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The Brook rearrangement in tandem bond formation strategies

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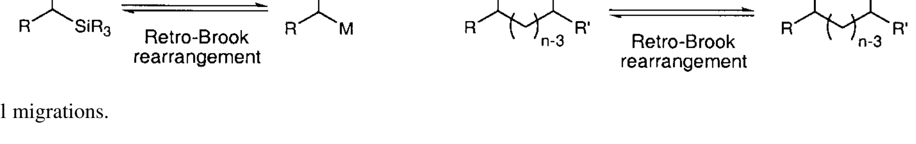
1. Introduction

The intramolecular 1,2-anionic migration of a silyl group from a carbon atom to an oxygen atom was originally recognized and studied by A. G. Brook in the late 1950s and early 1960s.[1] The migratory aptitude of silyl groups in this context has since been observed to be more general, comprising a family of [1,*n*]-carbon to oxygen silyl migrations commonly referred to as Brook rearrangements[2] (Scheme 1). The reverse process, intramolecular migration of a silyl group from oxygen to carbon, was first reported by Speier in 1952,[3] and was later more carefully studied by West et al.[4] As with the carbon to oxygen migrations, further reports established the broad scope of oxygen to carbon migrations, which are now typically called retro-Brook rearrangements. The reversibility of the Brook/retro-Brook reaction manifold has been demonstrated under a variety of circumstances. In addition, many studies have provided evidence suggesting that these reactions proceed via the intermediacy of a pentacoordinate silyl species.[5]

Brook and retro-Brook rearrangements have found increasing use in organic synthesis. A review describing synthetic applications appeared in 1994,[6] and an overview of



Scheme 1. Anionic silyl migrations.

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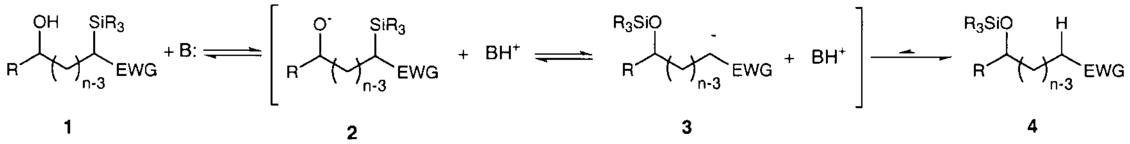


Scheme 2. Anionic silyl migrations as an equilibrium process.

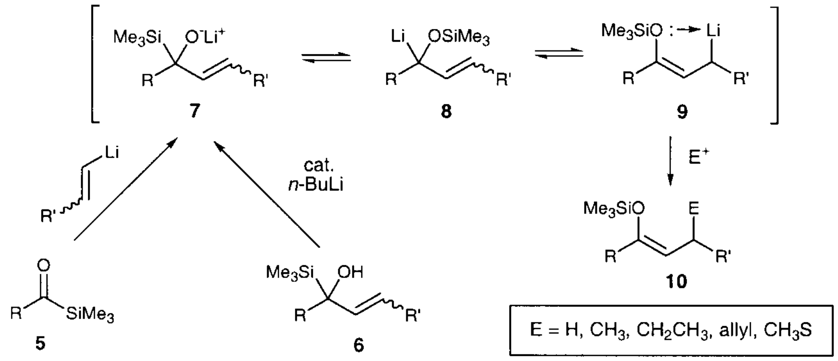
additional mechanistic and synthetic details was reported the following year.[7] Recent studies have further probed the mechanistic details of anionic silyl migrations,[8] with particular emphasis placed on the stereochemistry of the process.[9] In addition, significant interest has developed in the utility of Brook and retro-Brook rearrangements in tandem reactions,[10] or those combining the rearrangements with bond forming steps that precede and/or follow the silyl migration event. The purpose of this report is to highlight synthetically useful applications of the Brook rearrangement that successfully implement a tandem bond formation strategy.

2. General features

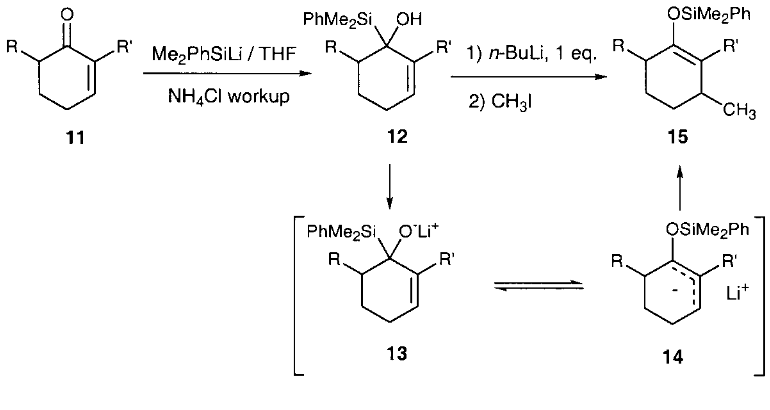
A challenge inherent in the implementation of Brook rearrangement-mediated tandem bond formation strategies is the control of the direction and/or rate of the silyl migration. In this regard, it is instructive to view the reversible silyl migration in terms of an equilibrium process. Assuming the silyl migration has a low energy of activation, the position of the equilibrium is determined by the relative thermodynamic stabilities of the competing species. Consideration of the factors that control the stabilities of the species is therefore paramount in controlling the position of the equilibrium.

