

4.4.41 **Product Subclass 41:**
 β -Silyl Carbonyl Compounds

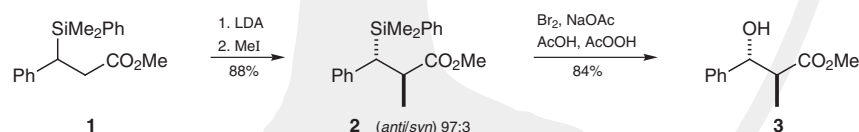
Ian Fleming

General Introduction

A silyl group placed β to a carbonyl group is, in one sense, separated from the functionality, with the result that it is firmly attached to the molecule – except for the specific reactions described below, only the most violent acidic or basic conditions will dislodge it, and even then it is not necessarily the bond from the silyl group to the β -carbon atom that is most at risk. Thus, 4-(trimethylsilyl)butan-2-one dissolves in concentrated sulfuric acid, but all that occurs is the loss of one of the methyl groups as methane, leaving the β -silyl carbonyl system intact.^[1] Nevertheless, there are five reactions that can be used in synthesis to take advantage of this functional array.

One is that the silyl group, if it has appropriate substituents on it, can be converted into a hydroxy group, with retention of configuration (see Section 4.4.18).^[2,93,94] For this reaction to take place, one of the substituents must be an electronegative heteroatom, like alkoxy or dialkylamino, or a carbon group, like aryl or allyl, that can be displaced by an electronegative heteroatom in the course of an electrophilic substitution reaction. If these conditions are met, a β -silyl carbonyl compound can serve as a masked β -hydroxy carbonyl compound (Scheme 1). Since the silyl group can control the stereochemistry of alkylation at the α -carbon, it is possible to set up the α - and β -stereocenters of an aldol reaction in a sequence entirely different from the aldol reaction itself. Thus, the ester **1** can be alkylated stereoselectively to give the 2,3-*anti* relationship in the ester **2**,^[3] and the dimethyl(phenyl)silyl group converted into a hydroxyl group to give the *anti*-aldol product **3**.^[4] Similarly, enolate protonation gives the *syn*-diastereomer of **2**, and hence the diastereomer of **3**. A β -silyl group has the advantage that it may be retained through a number of reaction steps, before it is converted into the hydroxyl group, with none of the risk of β -elimination inherent in the aldol products themselves.

Scheme 1 Enolate Alkylation and Silyl-to-Hydroxy Conversion^[3,4]

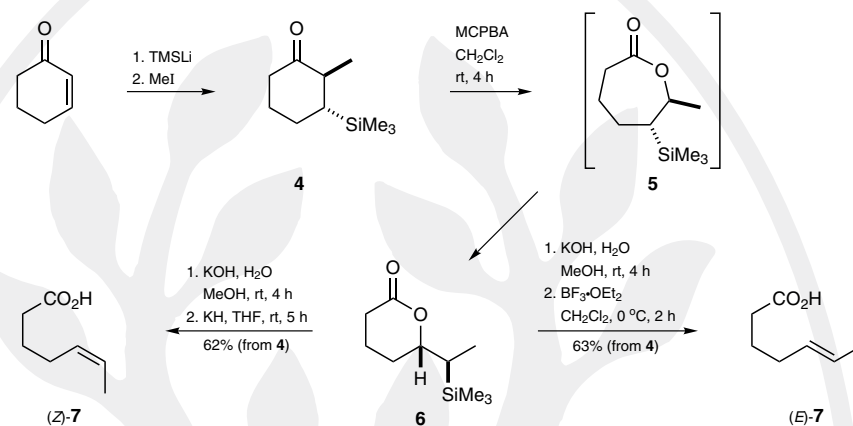


A second possibility, when the carbonyl group is a ketone group, is to carry out a Baeyer–Villiger reaction (Scheme 2). Other things being equal, this proves to be selective for insertion of the oxygen atom into the bond on the side of the ketone carrying the β -silyl group, and it sets up an ester or a lactone of a β -silyl alcohol (see Section 4.4.37).^[5,6] This group is then susceptible to β -elimination giving an alkene and a carboxylic acid. If the α - and β -carbons have been set up with stereocontrol, as in the alkylated ketone **4**, the geometry of the double bond can be controlled to be *Z* or *E* [(*Z*)-**7** or (*E*)-**7**] by choosing a *syn*- or *anti*-stereospecific method for the β -elimination. A minor but interesting complication is that the first-formed Baeyer–Villiger product **5** rearranges stereospecifically to the isomeric lactone **6**. There are several variants of the cleavage: (1) Beckmann-like, stereospecific *anti* fragmentations from the oxime acetates of the ketones gives the corresponding nitriles,^[7]

for references see p 945

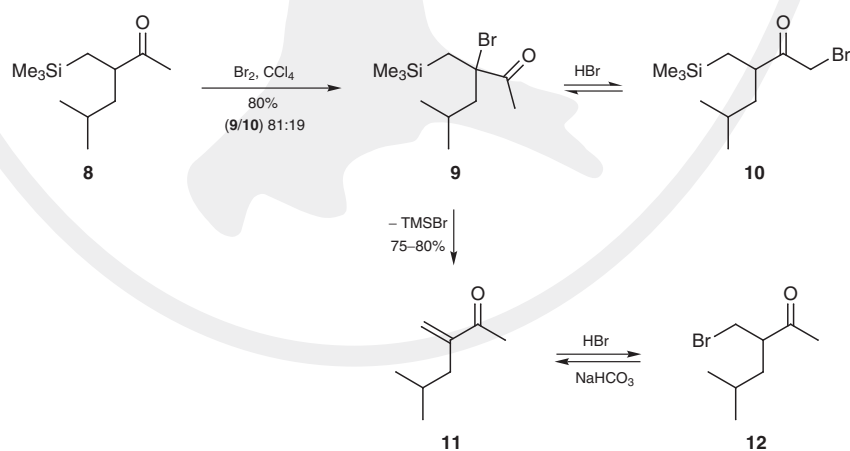
(2) anodic or lead(IV) acetate induced decarboxylative elimination of a β -silyl carboxylic acid gives alkenes,^[8,9] and (3) saturated β -silyl ketones undergo Norrish Type I photo-cleavage, which is also selective for the side of the ketone carrying the silyl group, and favors formation of an aldehyde and an alkene.^[10,11]

Scheme 2 Baeyer–Villiger Reaction and Alkenoic Acid Synthesis^[5,6]



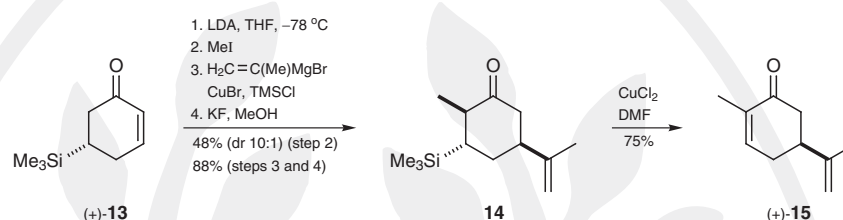
A third possibility is to use the β -silyl carbonyl compound as a masked α,β -unsaturated carbonyl compound (Scheme 3),^[12] since bromination of the carbonyl group in a ketone (e.g., **8**), giving an α -bromo- β -silyl carbonyl compound **9**, reconnects the silyl group to the functionality, allowing it to be removed by β -elimination (**9** \rightarrow **11**), just like any other β -halosilane (see Section 4.4.36). If bromination takes place on the other side of the ketone, giving the alternative bromo ketone (ratio **9/10** 81:19 in this case), equilibration of the regioisomeric β -bromo ketones (**9** and **10**) can be achieved using dry hydrobromic acid. The β -elimination **9** \rightarrow **11** takes place under these conditions, and the α,β -unsaturated ketone then adds hydrobromic acid to give the β -bromo ketone **12**. This, of course, can be treated with mild base to restore the α,β -unsaturation specifically on the side originally carrying the silyl group, so that the overall result is not dependent upon which side the ketone is initially brominated. The whole sequence, halogenation, equilibration, and elimination, can also be induced by treating a β -silyl ketone with copper(II) bromide^[13] or chloride.^[14]

Scheme 3 Enone Formation from β -Silyl Ketones^[12]



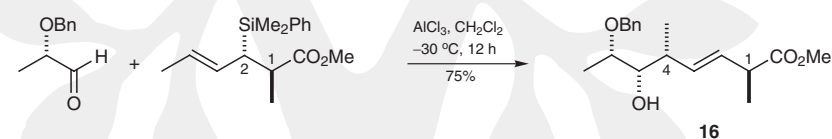
The silyl group in a cyclic ketone can be used to control the stereochemistry across the ring, as well as adjacent to it, as in the enolate alkylation followed by conjugate addition of a cuprate to the enone (+)-**13** (Scheme 4).^[15,16] The halogenation–elimination sequence then removes two of the stereocenters in the intermediate **14**, but leaves behind the one stereocenter in (+)-carvone (**15**).

Scheme 4 5-(Trimethylsilyl)cyclohex-2-enone in a Synthesis of (+)-Carvone^[15,16]



A fourth use of β -silyl carbonyl compounds is as precursors to γ -silyl alcohols (see Section 4.4.42),^[17] which can be used in cationic rearrangements; a fifth use is as precursors in the synthesis of allylsilanes by the aldol and decarboxylative elimination route (see Section 4.4.40).^[18] A special case is provided by those β -silyl carbonyl compounds that are also allylsilanes (Scheme 5),^[19] where the β -silyl carbonyl part of the molecule can be used in a stereocontrolled alkylation to set up a 1,2-relationship, and the allylsilane function can be used in a stereospecific *anti* $\text{S}_{\text{E}}2'$ reaction, for example, giving the β,γ -unsaturated ester **16** with 1,4-related stereocenters.^[20]

Scheme 5 β -Silyl Carbonyl Compounds That Are Also Allylsilanes^[19,20]



α,β -Unsaturated β -silyl carbonyl compounds can be converted into saturated β -silyl carbonyl compounds, amenable to any of the applications described above, by hydrogenation,^[4] by Diels–Alder reactions,^[8,21,22] and by conjugate addition by cuprates,^[23] simple enolates,^[21] and β -dicarbonyl enolates.^[24] They can be used in Nazarov cyclizations, with the silyl group controlling the position of the double bond in the cyclopentenone product,^[25–27] and, by Wittig and Peterson reactions, in the synthesis of 1-silylbutadienes;^[28] they also form tricarbonyliron complexes with further applications in organic synthesis.^[29]

β -Silyl carbonyl compounds can be prepared in a large number of ways, of which the most common are electrophilic or nucleophilic silylation of a three-carbon unit, hydrosilylation of a propargylic or allylic alcohol, hydrosilylation–carbonylation of an alkyne or alkene, hydroformylation of an ethynyl- or vinylsilane, connective methods putting the three-carbon unit together by C–C bond formation, and by Claisen rearrangement.

