise unstable compounds, e.g. containing unusual bond types,[723-728] unusual oxidation states, e.g. Al^I in $(AlSi^tBu_3)_x$,[729] or interesting cage systems such as the P_7 cage **369**[730] or the Si_4 tetrahedron **370** (Scheme 135).[731]

Scheme 135



In organometallic chemistry the corresponding silanolate ("silox"), silyl amide or silyl imide are used as inert bulky ligands.[732-746] The potential value of the ^{t}Bu$_3$Si group is clearly seen in the facts that ^{t}Bu$_3$SiCl, in contrast to most other triorganosilyl chlorides, does not react with $NaBF_4$,[747] and that the cation radical ^{t}Bu$_3$SiH$^{\bullet+}$ is an observable species.[713]

However, there seem to be no applications of ^{t}Bu$_3$Si in preparative organic chemistry. (For an exception, hydrogenation of C=C by ^{t}Bu$_3$SiH, see reference 748a. The ^{t}Bu$_3$Si group here is not incorporated into the organic compound.) This can be traced to three reasons.

(i) Until recently the ^{t}Bu$_3$Si group was not easily made. Along with ^{t}BuLi its synthesis either required SiF_4 or $SiHF_3$ as starting materials, or using $SiHCl_3$ an intermediate fluorination step was needed.[468,727,749]

(ii) ^{t}Bu$_3$Si is not easily introduced into an organic molecule by silylation. The silyl chloride,[750] iodide,[751] perchlorate,[752] and triflate[723,751,753] are all rather unreactive compounds, long reaction times under harsh conditions are required to produce the ^{t}Bu$_3$Si ether even of methanol. This compound can be prepared using 1,3-bis(tri-*tert*-butylsilyl)-triazene.[691] The trifluoroacetate ^{t}Bu$_3$SiOCOCF$_3$ reacts with MeOH under O-acyl cleavage to produce ^{t}Bu$_3$SiOH.[754] Therefore special methods had to be used for the preparation of ^{t}Bu$_3$Si compounds.[755,756] Now with ^{t}Bu$_3$Si-OTf readily available in one simple step from a commercial material, these problems should be somewhat alleviated.[753]

(iii) A ^{t}Bu$_3$Si ether, prepared by hydrosilylation of a C=O double bond, is not easily cleaved, instead

elimination of silanol or substitution of silanolate prevail.[748b]

Therefore very few organic compounds containing $^tBu_3Si$ exist. Two such compounds, $^tBu_3SiC{\equiv}CNO_2$ [611] and *cis*-2-(tri-*tert*-butylsilyl)-3-methyloxirane [572a] are referenced, but in the original papers cited,[610,572b] their preparation is in fact not described. Instead the latter paper deals with *cis*-2-(trimethylsilyl)-3-*tert*-butyloxirane. A third such compound, $^tBu_3Si$-CO-CH_3, is reported not to be reduced by (−)-*B*-chlorodiisopinocampheylborane, but no source, preparation, property, reaction, or reference is given.[670] Therefore it may be suspected that the compound not reacting with the borane was actually Me_3Si-CO-^{t}Bu.

Another very hindered silyl group, $^tBu_2{}^c$PnSi, can be introduced into primary and secondary alcohols by silylation with the corresponding cyclopentaannulated silirane in the presence of KF and 18-C-6.[757] The reagent is prepared from $^tBu_2SiCl_2$, cyclopentene, and Li in THF under ultrasound irradiation.[758] Nothing is known about the chemistry of this group. The silanes $^tBu_2{}^s$BuSiH and $^tBu_2{}^c$HxSiH can be prepared from di-*tert*-butyl-siliranes which are obtained from $^tBu_2SiCl_2$, Li, and butene or cyclohexene, respectively. From $^tBu_2{}^s$BuSiH, a trityl borate and a nitrile a stable silylnitrilium salt can be obtained which reacts with alcohols ROH to the corresponding silyl ethers $^tBu_2{}^s$BuSi-OR.[709]

$^tBu_2$MeSi (DTBMS)[752] was used to prepare stable alkynyl ethers,[213] to provide carboxylic acid silyl esters that were not reduced by LiR_3AlH and were not cleaved by py·HOTs in warm EtOH, and to prevent 1,4 addition of MeLi to a β-silyloxy α,β-unsaturated ketone.[759]

$^tBu^iPr_2Si$ is mentioned in a Japanese patent.[760]

Tricyclohexylsilyl found no use in synthesis.[40]

Two silyl groups similar to TIPS, but containing an aromatic group, were prepared, [1-(5-dimethylamino)naphthyl]diisopropylsilyl[55] and 4-biphenylyldiisopropylsilyl (BDIPS).[585] Their chemistry is similar to that of TIPS, and substances containing these groups are fluorescent and therefore easily detected. A photoremovable version of TIPS, (hydroxystyryl)-diisopropylsilyl (HSDIS), was recently proposed.[761]

A silyl group less bulky than TIPS, $Et_2{}^i$PrSi (DEIPS), has properties sufficiently different from TBDMS,[762] and as such found some applications in synthesis.[74,131,763] DEIPS-OTf quantitatively silylated a tertiary alcohol.[764]

The thexyldimethylsilyl group is a slightly enlarged version of TBDMS. The corresponding silyl chloride is more easily made and handled than TBDMS-Cl. Thexyldimethylsilyl derivatives are generally 2−3 times slower in desilylation than the corresponding TBDMS derivatives.[765]

A slightly diminished version of TBDMS, ^{i}PrMe$_2$Si (IPDMS), was seldom used.[314]

The sila analog of TBDMS, Si_2Me_5, recently proved to be a useful precursor of a tertiary OH function.[766]

TBDPS is a valuable protective group for primary amines[470] and for primary and secondary alcohols.[65,767] However, O-TBDPS is not completely stable toward catalytic hydrogenation, thus inadvertently it was reduced to O-^{t}Bu^{c}Hx$_2$Si when treated with H_2/Pd(OH)$_2$/C.[162] Another disadvantage of TBDPS is that the triflate is not available, since an aryl group is easily exchanged on treatment of an arylsilane with triflic acid.[45]

The group $-{}^i$Pr$_2$Si− was recently used as a linker in place of $-PO_2^-$− in oligonucleotide analogs,[768] and as a clamp to prevent epimerization on lithiation of a 1-silyl epoxide (ring formation between the anionic C and a nearby tertiary alcohol function).[769,572] Cl^{i}Pr$_2$Si− on a polystyrene resin was used to link oligosaccharides to a solid support in the synthesis of blood group determinants.[257b]

X. Conclusion

It is shown in this review that after several years of an induction period,[770] the use of TIPS has rapidly increased in recent years. The bulkiness of TIPS seems to be of the correct magnitude as to exhibit a good compromise between useful steric effects on the one hand, and ease of introduction and removal on the other. It cannot be overlooked, however, that there are more effects than explanations, and more ad hoc rationalizations than true insight. Predictions on the role of TIPS compared to other silyl groups in a particular reaction are almost never made. This cannot come as a surprise, remembering that even a selectivity reversal of, say, from 5:1 to 1:5 corresponds to a $\Delta\Delta G^{\ddagger}$ of less than 2 kcal/mol at room temperature, or less than 1.3 kcal/mol at −78 °C. Anyway, the difference often found in the behavior of TIPS-containing compounds to those containing more traditional silyl groups such as TBDMS, combined with the fact that TIPS is easily available (it is not even more expensive than TBDMS), render the prediction safe that use of this group and relatives will on many occasions in the future help synthetic chemists in achieving their evermore demanding goals.

XI. References

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