When catalytic amounts of base are utilized to facilitate Brook rearrangements, the relative stabilities of the neutral silyl carbinols **1** and silyl ethers **4** govern the position of the equilibrium (Scheme 2).[2a] Provided an electron-withdrawing group (EWG) is present to kinetically facilitate carbanion formation, the strength of the oxygen–silicon bond (120–130 kcal mol^{-1}) compared to the carbon–silicon bond (75–85 kcal mol^{-1}) provides sufficient driving force for complete conversion of α-, β-, or γ-silyl carbinols to the corresponding silyl ethers. The typically rapid and essentially irreversible protonation of the carbanion either by the conjugate acid or by the starting alcohol, however, renders this method ineffective for strategies involving carbon–carbon bond formation subsequent to the silyl migration.

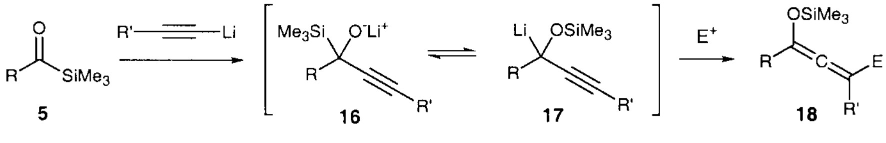
In contrast, for anionic systems (i.e. in the presence of an excess of strong base) the equilibrium is determined by the relative stabilities of the alkoxide **2** and carbanion **3**. In this



Scheme 3. Stereoselective silyl enol ether formation via 1,2-silyl migration.



Scheme 4. Regioselective cyclic silyl enol ether formation.



Scheme 5. Formation of siloxyallenes via 1,2-silyl migration.

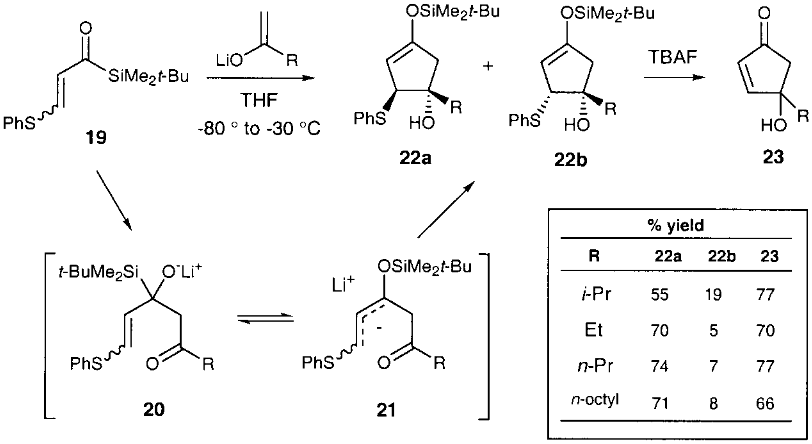
situation, the most important factors are the basicity of the carbanion and the identity of the counterion.[2a,7] The presence of EWGs stabilizes the developing negative charge of the carbanion and favors carbon to oxygen migration of the silyl group. The stability of the alkoxide, on the other hand, correlates with the ion pairing capability of the counterion. The highly aggregated state and tight ion pairing characteristic of lithium alkoxides stabilizes intermediates such as **2** and favors oxygen to carbon silyl migration. Weaker ion pairing exists in the presence of sodium or potassium cations, which increases the reactivity of the alkoxide and shifts the equilibria in favor of the silyl ether **3**. Destabilization of alkoxides can also be accomplished by the addition of reagents that chelate metal counterions, such as crown ethers or TMEDA, or through solvation of the cation with polar aprotic solvents such as THF, DME, HMPA, or DMPU.

3. [1,2] Silyl migrations

The [1,2] silyl migration has been utilized for the regio- and stereoselective formation of silyl enol ethers. Kuwajima et al.[11] and Reich et al.[12] independently reported the carbon to oxygen shift and subsequent γ-protonation of α-silyl vinyl alkoxides **7** to afford (*Z*) silyl enol ethers **10** (Scheme 3). Kuwajima et al.'s method to effect this transformation involved treatment of α-silyl alcohol precursors **6** with catalytic amounts of *n*-BuLi, whereas Reich et al.'s strategy entailed formation of alkoxides **7** via addition of equimolar amounts of vinyllithium reagents to acylsilanes **5**, followed by hydrolysis with H_2O–MeOH. The facile formation of the observed products at low temperatures in both studies demonstrates that the silyl migration is kinetically very rapid. Although it is not clear whether the alkoxide **7** or allyl-stabilized carbanion **8** is thermodynamically favored under the reported reaction conditions, the highly stereoselective formation of the (*Z*) isomers suggests the predominance of the coordination-stabilized species **9** in solution.