4.4.41.1 **Method 1:** **Hydrosilylation of Alkynes and Alkenes**

The catalyzed addition of a silicon hydride to a triple or double bond carrying a carbonyl or latent carbonyl group usually sets up the connection of atoms Si–C–C–CO with the silyl group β to the carbonyl group. Alternatively, it can be set up from any terminal al-

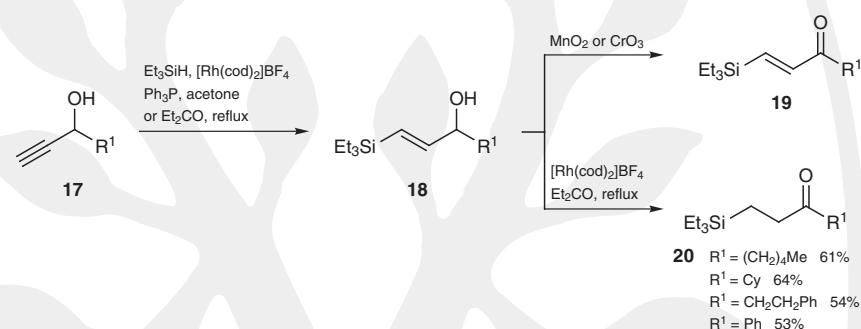
for references see p 945

kyne by the addition of a silyl group from a silicon hydride and a carbonyl group from carbon monoxide, with the silyl group placed selectively at the terminus.

4.4.41.1.1 Variation 1: Hydrosilylation of Propargyl Alcohols, and Oxidation or Isomerization

Hydrosilylation of propargyl alcohols **17** using a variety of catalysts places the silyl group at the terminus (Scheme 6). The allylic alcohol **18** could then be oxidized to give an α,β -unsaturated β -silyl aldehyde or ketone **19**, or used as a precursor for the Claisen rearrangement (see Section 4.4.41.6). If a cationic rhodium catalyst is used for the hydrosilylation, the allylic alcohol can be isomerized at a higher temperature to give the saturated β -silyl ketone **20** in one operation.^[30] Hydrosilylation of acetals of acrolein, followed by hydrolysis of the acetal group,^[31] or hydrosilylation of allylic alcohol itself, followed by oxidation, gives β -silylpropanals.^[32]

Scheme 6 Hydrosilylation of Propargyl Alcohols, and Oxidation or Isomerization^[30]

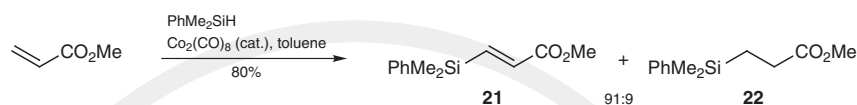


1-(Triethylsilyl)octan-3-one [20, $\text{R}^1 = (\text{CH}_2)_4\text{Me}$]; Typical Procedure:^[30]

A two-necked flask equipped with a magnetic stirring bar was charged with $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (8.1 mg, 0.04 mmol) and Ph_3P (10.5 mg, 0.04 mmol), evacuated, and filled with argon. Diethyl ketone (3.0 mL) was added and the mixture was stirred for 5 min. Oct-1-yn-3-ol (0.252 g, 2 mmol) was added via syringe followed by the similar addition of Et_3SiH (0.47 g, 4 mmol). The mixture was stirred and refluxed for 16 h, and then concentrated in vacuo. Chromatography of the residue gave the saturated ketone **20** [yield: 0.281 g (61%)], together with the triethylsilyl ether of 1-(triethylsilyl)oct-1-en-3-ol (yield: 21%).

4.4.41.1.2 Variation 2: Hydrosilylation and Dehydrogenation

Hydrosilylation of methyl acrylate would normally have the same consequence (*vide supra*) of setting up the saturated β -silyl ester **22** but, if the catalyst is octacarbonyldicobalt, the organometallic intermediate can be diverted to a large extent into β -elimination, making the α,β -unsaturated ester **21** the major product (Scheme 7). The cobalt hydride created in this step is removed by having a large excess of methyl acrylate, which is reduced to methyl propionate.^[33] The ester **21** is particularly useful for the preparation of β -silyl acrylic derivatives attached to chiral auxiliaries, notably those of Koga and Oppolzer, suitable for conjugate addition of alkyl or aryl groups, stereoselectively setting up an Si–C bond attached to a stereogenic center.^[34,35]

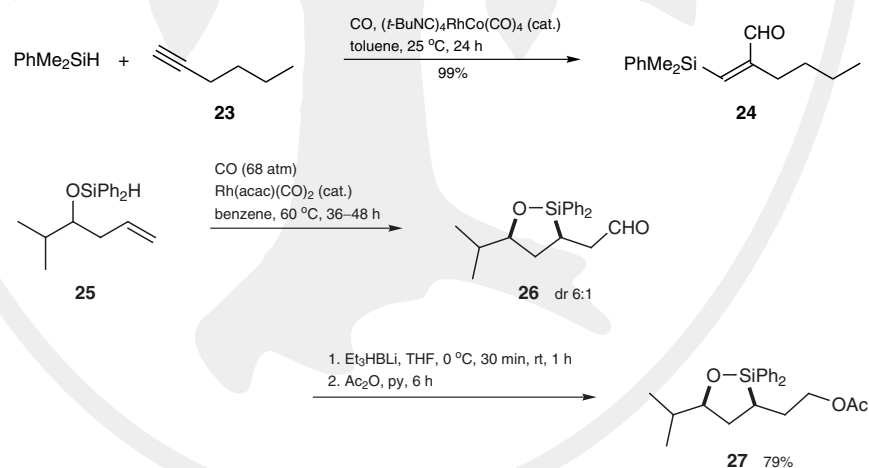
Scheme 7 Hydrosilylation and Dehydrogenation of Methyl Acrylate^[33]**Methyl 3-[Dimethyl(phenyl)silyl]propenoate (21); Typical Procedure:**^[33,36]

PhMe_2SiH (7 g, 51.5 mmol) and $\text{Co}_2(\text{CO})_8$ (0.4 g, 1.2 mmol) in dry toluene (30 mL) were put into a three-necked flask fitted with rubber septa and a magnetic stirrer bar. The flask was flushed with argon, evacuated, and refilled with argon twice. Methyl acrylate (freshly distilled; 21.5 g, 250 mmol) was added dropwise and the mixture was stirred at rt for 22 h, cooled, and filtered through Celite. The solvent, the excess acrylate, and the methyl propionate were evaporated in vacuo to give an inseparable mixture of methyl 3-[dimethyl(phenyl)silyl]propenoate (**21**) and methyl 3-[dimethyl(phenyl)silyl]propionate (**22**), typically in a ratio of 91:9; yield: 9.1 g (80%); bp 79–81 °C/0.05 Torr; bp 90–95 °C/1.5 Torr.

4.4.41.1.3

**Variation 3:
Hydrosilylation–Carbonylation**

If a terminal alkyne, for example **23**, does not have a carbonyl or latent carbonyl group, transition-metal catalyzed hydrosilylation can be combined with carbonylation in the presence of carbon monoxide to give α -substituted (*Z*)- α,β -unsaturated β -silyl aldehydes (e.g., **24**, Scheme 8).^[37–39] The *E*-stereoisomer can be prepared from the *Z*-isomer by isomerization using iodine.^[39] Yields are excellent when dimethyl(phenyl)silane is employed; the major byproducts with other hydrosilanes are the products of simple hydrosilylation (especially with alkoxy silanes), and a cyclopentenone product of carbocyclization (especially with trialkylsilanes). The corresponding intramolecular reaction gives β -substituted or α,β -disubstituted (*Z*)- α,β -unsaturated β -silyl aldehydes,^[40,41] and the intramolecular reaction with a terminal alkene using pressure gives a saturated aldehyde, for example **26**, with the opposite regiochemistry.^[42]

Scheme 8 Hydrosilylation–Carbonylation of Alkynes and Alkenes^[37–39,42]

for references see p 945

(Z)-2-Butyl-3-[dimethyl(phenyl)silyl]propenal (24); Typical Procedure:^[37]

A Schlenk tube fitted with a CO line at atmospheric pressure was charged with [(*t*-BuNC)₄RhCo(CO)₄] (4 mg, 0.008 mmol) in toluene (15 mL), and hex-1-yne (0.33 g, 4 mmol) and dimethyl(phenyl)silane (0.55 g, 4 mmol) were added by syringe. The mixture was stirred at 25 °C for 24 h. The solvent was removed and the aldehyde [yield: 99% (by GC)] isolated by bulb-to-bulb distillation.

cis-5-Isopropyl-2,2-diphenyl-1-oxa-2-silacyclopentane-3-acetaldehyde (26);**Typical Procedure:**^[42]

[Rh(acac)(CO)₂] (5.2 mg, 0.02 mmol) and benzene (10 mL) were placed in an oven-dried stainless steel pressure vessel equipped with a magnetic stirring bar and a glass liner, and the vessel was cooled to -78 °C. 4-(Diphenylsiloxy)-5-methylhex-1-ene (**25**; 0.59 g, 2 mmol) was added, and the pressure gauge assembled. The apparatus was pressurized to 68 atm with CO and then vented, and the procedure repeated twice. The apparatus was pressurized again with CO to 68 atm and then heated by immersion in an oil bath at 60 °C, with magnetic stirring. After 36–48 h, the apparatus was cooled in an ice bath and then vented. N₂ was bubbled through the mixture for 10 min to remove any remaining CO. An aliquot (100 μL) was removed, concentrated, and analyzed by ¹H NMR spectroscopy, to show that the aldehyde **26** had been formed, and to measure the ratio of diastereomers.

For isolation of a stable product, the mixture was cooled to 0 °C and 1 M Et₃HBLi in THF (6 mL, 6 mmol) was added. After 30 min at this temperature, and 1 h at rt, pyridine (2 mL) and Ac₂O (0.4 mL, 4.24 mmol) were added and the mixture was stirred at rt for 1 h. An additional portion of Ac₂O (0.4 mL, 4.24 mmol) was added and the mixture stirred for 5 h. EtOAc and aq NH₄Cl were added and the layers separated. The aqueous phase was extracted with EtOAc (2 ×). The combined organic layers were dried (MgSO₄), filtered, and concentrated. The residue was flash chromatographed (silica gel, EtOAc/hexanes) to give *cis*-3-(2-acetoxyethyl)-5-isopropyl-2,2-diphenyl-1-oxa-2-silacyclopentane (**27**); yield: 0.58 g (79%).