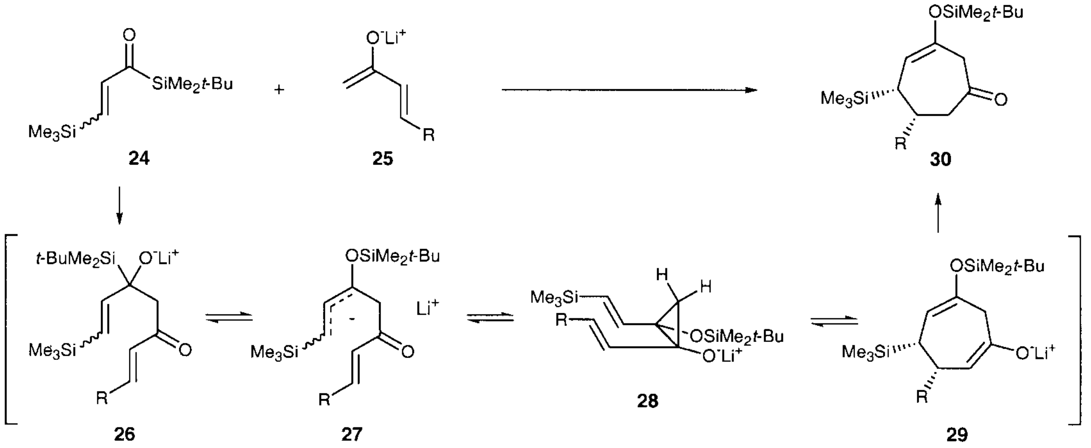
Reich et al. anticipated that the anionic conditions of their method would allow carbanion **9** to be trapped with electrophiles other than protons. The realization of this idea was initially problematic, as conversion of **7** to **9** was more rapid than the rate-determining addition of vinyllithium reagents to acylsilanes **5**. This resulted in attack of carbanion **9** on remaining starting material **5** that was competitive with the desired alkylation. It was observed, however, that slow addition of the acylsilane to a mixture of the vinyllithium and electrophile minimized the concentration of **5** in the presence of **9** and enabled γ-alkylations and sulfenylations to be achieved with good efficiency.

In a related application of this strategy, Koreeda and Koo generated the requisite α-silyl alkoxides via the regiospecific 1,2-addition of $Me_2PhSiLi$ to cyclic α,β-unsaturated ketones **11** in THF at −23°C (Scheme 4).[13] In contrast to the studies of Kuwajima and Reich, no products arising from carbon to oxygen silyl migration were observed, even by quenching the anion after extended times at elevated temperatures. Nonetheless, treatment of purified silyl carbinols **12** with 1 equiv. of *n*-BuLi and subsequent addition of iodomethane resulted in alkylation exclusively at C-3. These results suggest an equilibrium that greatly favors lithium alkoxide **13** over the silyl ether **14** under the conditions of the experiment. The importance of coordination-stabilized intermediates such as **9** in determining the equilibrium position is evident, since similar coordination is precluded in the cyclic system. Regardless of the equilibrium position, it is noteworthy that alkylation at the carbon center can be favored through the use of a very soft electrophile, thereby allowing complete conversion to the observed silyl enol ether.



	% yield		
R	22a	22b	23
i-Pr	55	19	77
Et	70	5	70
n-Pr	74	7	77
n-octyl	71	8	66

Scheme 6. Formal [3+2] annulations mediated by 1,2-silyl migrations.



Scheme 7. Formal [4+3] annulations mediated by 1,2-silyl migrations.

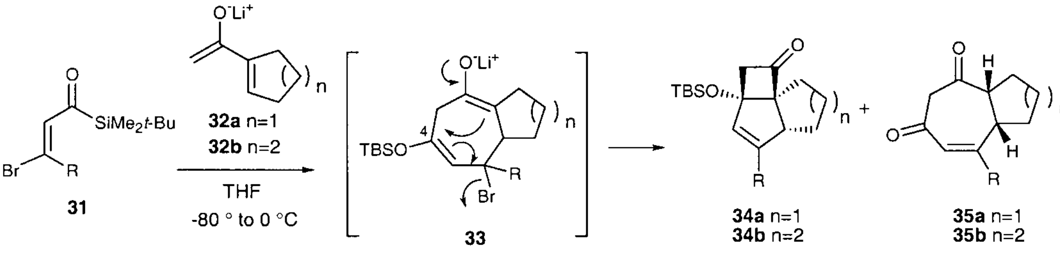
Alkynyllithium reagents are also suitable nucleophiles for the initial step of this process. As depicted in Scheme 5, Reich et al. demonstrated that addition of alkynyllithiums to acylsilanes **5** was smoothly followed by silyl migration and electrophilic trapping to regiospecifically afford siloxyallenyl products **18**.[12] As with the vinyllithium reagents, addition of acylsilanes to a mixture of alkynyllithium and electrophile was necessary to maximize the yield of **18**. If lithiated propargyl ethers[14a] or propargyl chlorides[14b] are utilized as the initial nucleophile, silyl migration is followed by an E2′-type elimination within the propargylic group to afford siloxy trienes.