4.4.41.2

Method 2:**Silylmetalation of Alkynes and Alkenes**

The β-silyl carbonyl system can be set up by the addition of a silylmetal compound to a triple or double bond. If a carbonyl group is already present, the intermediate enolate may be treated directly with a proton or a more substantial electrophile to introduce substituents *syn* stereoselectively at the α-position of the β-silyl carbonyl compound. Alternatively, if there is no carbonyl group present, and the substrate is an alkyne, the intermediate organometallic reagent may be acylated to give a β-silyl enone.

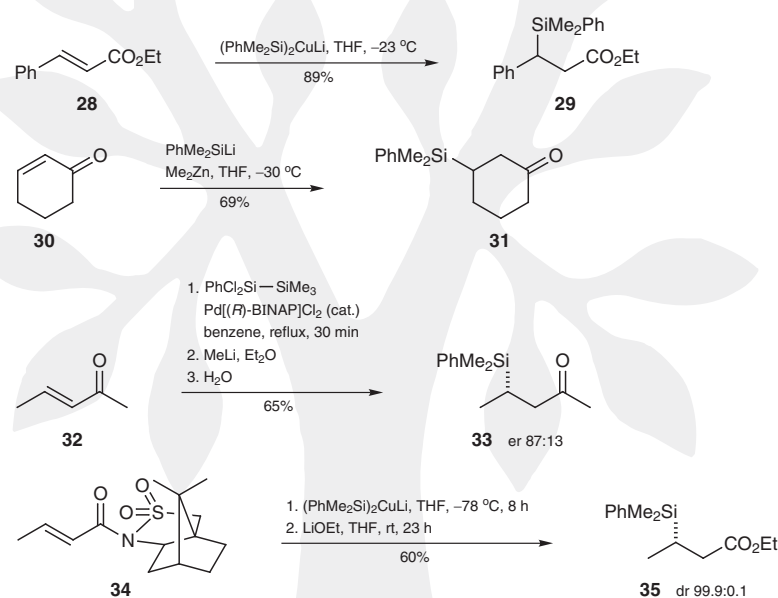
4.4.41.2.1

Variation 1:**Silylmetalation of α,β-Unsaturated Carbonyl Compounds**

In the addition of a silylmetal compound to a double (or triple) bond carrying a carbonyl group, several metals have been used, including silicon (catalyzed by palladium),^[43] aluminum,^[44] zinc,^[45,46] copper,^[13,47] and lithium.^[48] In one form or another, this is one of the most frequently used methods for setting up a β-silyl carbonyl compound in synthesis. The reagents most often employed are the zincates^[45,46] and the cuprates^[13,47] (Scheme 9), which react without additional Lewis acid catalysis with α,β-unsaturated esters (e.g., **28**) and amides, in contrast to the corresponding carbon-based reagents, as well as with α,β-unsaturated ketones (e.g., **30**) and their *N,N*-dimethylhydrazones.^[6] It is advantageous to have chlorotrimethylsilane present in the reaction mixture when the unsaturated carbonyl compound is unsubstituted in the β-position.^[49] The zincates may be prepared

from dimethylzinc itself or, more safely, from methyllithium and zinc(II) iodide in situ. A related reaction, but probably taking a mechanistically different course, is the reductive silylation of enone systems using a silyl chloride and an anode^[50] or a dissolving metal.^[51] The silyl-cuprate undergoes conjugate addition–elimination with methyl β -iodoacrylate, providing an alternative synthesis of the (*E*)- β -silylacrylate **21** (Scheme 7).^[52] The addition of the disilane across the enone system **32** requires catalysis by a palladium reagent, which gives an opportunity to use a homochiral ligand, and to impart enantiomeric enrichment in the product **33**.^[43] More recently, copper(I) trifluoromethanesulfonate has been found to catalyze 1,4-addition to α,β -unsaturated carbonyl systems by cleavage of disilanes,^[53] including those disilanes such as hexamethyldisilane which cannot be cleaved by lithium and hence used as cuprates or zincates. With silylzincates and silylcuprates, no homochiral catalyst has yet been found, but a chiral auxiliary attached to the carbonyl group, as in the imide **34**, has been used to give, after recrystallization, very high levels of diastereomeric enrichment in the intermediate imide, which can be cleaved to give correspondingly high enantiomeric enrichment in the ester **35**.^[34]

Scheme 9 Addition of Silylmetal Compounds to α,β -Unsaturated Carbonyl Compounds^[3,13,43,46,54,55]



Ethyl (3*RS*)-3-[Dimethyl(phenyl)silyl]-3-phenylpropionate (**29**);

Typical Silylcupration Procedure:^[3,13]

0.85 M PhMe_2SiLi in THF (4 mL, 3.4 mmol) was added to CuCN (153 mg, 1.7 mmol) or CuI (323 mg, 1.7 mmol) in THF (3 mL) under N_2 , either at 0°C and stirred for 30 min or at -23°C and stirred for 3 h. The soln was cooled to -78°C , ethyl cinnamate (90 mg, 1.8 mmol) was added, and the mixture was brought to -23°C over 1–3 h. The soln was brought to rt, and Et_2O (10 mL) and basic NH_4Cl soln (5 mL) were added. The aqueous layer was washed with Et_2O (10 mL), and the combined organic layers washed with basic NH_4Cl soln. The organic layer was dried (MgSO_4) and evaporated in vacuo. Flash chromatography [silica gel, petroleum ether (bp $60\text{--}80^\circ\text{C}$)/ EtOAc 15:1] gave the ester **29**; yield: 0.5 g (89%).

3-[Dimethyl(phenyl)silyl]cyclohexanone (**31**); Typical Silylzincation Procedure:^[46]

A round-bottomed flask was charged with dry ZnI_2 (0.319 g, 1 mmol) and freshly distilled dry THF (5 mL) and the air flushed out with argon. 1.5 M MeLi in Et_2O (1.33 mL, 2 mmol)

for references see p 945

was added dropwise by syringe with stirring at 0 °C, and the mixture was stirred for 30 min. The soln was cooled to –30 °C and 1 M PhMe₂SiLi in THF (5 mL, 5 mmol) was added dropwise by syringe, and the mixture stirred for another 30 min. Cyclohex-2-enone (240 mg, 2.5 mmol) in THF (3 mL) was added by syringe and the mixture was stirred for an additional 3 h at –30 °C. H₂O (10 mL) was added and the mixture extracted with Et₂O. The combined extracts were dried, concentrated in vacuo, and the residue chromatographed (silica gel, hexane/EtOAc 10:1) to give the ketone **31**; yield: 0.39 g (69%).

(S)-4-[Dimethyl(phenyl)silyl]pentan-2-one (33); Typical Procedure:^[43]

Pent-3-en-2-one (84 mg, 1 mmol), PhCl₂SiSiMe₃ (500 mg, 2 mmol), and Pd[(R)-BINAP]Cl₂ (4 mg, 0.005 mmol) were refluxed in benzene (2 mL) under argon for 30 min. The mixture was cooled to rt, diluted with Et₂O (2 mL), and then cooled to –70 °C. 1.9 M MeLi in Et₂O (3.2 mL, 6 mmol) was added and the mixture stirred at –70 °C for 10 min, and then quenched with dil HCl. The mixture was extracted with Et₂O, the combined Et₂O layers were washed with NaHCO₃ soln, dried (MgSO₄), and the solvent was removed in vacuo. Preparative TLC (hexane/Et₂O 2:1) gave the ketone **33**; yield: 143 mg (65%); [α]_D +21 (c 1, CHCl₃).

Ethyl (S)-3-[Dimethyl(phenyl)silyl]butyrate (35); Typical Procedure:^[54,55]

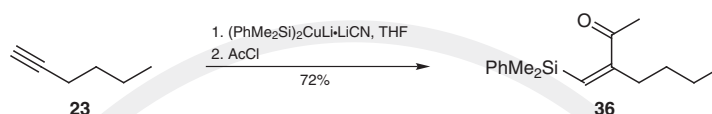
1M PhMe₂SiLi in THF (15 mL, 15 mmol) was added dropwise at 0 °C to CuCN (0.65 g, 7.3 mmol), and the resulting suspension was stirred for 20 min. The soln was cooled to –78 °C and (1S)-N-[(E)-but-2-enoyl]-2,10-camphorsultam (**34**; 1.39 g, 4.9 mmol) in dry THF (12 mL) was added dropwise during 2 h and kept for 6 h at –78 °C. The mixture was poured into CH₂Cl₂ (60 mL) at 0 °C, and stirred for 15 min. The mixture was filtered through Celite, and the organic layer was dried (MgSO₄), and evaporated. Flash chromatography (silica gel, hexane/EtOAc 95:5) and crystallization gave the S-diastereomer of the silylated intermediate; yield: 1.73 g (85%); mp 85–87 °C (hexane).

1.2 M BuLi in hexanes (9 mL, 11 mmol) was added dropwise with stirring to anhyd EtOH (0.7 g, 15 mmol) at 0 °C under argon (NOTE: if the methyl ester is desired, magnesium methoxide is superior to the lithium alkoxide). After 15 min the silylated imide (1.73 g, 3.1 mmol) in THF (20 mL) was added slowly by cannula and the mixture was allowed to warm to rt and maintained at this temperature for 23 h. The mixture was quenched with sat. NH₄Cl (20 mL). The aqueous layer was extracted with Et₂O (3 × 40 mL), the combined organic extracts were washed with brine (80 mL), dried (MgSO₄), and the solvent was evaporated under reduced pressure. The residue was triturated with a mixture of EtOAc and petroleum ether (bp 40–60 °C) (1:9) to precipitate the chiral sultam auxiliary; recovered yield: 0.8 g (73%). The crude ester in the mother liquor was concentrated under reduced pressure and the residue chromatographed [silica gel, EtOAc/petroleum ether (bp 40–60 °C) 6:94] to give ester **35**; yield: 0.55 g (71%); [α]_D +0.39 (c 7.47, CH₂Cl₂).

4.4.41.2.2

**Variation 2:
Silylmatalation and Acylation of Alkynes**

Silylcuprates react with terminal alkynes (e.g., **23**) with *syn* addition of the silyl group to the terminus and the copper to the internal atom. Acylation then results in a β -silyl (*Z*)-enone **36** (Scheme 10).^[56,57] Hexamethyldisilane and rhodium catalysis can be used similarly, but all in one pot, in the presence of an acid chloride.^[58]

Scheme 10 Addition of Silylmethyl Compounds to and Acylation of Alkynes^[56,57]**3-Butyl-4-[dimethyl(phenyl)silyl]but-3-en-2-one (36):**^[56]

0.4 M PhMe_2SiLi in THF (17.5 mL, 7 mmol) was added dropwise at 0°C to CuCN (dried in vacuo at 120°C for 10 h; 0.30 g, 3.5 mmol), and the resulting suspension was stirred for 20 min. Hex-1-yne (0.26 g, 3.2 mmol) in THF (1 mL) was added slowly at 0°C and the mixture stirred for 15 min (NOTE: These conditions for the silylcupration step are convenient, but certainly too vigorous, since lower temperatures work equally well). AcCl (495 mg, 7 mmol) was added and the mixture was stirred for 1 h. $\text{aq NH}_4\text{Cl}$ (1 mL) was added and the mixture was stirred for 5 min. Petroleum ether (bp $40\text{--}60^\circ\text{C}$) (10 mL) was added and the layers separated. The organic layer was washed with NH_4Cl soln, dried (MgSO_4), and concentrated in vacuo, and the residue was chromatographed (silica gel, petroleum ether/ Et_2O 19:1) to give **36**; yield: 0.60 g (72%).

4.4.41.3

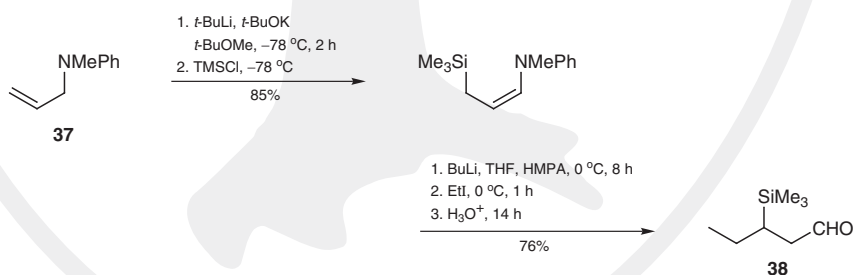
Method 3:**Electrophilic Silylation of Functionalized Three-Carbon Reagents**

A wide variety of nucleophilic three-carbon units, usually lithium or Grignard reagents with suitable functionality at C1, can be silylated by silyl halides at C3. The functional group is then converted into a carbonyl group by an appropriate and usually standard method to reveal the β -silyl carbonyl compound.

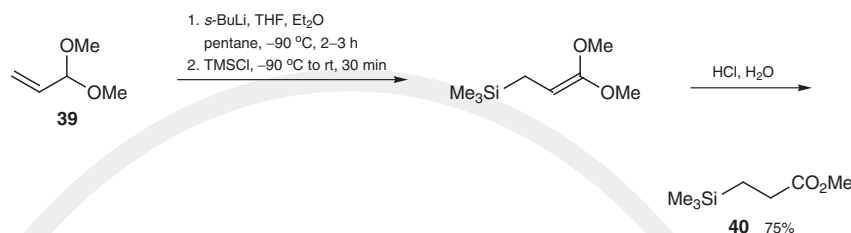
4.4.41.3.1

Variation 1:**Electrophilic Silylation of Allyllithium Reagents**

Allyllithium reagents carrying one or two oxygen or nitrogen atoms at one end of the allyl system can be silylated at the unsubstituted end of the allyl unit using a silyl halide. The resulting enol ether or enamine can be hydrolyzed to release the carbonyl group. Representative examples (Scheme 11) include allyllithium reagents derived from enamine **37**^[59,60] and enol ether **39**.^[61,62]

Scheme 11 Silylation of Allyllithium Reagents^[59–62]

for references see p 945

**3-(Trimethylsilyl)pentanal (38); Typical Procedure:**^[60]

1.6 M *t*-BuLi in pentane (7 mL, 11 mmol) was added by syringe to *N*-methyl-*N*-phenylprop-2-enamine (**37**; 1.47 g, 10 mmol) and *t*-BuOK (1.1 g, 11 mmol) in *tert*-butyl methyl ether (30 mL) with stirring under argon at -78 °C, and the mixture maintained at this temperature for 2 h. TMSCl (1.2 g, 11 mmol) was added by syringe, and the mixture kept at -78 °C for 15 min. The mixture was warmed to rt, washed with H₂O (3 × 20 mL), and dried (MgSO₄), the solvent was removed in vacuo, and the residue was distilled (Kugelrohr, 70 °C/0.05 Torr) to give the silylated enamine; yield: 1.86 g (85%).

1.4 M BuLi in hexane (4 mL, 5.5 mmol) was added by syringe to the silylated enamine (1.1 g, 5 mmol) in THF (20 mL) with stirring at 0 °C. HMPA (2 mL) was added, and the mixture maintained at this temperature for 8 h to complete the metalation. EtI (0.86 g, 5.5 mmol) was added by syringe, and the mixture stirred at 0 °C for 1 h. H₂O (20 mL) was added, and the organic layer separated, diluted with Et₂O (20 mL), and stirred with 4 M HCl (20 mL) for 14 h. CH₂Cl₂ (20 mL) was added, and the organic layer separated, washed with H₂O (2 × 15 mL), and dried (MgSO₄). The solvent was removed in vacuo, and the residue distilled (Kugelrohr) to give the aldehyde **38**; yield: 0.6 g (76%); bp 62 °C/13 Torr.

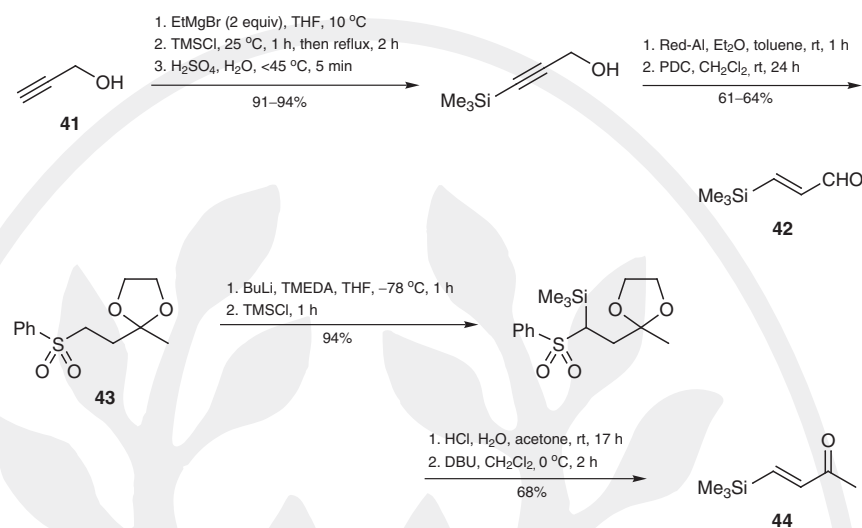
Methyl 3-(Trimethylsilyl)propionate (40); Typical Procedure:^[61]

A Morton flask, fitted with a paddle-type stirrer and a Claisen adapter carrying a low-temperature thermometer and a gas inlet tube, was flame-dried and then allowed to cool under a stream of argon. THF (75 mL), Et₂O (15 mL), pentane (15 mL), and acrolein dimethyl acetal (2.5 mL, 21 mmol) were placed in the flask, and the mixture cooled to -90 ± 5 °C by partial immersion in a liq N₂ filled Dewar flask. 1.1 M *s*-BuLi in cyclohexane (20 mL, 22 mmol) was added dropwise very slowly with stirring under argon, maintaining the temperature at -90 ± 5 °C. The yellow soln was stirred at -90 °C for 2–3 h, and TMSCl (3 g, 27.6 mmol) was added by syringe over 10 min. The milky white mixture was stirred at -90 °C for 30 min, and then allowed to warm to rt. Distillation at this stage, without an aqueous workup, gave the β-silyl dimethyl ketene acetal. Alternatively, the mixture was cannulated into a separatory funnel and treated successively with distilled H₂O, with 5% aq HCl (2 ×), and again with H₂O. The aqueous phases were extracted with pentane, and the combined organic phases were dried (MgSO₄) and concentrated in vacuo. The residue was trap-to-trap distilled (0.1 Torr) with collection in a flask cooled by liq N₂ to give the ester **40**; yield: 2.5 g (75%).

4.4.41.3.2

**Variation 2:
Electrophilic Silylation at C3 of Masked α,β-Unsaturated Aldehydes
and Ketones**

C-Silylation of carbanions derived from masked aldehydes and ketones takes several forms, of which the silylation of propargyl alcohol (**41**)^[63] and the silylation of acetals of β-sulfonyl ketones (e.g., **43**)^[64] provide representative examples (Scheme 12). In both cases the aldehyde **42** or ketone **44** is unmasked by conventional chemistry. The addition of carbon nucleophiles to the aldehyde **42** and oxidation of the resultant alcohols is often used to prepare α,β-unsaturated β-silyl ketones.

Scheme 12 β -Silylation of Masked Enones^[63,64]**(E)-3-(Trimethylsilyl)prop-2-enal (42); Typical Procedure:**^[28,63]

Reprinted from (Jones; Denmark, *Organic Syntheses*), Copyright (1990), p 524, with permission from John Wiley & Sons, Inc.

A 3-L, three-necked, round-bottomed flask (equipped with a mechanical stirrer and a thermometer) was fitted with a Claisen adapter on which was mounted a 250-mL pressure-equalizing addition funnel and a reflux condenser. The apparatus was flushed with N_2 and then charged with Mg turnings (48.7 g, 2 mol) and dry THF (1 L). EtBr (149.5 mL, 218.3 g, 2 mol) was added dropwise over 3 h while maintaining the temperature at 50 °C or less. After complete addition, the gray-green soln was heated at 50 °C for 1 h, and then cooled on ice to 5 °C. Propargyl alcohol (**41**; 41.6 mL, 40.5 g, 0.72 mol) in THF (42 mL) was added dropwise and cautiously to the gray suspension over 2.25 h, while maintaining the temperature at 10 °C or less. The soln was cooled to 5 °C on ice. TMSCl (254 mL, 217 g, 2 mol) was added from the addition funnel over 1 h, while maintaining the temperature at 25 °C or less by external cooling with ice. After complete addition, the mixture was refluxed for 2 h, and then cooled to 20 °C. 1.4 M aq H_2SO_4 (800 mL) was added cautiously over 45 min, keeping the temperature below 45 °C. The mixture was stirred for 5 min, and then Et_2O (600 mL) was added, and the mixture transferred to a separatory funnel. The aqueous phase was extracted with Et_2O (2×400 mL), and each Et_2O layer washed in series with H_2O (2×1 L) and sat. brine (800 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo, and the yellow-brown residue distilled to give 3-(trimethylsilyl)prop-2-yn-1-ol; yield: 82–86 g (91–94%); bp 76 °C/20 Torr.