Takeda et al. have utilized the concepts demonstrated by these studies to develop a series of Brook rearrangement-mediated annulation reactions for the synthesis of carbocyclic ring systems. The earliest example of this strategy, as depicted in Scheme 6, involved nucleophilic attack of lithium enolates on β-phenylthio-substituted α,β-unsaturated acylsilanes **19**, followed by 1,2-silyl migration and intramolecular cyclization of the resultant allyl stabilized carbanion **21**.[15] This sequence constitutes a formal [3+2] annulation process, and provided diastereomeric mixtures of cyclopentanols **22a,b** in good yield. The corresponding cyclopentenones **23** were readily accessed via treatment with TBAF, which effected desilylation and concomitant β-elimination of the phenylthio moiety. The utility of this process in a synthetic setting was demonstrated through the synthesis of the antitumor marine prostanoids clavulones II and III.[15c]

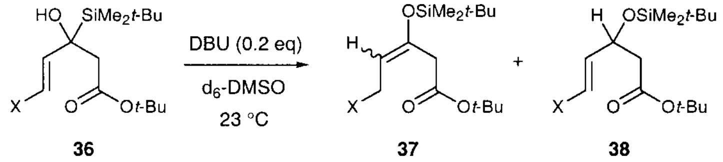
A formal [4+3] annulation was also achieved by addition of α,β-unsaturated enolates **25** to β-silyl α,β-unsaturated acylsilanes **24** (Scheme 7).[16] As with the [3+2] annulation process, the reaction is initiated by a 1,2-silyl migration from alkoxide adduct **26** to generate the allyl stabilized carbanion **27**. Subsequent Michael addition was considered as a possible mechanistic pathway to afford the observed cycloheptenone products **30**, but did not appear to provide a rationale for the stereospecific formation of the less stable 5,6-*cis* isomer from the (*E*)-acyl silanes **24**. Rather, an alternative pathway involving cyclopropanation from **27** to form 1,2-divinylcyclopropanediolate **28**, followed by an oxyanion-accelerated Cope rearrangement was proposed. Evidence to support this mechanism was provided by the observation of rapid and stereospecific Cope rearrangements of 1,2-divinylcyclopropanediolates synthesized by a separate method.

Although this [4+3] annulation represents an efficient method to prepare a variety of cyclic and fused bicyclic systems, the susceptibility of the process to small structural changes in the enolate and acyl silane reactant partners was clearly evidenced by additional studies.[17] For example, the addition of the lithium enolates of 1-acetyl-1-cyclopentene (**32a**) and 1-acetyl-1-cyclohexene (**32b**) to β-bromo-α,β-unsaturated acylsilanes **31** resulted in predominant formation of tricyclic ring systems **34a,b**, with the anticipated products **35a,b** formed in minor amounts (Scheme 8). Although the 1,2-silyl migration again serves as the key step, formation of the observed products appears to be due to an S_N2'-like intramolecular attack of the enolate at the C-4 position in the intermediate **33**.

In the aforementioned [3+2] and [4+3] annulation studies, it is critical to note that the presence of an additional



Scheme 8. Silyl migration-mediated formation of fused bi- and tricyclic ring systems.



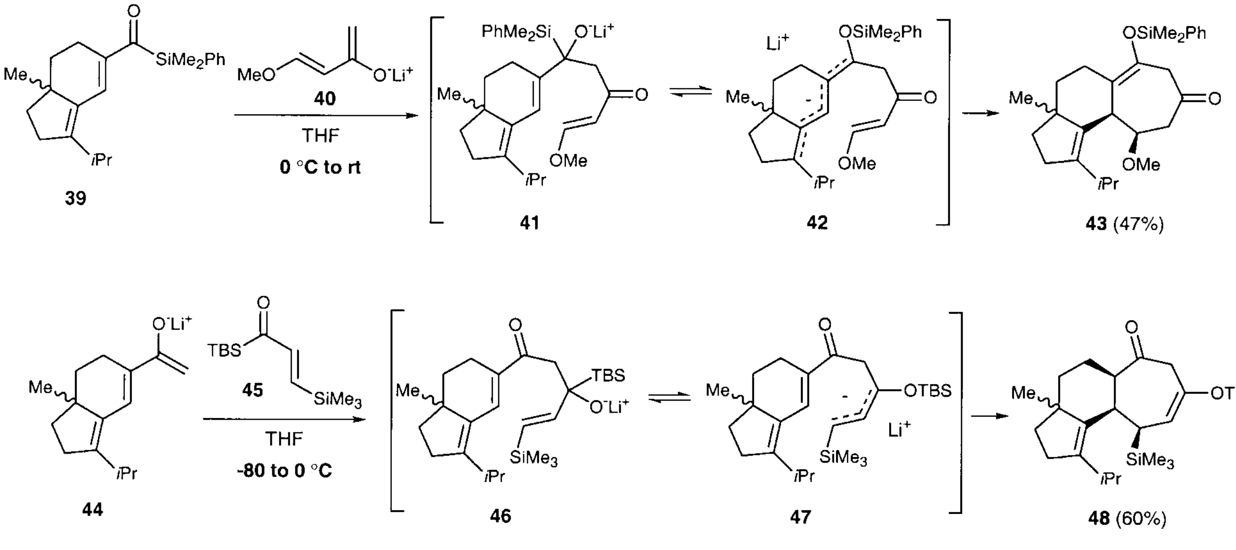
Scheme 9. The effect of β-substitution on rate of silyl migration.