3.4 M Red-Al in toluene (147 mL, 0.5 mol) and Et_2O (200 mL) were placed in a 2-L round-bottomed flask fitted with a thermometer, a N_2 inlet, a 250-mL pressure-equalizing addition funnel, and a magnetic stirrer bar. The soln was cooled to 3 °C on ice and then treated dropwise from the addition funnel with a soln of 3-(trimethylsilyl)prop-2-yn-1-ol (40 g, 0.31 mol) in Et_2O (180 mL) over 1.25 h, while maintaining the temperature at 5 °C or less. After 10 min, the ice bath was removed and the reaction allowed to go to completion over 1 h. The mixture was cooled to 0 °C and then quenched by the addition of 3.6 M aq H_2SO_4 (1 L). The layers were separated and the aqueous phase extracted with Et_2O (2×200 mL). Each Et_2O layer was washed in series with H_2O (2×200 mL) and sat. brine (200 mL). The combined Et_2O layers were dried ($MgSO_4$) and concentrated in vacuo, and the yellow residue distilled to give (*E*)-3-(trimethylsilyl)prop-2-en-1-ol; yield: 27.7–29.0 g (68–71%); bp 73–75 °C/20 Torr.

for references see p 945

Pyridinium dichromate (56.5 g, 0.15 mol) was added with stirring to (*E*)-3-(trimethylsilyl)prop-2-en-1-ol (13 g, 0.1 mol) in CH₂Cl₂ (180 mL) under N₂, and the mixture kept at rt for 24 h. The mixture was filtered through Celite, and the thick black residue washed with more CH₂Cl₂. The solvent was evaporated off, the residue was taken up in Et₂O and filtered again through Celite, and the Et₂O was evaporated off. The residue was purified by chromatography [silica gel (300 g), CH₂Cl₂] to give the aldehyde **42**; yield: 11.5 g (90%); bp 53–54 °C/30 Torr.

4-(Trimethylsilyl)but-3-en-2-one (**44**); Typical Procedure:^[64]

1.5 M BuLi in pentane (13.6 mL, 20.4 mmol) was added dropwise to a soln of the acetal **43** (4.11 g, 17 mmol) and TMEDA (5.93 g, 51 mmol) in THF (100 mL) at –78 °C and the mixture was stirred for 1 h. TMSCl (3.69 g, 34 mmol) was added and the soln was stirred for a further 1 h. The mixture was diluted with benzene and H₂O, and the organic layer was separated, dried, and concentrated in vacuo. The residue was chromatographed (silica gel, hexane/Et₂O 10:1) to give the silylated acetal; yield: 5.0 g (94%); mp 85–86 °C.

The silylated acetal (4.5 g, 14.3 mmol) was stirred at rt in acetone (100 mL) and 5 M aq HCl (100 mL) for 17 h. The mixture was extracted with benzene, and the extracts washed with H₂O, dried, and concentrated in vacuo. The residue was chromatographed (silica gel, hexane/Et₂O 10:1) to give the β-sulfonyl ketone; yield: 2.91 g (75%); mp 50–53 °C. This ketone (200 mg, 0.74 mmol) was stirred with DBU (225 mg, 1.48 mmol) in CH₂Cl₂ (7 mL) under N₂ at 0 °C for 2 h. To avoid loss of the relatively volatile product during evaporation of the CH₂Cl₂, the mixture was chromatographed (silica gel, pentane). The pentane was removed by careful distillation using a fractionating column, and the residue was distilled (Kugelrohr) in the presence of hydroquinone to give the enone **44**; yield: 86 mg (91%); bp 53–54 °C/30 Torr.

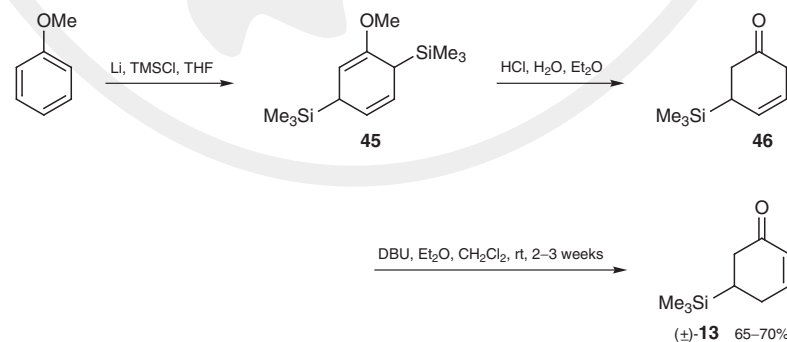
4.4.41.3.3

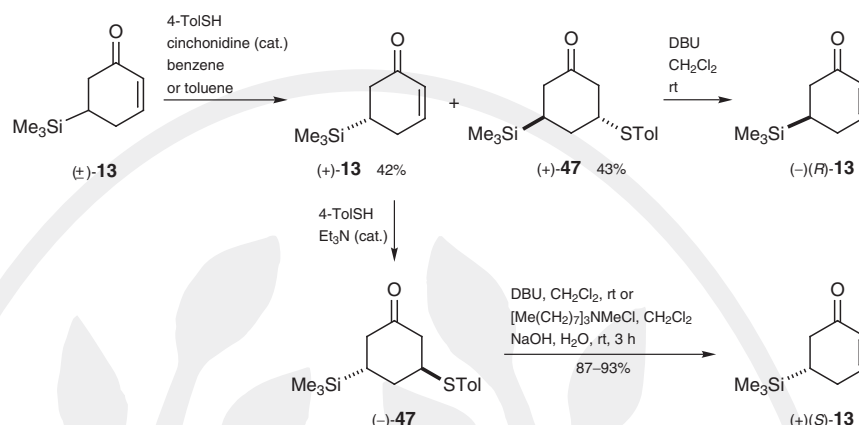
Variation 3:

Reductive Silylation of Anisole and Hydrolysis

Racemic 5-(trimethylsilyl)cyclohex-2-enone [(±)-**13**] can be prepared by reductive silylation of anisole using lithium and chlorotrimethylsilane (Scheme 13).^[65] The first-formed product **45** has a silyl group at C2, as well as at C5, but it is easily lost during hydrolysis, which can be stopped at the unconjugated ketone **46** or continued to the conjugated ketone (±)-**13**, in reactions that can be carried out on a fairly large scale.^[66] Kinetic resolution using a cinchonidine-catalyzed conjugate addition of 4-toluenethiol gives the enantiomerically enriched ketone (+)-**13** and the crystalline adduct (+)-**47**. The former is converted into the enantiomeric adduct (–)-**47**, and both the (+)- and (–)-adducts can be recrystallized to high enantiomeric purity in overall yields of 21% and 16%, respectively. The enantiomerically enriched ketones (+)- and (–)-**13** can then be prepared by base-catalyzed elimination of the 4-tolylsulfanyl group.^[66]

Scheme 13 Reductive Silylation of Anisole and Kinetic Resolution of 5-(Trimethylsilyl)cyclohex-2-enone^[65,66]





Racemic 5-(Trimethylsilyl)cyclohex-2-enone [(±)-13].^[66]

Powdered Li (30% suspension in oil; 100 g, 4.39 mol) suspended in THF (800 mL) was added dropwise with stirring, keeping the temperature between -20 and -10 °C, to a mixture of anisole (210 g, 1.94 mol) and TMSCl (750 mL). After the addition was complete, the mixture was stirred at rt overnight, and filtered under argon, taking care in the disposal of the solid residue, which could contain inflammable Li powder. The volatile components were distilled off in vacuo and the residue distilled to give the crude diene **45**; yield: 431–473 g; bp 95–105 °C/6 Torr. The product was divided in two, and one half in Et₂O (400 mL) transferred to a 3-L flask fitted with three efficient condensers. 2 M Aq HCl (35 mL) was added and the mixture stirred for 15 min, initiating a vigorous exotherm, causing the Et₂O to boil, which was moderated with cold H₂O on the outside of the flask. The mixture was stirred for a further 30 min after the exotherm had subsided. The Et₂O was neutralized with aqueous alkali, and the Et₂O layer concentrated to give the crude ketone **46**. The rest of the diene was treated similarly and the two crops combined, and dissolved in CH₂Cl₂ (700 mL) and Et₂O (700 mL). DBU (10 g) was added and the mixture kept at rt for 2–3 weeks. Workup as usual and distillation through an efficient column gave the ketone (±)-**13**; yield: 212–230 g (65–70%, based on anisole); bp 65.5–67 °C/2 Torr.

Resolution of 5-(Trimethylsilyl)cyclohex-2-enone [(+)(S)- and (-)(R)-13].^[66]

The racemic ketone (±)-**13** (90 g, 0.536 mol), 4-toluenethiol (36.3 g, 0.295 mol) and cinchonidine (1.58 g, 5.36 mmol) were kept at rt overnight in dry benzene or dry toluene (2.8 L). The volume was reduced to 1 L, and the mixture washed with 2 M aq HCl and dried (MgSO₄). Pentane (200 mL) was added and the mixture kept at 0 °C for 12 h, when the ketone (+)-**47** was filtered off; yield: 66.5 g (43%); 60% ee. Distillation of the filtrate gave the ketone (+)(S)-**13**; yield: 38 g (42%); 54% ee. A similar conjugate addition of 4-toluenethiol to (+)(S)-**13** using Et₃N gave the crystalline adduct (-)-**47**. Recrystallizations from hexane gave the two adducts essentially enantiomerically pure; yield of (+)-**47**: 33.4 g (21%); $[\alpha]_D^{20} +35.54$ (*c* 1.08, CHCl₃); yield of (-)-**47**: 24.5 g (16%); $[\alpha]_D^{20} -35.5$ (*c* 1.0, CHCl₃). Treatment of the adducts with DBU in CH₂Cl₂ at rt or with methyltriocetylammmonium chloride in a mixture of CH₂Cl₂ and 10% aq NaOH at rt for 3 h gave the unsaturated ketones (-)(R)-**13** and (+)(S)-**13** in 87–93% yield.