carbanion stabilizing group in the β-position is highly beneficial for efficiently promoting silyl migration in the carbon to oxygen direction. In a study aimed at quantifying this effect, Takeda et al. measured the relative rates of Brook rearrangements of β-substituted α,β-unsaturated alcohols **36** (Scheme 9).[18] This substrate was chosen to isolate the silyl migration event, as the resultant stabilized carbanion is not sufficiently reactive to attack the pendant ester carbonyl group. The alcohols **36** were thus treated with DBU (0.2 equiv.) in d_6-DMSO, and the carbon to oxygen silyl migration was monitored by ^{1}H NMR. The relative rates of Brook rearrangements, which occurred in the order where X=S(O)Ph>SPh>Ph≫SiMe$_3$≫Cl, Br, were suggested to correlate with the α-carbanion stabilizing ability of these groups. Notably, formation of the non-allylic transposition products **38** is observed in addition to **37** when X=SiMe$_3$, Cl, and Br, suggesting that the α-carbanion stabilizing abilities of these groups is similar to that of the siloxy group.

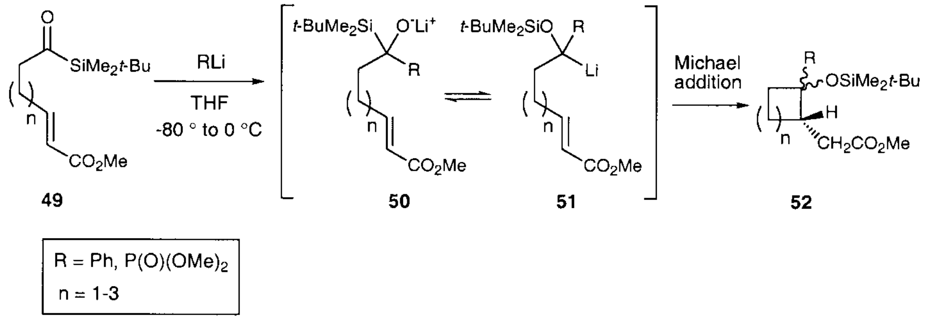
The importance of the carbanion-stabilizing group for promotion of silyl migration was further demonstrated in a synthesis of the tricyclic skeleton of the Cyanthin natural products (Scheme 10).[19] Two different pathways were envisaged for the use of the [4+3] annulation to generate the seven-membered ring. The first entailed addition of the lithium enolate of 4-methoxy-3-buten-2-one (**40**) to the α,β,γ,δ-unsaturated acylsilane **39**. Resonance stabilization of the carbanion **42** by the diene moiety apparently provided sufficient stabilization to promote the silyl migration step, although warming the reaction solution to room temperature was required. The desired tricyclic product **43** was produced in a modest 47% yield, along with recovery of **39** (14%). The efficiency of the annulation step was enhanced by addition of enolate **44** to α,β-unsaturated acylsilane **45**, which contains the additional carbanion-stabilizing trimethylsilyl group in the β-position. In this case, the silyl migration proceeded between −80 and 0°C, and afforded tricyclic product **48** in 60% yield. The stereoselectivity observed in this reaction was again consistent with an anionic oxy-Cope rearrangement of a *cis*-1,2-divinylcyclopropanediolate intermediate, as proposed earlier (Scheme 7).[16]

A commonality observed in the preceding examples utilizing α,β-unsaturated acylsilanes is that the tandem bond formations proceed with an overall allylic transposition. That is, new bond formations occur at the carbonyl carbon and the β-carbon of the original acylsilane, yielding the observed silyl enol ethers. In contrast, the use of α,β-saturated acylsilanes allows bis-functionalization of the original carbonyl carbon. The caveat in this case is that the initial nucleophile must possess sufficient electron-withdrawing capabilities to facilitate the subsequent carbon to oxygen silyl migration. For example, addition of phenyllithium and lithium dimethyl phosphite to THF solutions of acylsilanes **49** proceeds readily at −80°C, and the carbanion stabilizing ability of both of these groups promotes carbon to oxygen silyl migration upon warming the solution to 0°C (Scheme 11).[20] The resultant carbanion participates in intramolecular Michael additions with the tethered acrylate groups, providing a one-pot tandem sequence for the synthesis of four- to six-membered carbocyclic products **52**.

Perfluoroalkyl groups also provide sufficient carbanion stabilizing ability to promote Brook rearrangements. A recently reported example of this process involves the