4.4.41.4

Method 4:

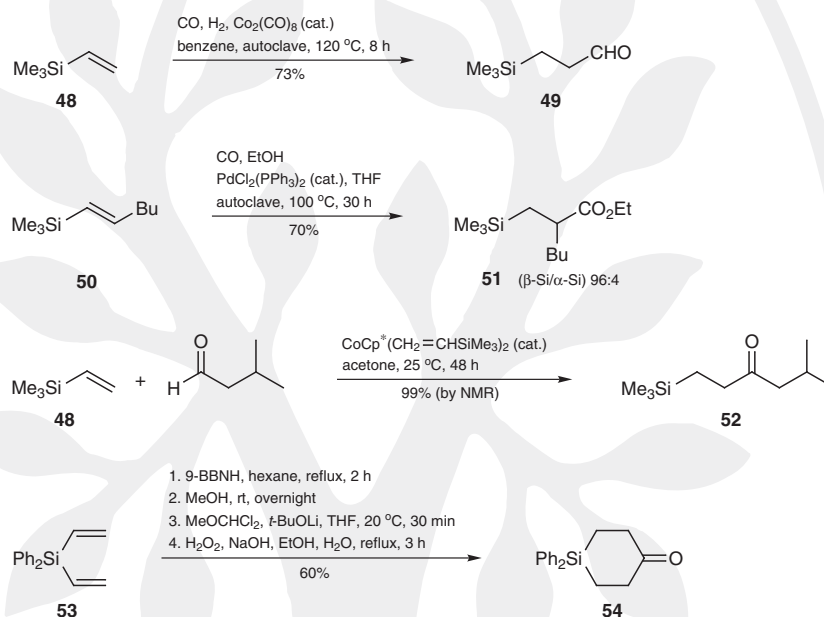
Carbonylation or Carboxylation of Vinylsilanes

Hydroformylation of the vinylsilane **48** using a cobalt catalyst gives the β -silylpropanal **49** with complete regioselectivity (Scheme 14),^[67] whereas the more reactive rhodium catalysts lead to mixtures of the regioisomeric aldehydes with selectivity up to 90:10. The re-

for references see p 945

gioselectivity can be increased to better than 98:2 if the silyl group is *tert*-butyldiphenylsilyl.^[68] The palladium-catalyzed addition of carbon monoxide in ethanol to the terminal vinylsilane **50** leads to an ethyl ester **51** with a β -silyl group, whereas a cobalt catalyst gives high α -selectivity, in contrast to the hydroformylation reaction.^[69] A similar reaction with an ethynylsilane leads to the corresponding unsaturated β -silyl ester.^[70] β -Silyl ketones, for example **52**, can be prepared in a similar way using a cobalt catalyst and an aldehyde in place of the carbon monoxide.^[71] Similarly, but stoichiometrically, hydroboration and carbonylation with dichloromethyl methyl ether then oxidation leads to β -silyl carbonyl compounds, in a reaction particularly useful for the synthesis of the silacyclohexanone **54** from diphenyldivinylsilane (**53**).^[72,73]

Scheme 14 Hydrocarbonylation of Vinylsilanes^[67,69,71,72]



3-(Trimethylsilyl)propanal (49); Typical Procedure:^[67]

A 50-mL stainless steel autoclave, equipped with a glass liner and a magnetic stirrer bar, was charged with benzene (10 mL), trimethyl(vinyl)silane (1.0 g, 10 mmol) and $\text{Co}_2(\text{CO})_8$ (freshly recrystallized from pentane; 1.7 mg, 0.005 mmol). The vessel was pressurized to $80 \text{ kg} \cdot \text{cm}^{-2}$ with a mixture of CO and H_2 (1:1) and heated at 120°C for 8 h. The mixture was distilled to give **49**; yield: 0.95 g (73%); bp $57\text{--}58^\circ\text{C}/30 \text{ Torr}$.

Ethyl 2-[(Trimethylsilyl)methyl]hexanoate (51); Typical Procedure:^[69]

EtOH (1.9 mL, 25 mmol), THF (10 mL), 1-(trimethylsilyl)hex-1-ene (0.78 g, 5 mmol), and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.035 g, 0.05 mmol) were placed in a stainless steel autoclave equipped with a glass liner and magnetic stirrer bar. The reactor was sealed and flushed with CO , and then pressurized with CO to $60 \text{ kg} \cdot \text{cm}^{-2}$. The mixture was stirred and heated at 100°C for 30 h. The cold reactor was opened, and the mixture distilled to give the β -silyl ester **51**; yield: 0.81 g (70%); bp $85^\circ\text{C}/7 \text{ Torr}$.

5-Methyl-1-(trimethylsilyl)hexan-3-one (52); Typical Procedure:^[71]

A flask with a Teflon screw cap was charged in a dry box under argon with $\text{CoCp}^*(\text{CH}_2=\text{CHSiMe}_3)_2$ (0.05 g, 0.127 mmol) and acetone (2–3.5 mL) to form a homogeneous soln. Trimethyl(vinyl)silane (0.635 g, 6.35 mmol) was added, followed by 3-methyl-

butanal (0.55 g, 6.35 mmol). The flask was sealed with the Teflon screw top and stirred at 25 °C for 48 h, or at 45 °C for 24 h. The flask was opened to the air, and the degree of conversion (99%) measured by $^1\text{H NMR}$ spectroscopy. For isolation, the mixture was filtered through a Celite plug, the volatiles were removed in vacuo, and the residue was chromatographed (silica gel, pentane/ Et_2O).

1,1-Diphenyl-1-silacyclohexan-4-one (54):^[72]

Diphenyldivinylsilane (23.6 g, 0.1 mol) and 9-BBNH (24.4 g, 0.1 mol) were refluxed in hexane (170 mL) for 2 h. The mixture was cooled and 2 M BMS in THF (50 mL, 0.1 mol) was added dropwise, and the mixture was refluxed for 1 h. MeOH (35 mL) was added to the cooled mixture, resulting in a rapid evolution of H_2 gas. The mixture was stirred at rt overnight, and then concentrated in vacuo at 35 °C. A soln of *t*-BuOLi was prepared from *t*-BuOH (47.4 mL, 0.5 mol) in THF (350 mL) by adding 1.6 M BuLi in THF (312 mL, 0.5 mol) at 0 °C and stirring for 15 min. Dichloromethyl methyl ether (8.9 mL, 0.1 mol) was added to the borinane in THF (300 mL), followed by the *t*-BuOLi soln, and the mixture was kept at 20 °C for 30 min. EtOH (120 mL), H_2O (35 mL), and NaOH pellets (12 g, 0.3 mol) were added successively, followed by dropwise addition of 30% H_2O_2 (33 mL), and the mixture was refluxed for 3 h. H_2O (1 L) was added and the mixture extracted with EtOAc (3 \times 500 mL). The combined organic layers were dried (MgSO_4), concentrated in vacuo, and the residue was chromatographed (silica gel, CH_2Cl_2 /cyclohexane 1:1) to give the ketone **54** as needles; yield: 16 g (60%); mp 92 °C.

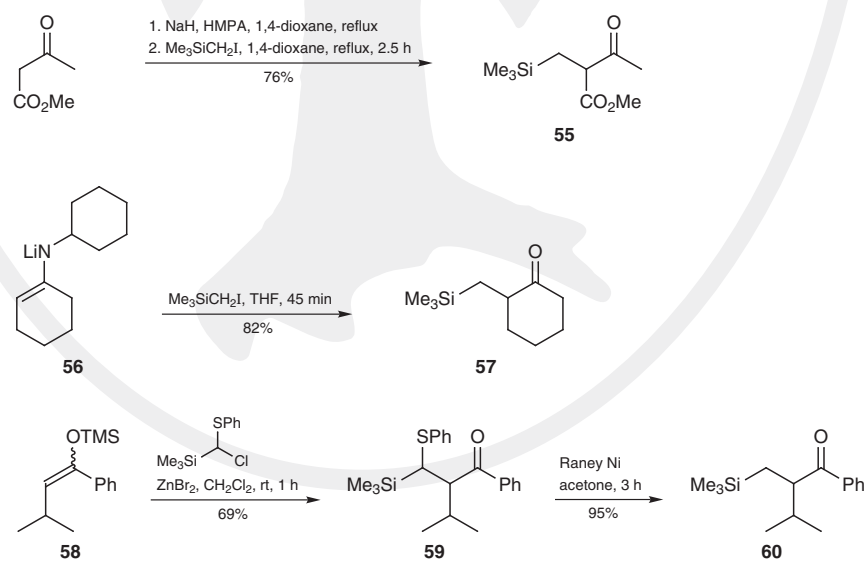
4.4.41.5

Method 5:

Trimethylsilylmethylation of Enolates and Enolate Equivalents

(Iodomethyl)trimethylsilane can be used to alkylate the enolates of β -dicarbonyl compounds (Scheme 15).^[12] The anions derived from nitriles^[74] and the azaenolate **56** derived from cyclohexanone can be alkylated even more easily, and then hydrolyzed to give a simple ketone.^[6,12] Alternatively, (phenylsulfanyl)(trimethylsilyl)methylation can be carried out on a silyl enol ether **58**, and the product **59** can be desulfurized to give the β -silyl ketone **60**.^[17,75,76]

Scheme 15 Silylmethylation of Enolates and Enolate Equivalents^[12,17]



for references see p 945

Methyl 3-Oxo-2-[(trimethylsilyl)methyl]butyrate (55); Typical Procedure:^[12]

Methyl acetoacetate (19.48 g, 168 mmol) in dry 1,4-dioxane (50 mL) was added dropwise to a stirred suspension of NaH (50% dispersion in oil, washed with hexane; 8.64 g, 180 mmol) in dry HMPA (40 mL) and dry 1,4-dioxane (60 mL) under reflux. After H₂ evolution had ceased, the flask was flushed with N₂, and Me₃SiCH₂I (25.68 g, 120 mmol) in dry 1,4-dioxane (50 mL) was added, and the mixture was refluxed for 2.5 h. The mixture was poured into brine, and extracted with petroleum ether (bp 40–60 °C). The combined organic layers were washed repeatedly with brine, dried (MgSO₄), and concentrated in vacuo. The residue was distilled to give the ester **55**; yield: 18.0 g (76%); bp 40–44 °C/0.1 Torr.

2-[(Trimethylsilyl)methyl]cyclohexanone (57); Typical Procedure:^[12]

N-Cyclohexylidenecyclohexylamine (freshly prepared; 18.4 g, 100 mmol) in dry THF (20 mL) was added dropwise to a stirred soln of LDA (105 mmol) in dry THF (200 mL) at 0 °C under N₂. The mixture was kept at 0 °C for 30 min, Me₃SiCH₂I (22.5 g, 105 mmol) was added, and the mixture stirred for 45 min. The mixture was poured into brine, and extracted with Et₂O. The combined Et₂O layers were shaken with AcOH (50 mL) and H₂O (50 mL) for 5 min, separated and washed repeatedly with sat. NaHCO₃ soln, dried (MgSO₄), and concentrated in vacuo. The residue was distilled to give the ketone **57**; yield: 15.1 g (82%); bp 73–75 °C/4.5 Torr.

3-Methyl-1-phenyl-2-[(trimethylsilyl)methyl]butan-1-one (60); Typical Procedure:^[17]

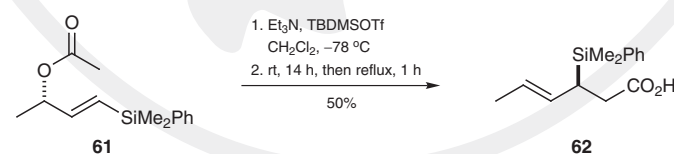
The silyl enol ether **58** (2.34 g, 10 mmol) (prepared from crotonophenone and lithium dimethylcuprate, followed by treatment in situ with TMSCl) and [chloro(phenylsulfanyl)methyl]trimethylsilane (2.31 g, 10 mmol) (prepared from Me₃SiCH₂SPh and NCS) were stirred with ZnBr₂ (50 mg) in CH₂Cl₂ (20 mL) for 1 h at rt. The mixture was diluted with pentane (20 mL), filtered through neutral alumina (10 g) and the filtrate was evaporated in vacuo. The residue was chromatographed [silica gel, Et₂O/petroleum ether (bp 30–40 °C) 5:95] to give the mixture of diastereomers **59**; yield: 2.45 g (69%).