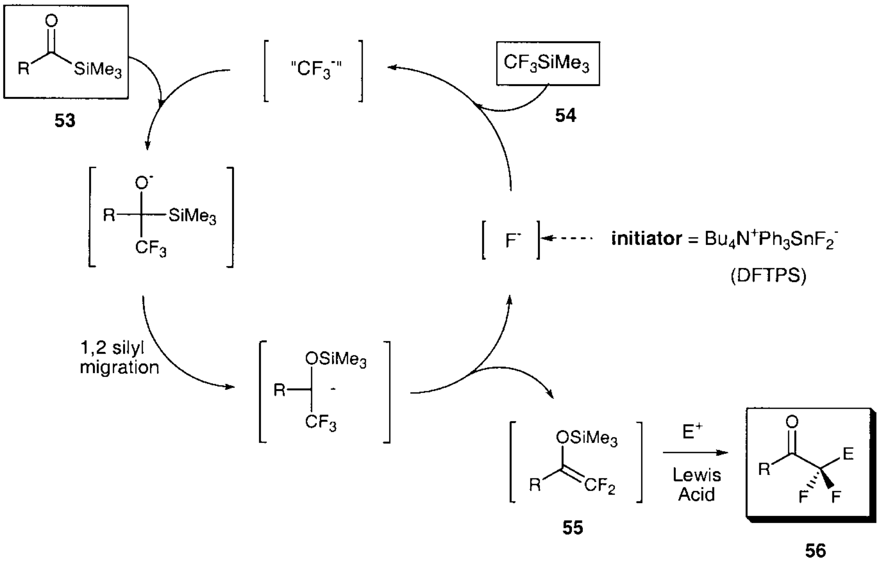


Scheme 10. Silyl migration-mediated [4+3] annulation approaches to the cyanthin ring system.

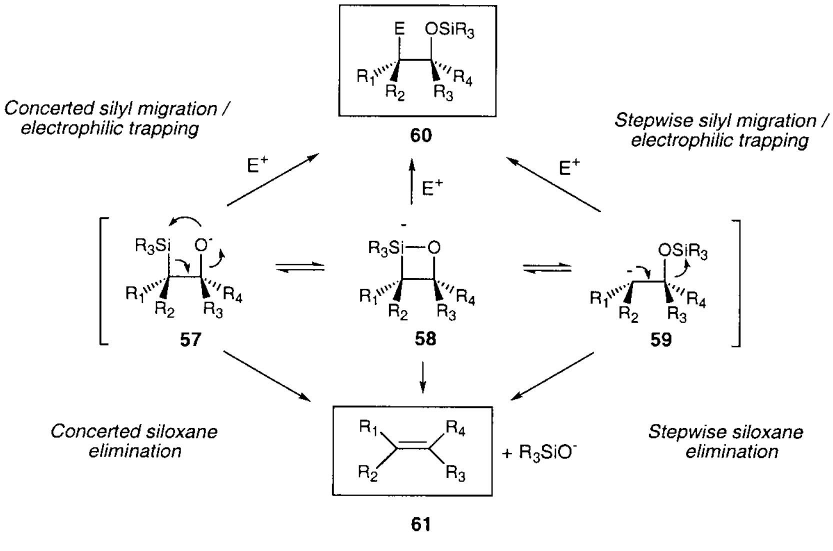


Scheme 11. Tandem silyl migration–intramolecular Michael additions.

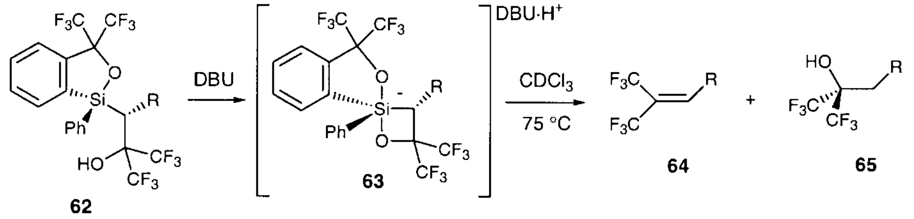
fluoride anion catalyzed conversion of acylsilanes **53** to difluoroenoxysilanes **55** (Scheme 12).[21] Tetrabutylammonium difluorotriphenylstannane (DFTPS) serves as the catalytic source of fluoride anion, which converts trifluoromethyltrimethylsilane (TFMTS, **54**) to the trifluoromethyl anion. Addition of this anion to the acylsilane is followed by Brook rearrangement and fluoride elimination, thus generating the difluoroenoxysilane **55** and a fluoride anion that continues the chain reaction. The difluoroenoxysilanes **55** participated in subsequent reactions with a variety of



Scheme 12. Trifluoromethyl promoted silyl migration sequence.



Scheme 13. Possible mechanistic pathways for β-silyl alkoxides.



Scheme 14. Isolation and reactivity of pentacoordinate 1,2-oxasiletanides.

electrophilic substrates in situ, affording an efficient one-pot methodology for the synthesis of *gem*-difluoro functionalized derivatives of diketones, cyclohexenones, terpenes, and *C*-glycosides.