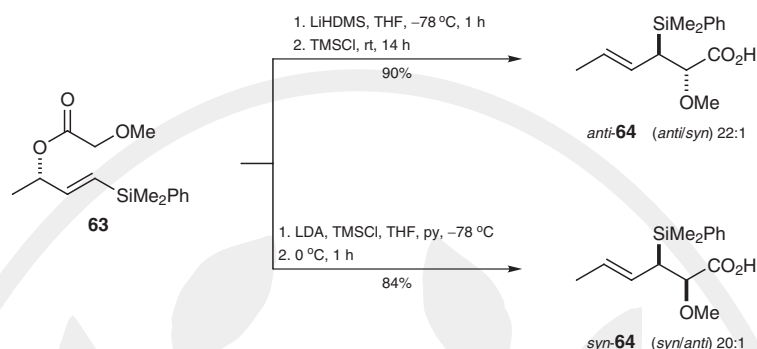
This mixture (2.13 g, 6 mmol) and Raney nickel (9 g) were stirred in acetone (30 mL) for 3 h. The mixture was filtered and the solvent evaporated under reduced pressure to give the ketone **60**; yield: 1.41 g (95%).

4.4.41.6

Method 6:**Claisen Rearrangement of Esters of 3-Silylallyl Alcohols**

The Ireland–Claisen rearrangement of the acetate ester **61** gives the acid **62**, and the corresponding reaction with the substituted ester **63** can be made to give either the *anti*- or *syn*-acid **64**, depending upon the choice of geometry in the intermediate silyl enol ether (Scheme 16).^[77] A variation is use of the Eschenmoser–Claisen rearrangement directly from the allylic alcohol with the dimethyl acetal of *N,N*-dimethylacetamide, giving an amide.^[78]

Scheme 16 Claisen Rearrangements^[77]

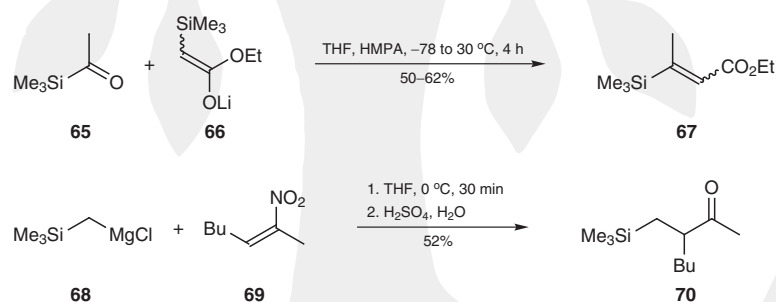


These methods are particularly powerful for the synthesis of enantiomerically enriched β -silyl carbonyl compounds, because of the ease with which the β -silylallyl alcohols can be prepared enantiomerically enriched, by kinetic resolution (by Sharpless asymmetric epoxidation^[79,80]), by enzymatic hydrolysis of their esters,^[39] or by resolution of their allylic isomers and palladium-catalyzed 1,3-allylic rearrangement of those esters.^[81,95] The resulting compounds are simultaneously allylsilanes and β -silyl carbonyl compounds, and are usually used as allylsilanes (Scheme 5). A procedure for their synthesis is included in the section on allylsilanes (Section 4.4.40.14.2).

4.4.41.7 Additional Methods

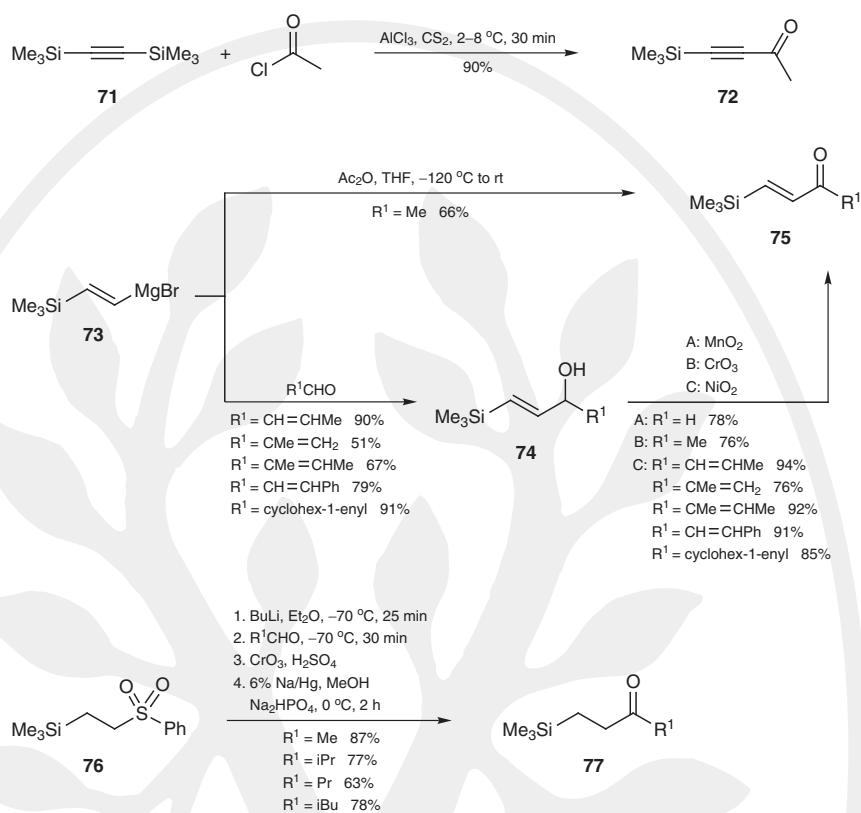
Among methods forming the central C—C bond (Scheme 17), aldol condensations on acylsilanes result in β -silyl carbonyl compounds, with the Peterson variant (e.g., **65**→**67**) probably the best.^[82] The trimethylsilylmethyl Grignard reagent **68** reacts with nitroethenes (e.g., **69**) to give the Nef product **70**.^[83]

Scheme 17 Other Methods Forming the Central C—C Bond^[82,83]

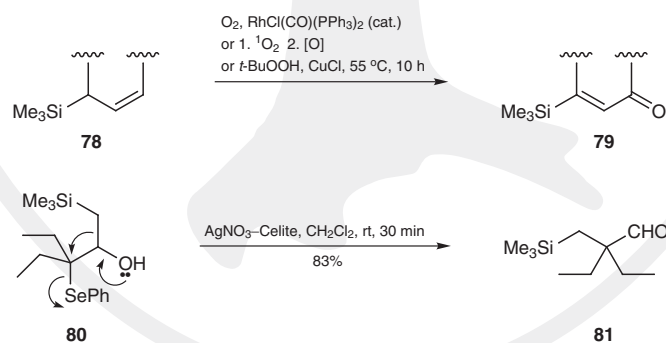


Among methods forming the C—C bond to the acyl group (Scheme 18), the ethynylsilane **71** can be acylated to remove only one of the silyl groups to provide **72**.^[84,85] The corresponding disilylethene behaves similarly.^[86] The Grignard reagent **73** reacts with acetic anhydride^[87] or with aldehydes,^[25] and in the latter case the allyl alcohol **74** can be oxidized with manganese(IV) oxide,^[28] several of the common chromium-based reagents,^[28] and, if it is doubly allylic, with nickel peroxide or barium permanganate,^[25] to give the unsaturated ketones **75**. At the saturated level, the carbanion derived from the sulfone **76** reacts with aldehydes, and the alcohols so produced can be successively oxidized and desulfurized to give the ketones **77**.^[88]

for references see p 945

Scheme 18 Other Methods Forming the C—C Bond to the Acyl Group^[25,28,84,85,87,88]

Among methods simply changing the functionality on an intact carbon skeleton (Scheme 19), allylsilanes **78** can be oxidized to give β-silyl enones **79**.^[89–91] There is also a method using the cationic rearrangement of a trimethylsilylmethyl group from a carbinol carbon to a neighboring atom carrying a selenide leaving group (see **80**), which gives the aldehyde **81**, with silver ion catalysis.^[92]

Scheme 19 Other Methods Using or Rearranging an Intact Carbon Skeleton^[89–92]