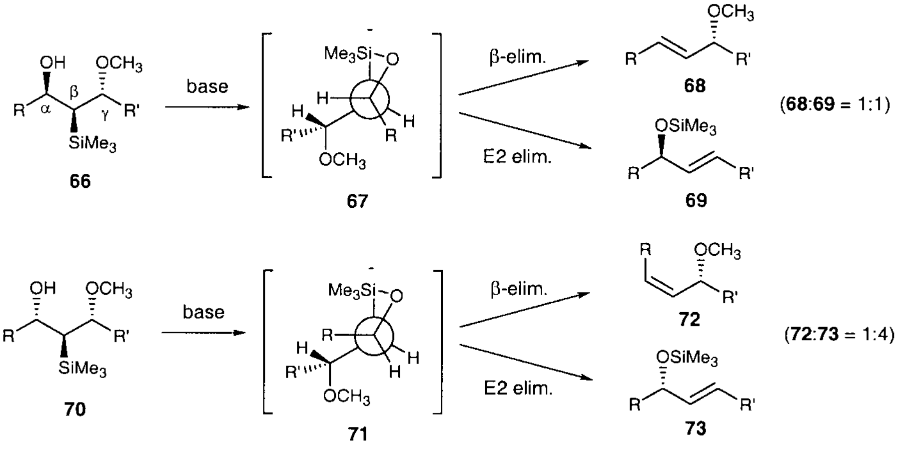
4. [1,3] Silyl migrations

In comparison with [1,2] silyl migrations, the design of tandem reactions involving [1,3] silyl migrations is problematic due to the competitive olefin formation via 1,2-elimination of β-silyl alkoxides known as the Peterson reaction.[22] As depicted in Scheme 13, the two reaction pathways are clearly mechanistically intertwined, although the exact details for both remain under investigation. It has been speculated that both siloxy elimination and silyl migration/electrophilic trapping can proceed through an identical pentacoordinate 1,2-oxasiletanide intermediate such as **58**. Evidence for this hypothesis was provided by Kawashima and co-workers, who isolated the stable pentacoordinate 1,2-oxasiletanide salt **63** and observed formation of both Peterson reaction product **64** and Brook rearrangement-related product **65** upon thermolysis (Scheme 14).[5b,c] However, even if oxasiletanides are accepted as reaction intermediates, the mechanistic question remains whether subsequent elimination or electrophilic trapping takes place in a concerted fashion, or stepwise via a carbanion such as **59**. A concerted pathway accounts for the high stereoselectivity typically observed for the Peterson reaction, although theoretical calculations indicate that a stepwise process is indeed feasible.[23] Regardless of the timing of either the elimination or electrophilic trapping processes, it appears that both the structural features of the substrate and the reaction conditions are critical in determining the predominant pathway, and a variety of methods to favor one over the other have been developed.

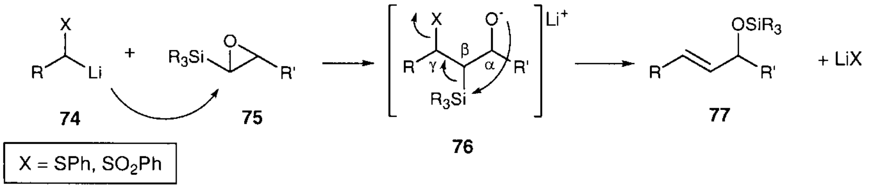
4.1. Silyl migration/elimination sequences

Prior to the development of any bis-alkylation methods, it was observed that treatment of β-silyl alcohols bearing an additional leaving group in the γ-position with base promotes competition between Peterson reaction and an E2-type elimination of the γ-leaving group (Scheme 15). The stereochemical dependence of the process was studied by Yamamoto and co-workers, who demonstrated the preference for *syn* β-elimination of the siloxy group or *anti* E2-elimination of the γ-leaving group from the postulated oxasiletanide intermediates **67** and **71**.[24] The Peterson reaction to form (*E*) alkenes such as **68** proceeds more rapidly than that to form (*Z*) alkenes such as **72**, so that elimination of the γ-leaving group predominated with starting materials bearing the same relative stereochemistry as **70**.

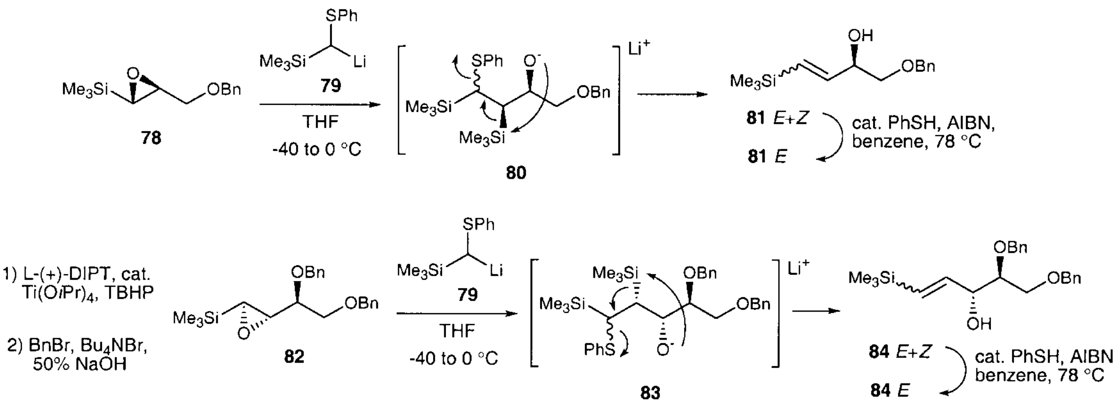
A more important factor in the competition between Peterson elimination and γ-elimination is the identity of the leaving group in the γ-position. In general, functional groups with enhanced leaving abilities allow the concerted γ-elimination to occur with significant preference over the Peterson reaction. Thus, Yamamoto et al. found that the γ-elimination of a methoxymethyl (MOM) group proceeded with a five-fold rate increase over the methoxy group.[24b] Masnyk and Wicha later achieved chemoselective γ-eliminations with thiophenyl or phenylsulfonyl leaving groups.[25] Masnyk and Wicha's method, outlined in Scheme 16, takes advantage of the regioselective ring opening of siloxiranes **75** with thiophenyl or phenylsulfonyl stabilized



Scheme 15. Stereochemical dependence in elimination reactions.