References

- [1] Sommer, L. H.; Pioch, R. P.; Marans, N. S.; Goldberg, G. M.; Rockett, J.; Kerlin, J., *J. Am. Chem. Soc.*, (1953) **75**, 2932.
- [2] Fleming, I., *Chemtracts, Org. Chem.*, (1996) **9**, 1.
- [3] Crump, R. A. N. C.; Fleming, I.; Hill, J. H. M.; Parker, D.; Reddy, N. L.; Waterson, D., *J. Chem. Soc., Perkin Trans. 1*, (1992), 3277.
- [4] Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J., *J. Chem. Soc., Perkin Trans. 1*, (1995), 317.
- [5] Hudrlik, P. F.; Hudrlik, A. M.; Nagendrappa, G.; Yimenu, T.; Zellers, E. T.; Chin, E., *J. Am. Chem. Soc.*, (1980) **102**, 6894.
- [6] Hudrlik, P. F.; Hudrlik, A. M.; Yimenu, T.; Waugh, M. A.; Nagendrappa, G., *Tetrahedron*, (1988) **44**, 3791.
- [7] Nishiyama, H.; Sakuta, K.; Osaka, N.; Arai, H.; Matsumoto, M.; Itoh, K., *Tetrahedron*, (1988) **44**, 2413.
- [8] Hermeling, D.; Schäfer, H. J., *Chem. Ber.*, (1988) **121**, 1151.
- [9] Nishiyama, H.; Matsumoto, M.; Arai, H.; Sakaguchi, H.; Itoh, K., *Tetrahedron Lett.*, (1986) **27**, 1599.
- [10] Hwu, J., In *Modern Methodology in Organic Synthesis*, Shono, T., Ed.; VCH: Weinheim, (1992); pp 149-163.
- [11] Tietze, L. F.; Wünsch, J. R., *Synthesis*, (1990), 985.
- [12] Fleming, I.; Goldhill, J., *J. Chem. Soc., Perkin Trans. 1*, (1980), 1493.
- [13] Ager, D. J.; Fleming, I.; Patel, S. K., *J. Chem. Soc., Perkin Trans. 1*, (1981), 2520.
- [14] Asaoka, M.; Shima, K.; Takei, H., *J. Chem. Soc., Chem. Commun.*, (1988), 430.
- [15] Asaoka, M.; Shima, K.; Fujii, N.; Takei, H., *Tetrahedron*, (1988) **44**, 4757.
- [16] Asaoka, M.; Aida, T.; Sonoda, S.; Takei, H., *Tetrahedron Lett.*, (1989) **30**, 7075.
- [17] Fleming, I.; Patel, S. K.; Urch, C. J., *J. Chem. Soc., Perkin Trans. 1*, (1989), 115.
- [18] Fleming, I.; Gil, S.; Sarkar, A. K.; Schmidlin, T., *J. Chem. Soc., Perkin Trans. 1*, (1992), 3351.
- [19] Masse, C. E.; Panek, J. S., *Chem. Rev.*, (1995) **95**, 1293.
- [20] Panek, J. S.; Beresis, R., *J. Org. Chem.*, (1993) **58**, 809.
- [21] Wilson, S. R.; Di Grandi, M. J., *J. Org. Chem.*, (1991) **56**, 4766.
- [22] Kolb, H. C.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J., *J. Chem. Soc., Perkin Trans. 1*, (1992), 2735.
- [23] Fleming, I.; Perry, D. A., *Tetrahedron*, (1981) **37**, 4027.
- [24] Oliver, J. E.; Waters, R. M.; Lusby, W. R., *Tetrahedron*, (1990) **46**, 1125.
- [25] Jones, T. K.; Denmark, S. E., *Helv. Chim. Acta*, (1983) **66**, 2377.
- [26] Denmark, S. E.; Habermas, K. L.; Hite, G. A., *Helv. Chim. Acta*, (1988) **71**, 168.
- [27] Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utimoto, K., *J. Org. Chem.*, (1992) **57**, 1973.
- [28] Carter, M. J.; Fleming, I.; Percival, A., *J. Chem. Soc., Perkin Trans. 1*, (1981), 2415.
- [29] Gibson, S. E.; Tustin, G. J., *J. Chem. Soc., Perkin Trans. 1*, (1995), 2427.
- [30] Takeuchi, R.; Nitta, S.; Watanabe, D., *J. Org. Chem.*, (1995) **60**, 3045.
- [31] Birkofer, L.; Quittmann, W., *Chem. Ber.*, (1985) **118**, 2874.
- [32] Fleming, I.; Kilburn, J. D., *J. Chem. Soc., Perkin Trans. 1*, (1998), 2663.
- [33] Takeshita, K.; Seki, Y.; Kawamoto, K.; Murai, S.; Sonoda, N., *J. Org. Chem.*, (1987) **52**, 4864.
- [34] Fleming, I.; Kindon, N. D., *J. Chem. Soc., Perkin Trans. 1*, (1995), 303.
- [35] Oppolzer, W.; Mills, R. J.; Pachinger, W.; Stevenson, T., *Helv. Chim. Acta*, (1986) **69**, 1542.
- [36] Zwicky, A. B., M. Sc. Thesis, University of Cambridge, (1998).
- [37] Ojima, I.; Donovan, R. J.; Eguchi, M.; Shay, W. R.; Ingallina, P.; Korda, A.; Zeng, Q., *Tetrahedron*, (1993) **49**, 5431.
- [38] Matsuda, I.; Ishibashi, H.; Ii, N., *Tetrahedron Lett.*, (1995) **36**, 241.
- [39] Jain, N. F.; Cirillo, P. F.; Schaus, J. V.; Panek, J. S., *Tetrahedron Lett.*, (1995) **36**, 8723.
- [40] Monteil, F.; Matsuda, I.; Alper, H., *J. Am. Chem. Soc.*, (1995) **117**, 4419.
- [41] Ojima, I.; Vidal, E.; Tzamarioudaki, M.; Matsuda, I., *J. Am. Chem. Soc.*, (1995) **117**, 6797.
- [42] Leighton, J. L.; Chapman, E., *J. Am. Chem. Soc.*, (1997) **119**, 12416.
- [43] Matsumoto, Y.; Hayashi, T.; Ito, Y., *Tetrahedron*, (1994) **50**, 335.
- [44] Altnau, G.; Rösch, L.; Jas, G., *Tetrahedron Lett.*, (1983) **24**, 45.
- [45] Crump, R. A. N. C.; Fleming, I.; Urch, C. J., *J. Chem. Soc., Perkin Trans. 1*, (1994), 701.
- [46] MacLean, B. L.; Hennigar, K. A.; Kells, K. W.; Singer, R. D., *Tetrahedron Lett.*, (1997) **38**, 7313.
- [47] Fleming, I., In *Organocopper Reagents: A Practical Approach*, Taylor, R. J. K., Ed.; Oxford University Press: Oxford, (1995); pp 257-292.

- [48] Still, W. C.; Mitra, A., *Tetrahedron Lett.*, (1978), 2659.
- [49] Fleming, I.; Lee, D., *J. Chem. Soc., Perkin Trans. 1*, (1998), 2701.
- [50] Ohno, T.; Nakahiro, H.; Sanemitsu, K.; Hirashima, T.; Nishiguchi, I., *Tetrahedron Lett.*, (1992) **33**, 5515.
- [51] Dunoguès, J.; Calas, R.; Bolourtchian, M.; Biran, C.; Duffaut, N., *J. Organomet. Chem.*, (1973) **57**, 55.
- [52] Brosius, A. D.; Overman, L. E.; Schwink, L., *J. Am. Chem. Soc.*, (1999) **121**, 700.
- [53] Ito, H.; Ishizuka, T.; Tateiwa, J.; Sonoda, M.; Hosomi, A., *J. Am. Chem. Soc.*, (1998) **120**, 11196.
- [54] Palomo, C.; Aizpurua, J. M.; Iturburu, M.; Urchegui, R., *J. Org. Chem.*, (1994) **59**, 240.
- [55] Martinez-Barrasa, V., unpublished work, University of Cambridge, (1998).
- [56] Fleming, I.; Newton, T. W.; Roessler, F., *J. Chem. Soc., Perkin Trans. 1*, (1981), 2527.
- [57] Fleming, I.; Newton, T. W.; Sabin, V.; Zammattio, F., *Tetrahedron*, (1992) **48**, 7793.
- [58] Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M., *J. Organomet. Chem.*, (1998) **560**, 217.
- [59] Ahlbrecht, H.; Simon, H., *Synthesis*, (1983), 58.
- [60] Ahlbrecht, H.; Sudheendranath, C. S., *Synthesis*, (1982), 717.
- [61] Seyferth, D.; Mammarella, R. E.; Klein, H. A., *J. Organomet. Chem.*, (1980) **194**, 1.
- [62] Nakahira, H.; Ryu, I.; Ikebe, M.; Kambe, N.; Sonoda, N., *Angew. Chem.*, (1991) **103**, 178; *Angew. Chem., Int. Ed. Engl.*, (1991) **30**, 177.
- [63] Jones, T. K.; Denmark, S. E., *Org. Synth., Coll. Vol. VII*, (1990), 524.
- [64] Otera, J.; Mandai, T.; Shiba, M.; Saito, T.; Shimohata, K.; Takemori, K.; Kawasaki, Y., *Organometallics*, (1983) **2**, 332.
- [65] Laguerre, M.; Dunoguès, J.; Calas, R.; Duffaut, N., *J. Organomet. Chem.*, (1975) **93**, C17.
- [66] Asaoka, M.; Shima, K.; Takei, H., *Tetrahedron Lett.*, (1987) **28**, 5669.
- [67] Takeuchi, R.; Sato, N., *J. Organomet. Chem.*, (1990) **393**, 1.
- [68] Doyle, M. M.; Jackson, W. R.; Perlmutter, P., *Tetrahedron Lett.*, (1989) **30**, 233.
- [69] Takeuchi, R.; Ishii, N.; Sugiura, M.; Sato, N., *J. Org. Chem.*, (1992) **57**, 4189.
- [70] Takeuchi, R.; Sugiura, M., *J. Chem. Soc., Perkin Trans. 1*, (1993), 1031.
- [71] Lenges, C. P.; White, P. S.; Brookhart, M., *J. Am. Chem. Soc.*, (1998) **120**, 6965.
- [72] Damour, D.; Renaudon, A.; Mignani, S., *Synlett*, (1995), 111.
- [73] Soderquist, J. A.; Negron, A., *J. Org. Chem.*, (1989) **54**, 2462.
- [74] Tanino, K.; Katoh, T.; Kuwajima, I., *Tetrahedron Lett.*, (1988) **29**, 1815.
- [75] Ager, D. J., *Tetrahedron Lett.*, (1983) **24**, 419.
- [76] Yamamoto, I.; Okuda, K.; Nagai, S.; Motoyoshiya, J.; Gotoh, H.; Matsuzaki, K., *J. Chem. Soc., Perkin Trans. 1*, (1984), 435.
- [77] Sparks, M. A.; Panek, J. S., *J. Org. Chem.*, (1991) **56**, 3431.
- [78] Jenkins, P. R.; Gut, R.; Wetter, H.; Eschenmoser, A., *Helv. Chim. Acta*, (1979) **62**, 1922.
- [79] Carlier, P. R.; Mungall, W. S.; Schröder, G.; Sharpless, K. B., *J. Am. Chem. Soc.*, (1988) **110**, 2978.
- [80] Kitano, Y.; Matsumoto, T.; Sato, F., *Tetrahedron*, (1988) **44**, 4073.
- [81] Panek, J. S.; Sparks, M. A., *Tetrahedron Asymmetry*, (1990) **1**, 801.
- [82] Larson, G. L.; Soderquist, J. A.; Claudio, M. R., *Synth. Commun.*, (1990) **20**, 1095.
- [83] Hwu, J. R.; Gilbert, B. A., *J. Am. Chem. Soc.*, (1991) **113**, 5917.
- [84] Birkofer, L.; Ritter, A.; Uhlenbrauck, H., *Chem. Ber.*, (1963) **96**, 3280.
- [85] Walton, D. R. M.; Waugh, F., *J. Organomet. Chem.*, (1972) **37**, 45.
- [86] Pillot, J.-P.; Dunoguès, J.; Calas, R., *C. R. Hebd. Seances Acad. Sci. Ser. C*, (1974) **278**, 789.
- [87] Brook, A. G.; Duff, J. M., *Can. J. Chem.*, (1973) **51**, 2024.
- [88] Hsiao, C.-N.; Shechter, H., *J. Org. Chem.*, (1988) **53**, 2688.
- [89] Reuter, J. M.; Sinha, A.; Salomon, R. G., *J. Org. Chem.*, (1978) **43**, 2438.
- [90] Dubac, J.; Laporterie, A.; Iloughmane, H.; Pillot, J.-P.; Deleris, G.; Dunoguès, J., *J. Organomet. Chem.*, (1985) **282**, 149.
- [91] Au-Yeung, B.-W.; Wang, Y., *J. Chem. Soc., Chem. Commun.*, (1985), 825.
- [92] Nishiyama, H.; Kitajima, T.; Yamamoto, A.; Itoh, K., *J. Chem. Soc., Chem. Commun.*, (1982), 1232.
- [93] Jones, G. R.; Landais, Y., *Tetrahedron*, (1996) **52**, 7599.
- [94] Tamao, K., *Adv. Silicon Chem.*, (1996) **3**, 1.
- [95] Panek, J. S.; Sparks, M. A., *J. Org. Chem.*, (1990) **55**, 5564.