Scheme 16. Preferential elimination of γ-leaving groups.



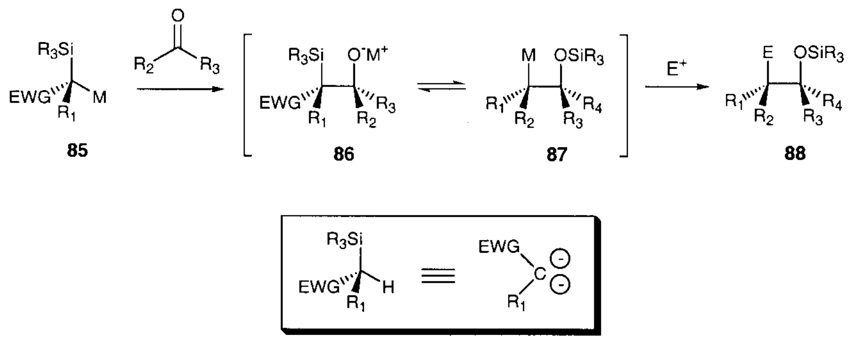
Scheme 17. Iterative synthesis of optically active 1,2-diols via a tandem silyl migration, γ-elimination process.

nucleophiles **74** to form the initial carbon–carbon bond and generate the requisite β-silyl alkoxide intermediate **76**.

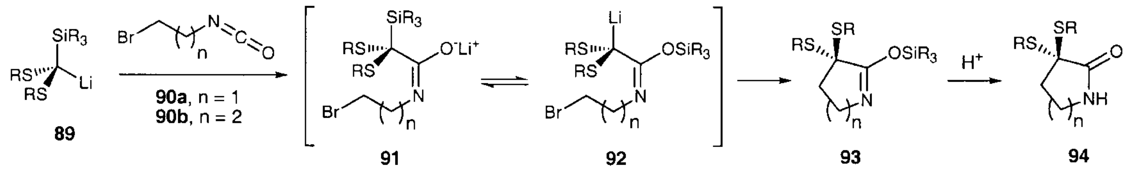
The thiophenyl elimination protocol provided the basis for Raubo and Wicha's iterative synthesis of optically active 1,2-polyol units (Scheme 17).[26] Stereodefined siloxirane **78** was prepared by Katsuki–Sharpless asymmetric epoxidation of (*E*)-3-(trimethylsilyl)allyl alcohol, followed by protection as the corresponding benzyl ether. Treatment of **78** with the thiophenyl(trimethylsilyl)methane anion **79** triggered the tandem nucleophilic ring opening/1,3-silyl migration and γ-thiophenyl elimination sequence to provide, after aqueous workup, vinylsilane **81** in good yield. Although the elimination step proceeds with low stereoselectively, the mixture of (*E*) and (*Z*) alkenes can be treated with catalytic amounts of thiophenol and AIBN without isolation to effect complete isomerization to the (*E*) isomer. Subsequent epoxidation, alcohol protection, and homologation under the identical conditions completes the second cycle, providing the *anti*-1,2-diol **84**, which again contains the vinylsilane moiety necessary for successive iterations. The stereochemical diversity of the approach was demonstrated by inversion of the newly generated carbinol center by the Mitsunobu reaction, providing the corresponding *syn*-1,2-diol isomer. In addition, the related elimination of phenylsulfonyl groups triggered by a 1,5-silyl migration has been exploited in an iterative synthesis of *syn*-1,3,5-triol units.[27]

4.2. Silyl migration/alkylation sequences

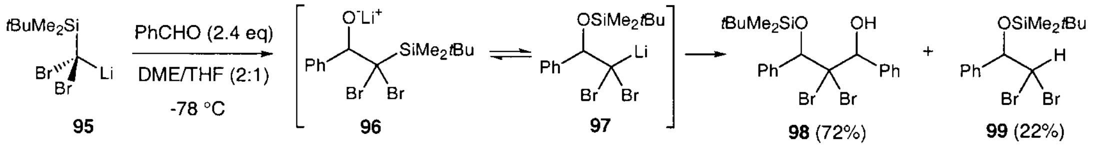
In addition to the aforementioned elimination strategies, the putative carbanion generated from anionic [1,3] silyl migrations can also be trapped by electrophiles in tandem bis-alkylation sequences. If the initial β-silyl alkoxide **86** is prepared by nucleophilic addition of a silyl-substituted carbanion **85** to an electrophilic carbonyl group, successful silyl migration and electrophilic trapping renders the original silyl-bearing carbon a formal dianion synthon (Scheme 18). In the application of this strategy, the presence of a carbanion-stabilizing group is critical both for the formation of the initial carbanion **85** and to facilitate the carbon to oxygen silyl migration **86** to **87**.



Scheme 18. Silyl-bearing precursors as dianion synthons in tandem reactions.



Scheme 19. Lactam formation via silyl migration–intramolecular alkylation sequence.



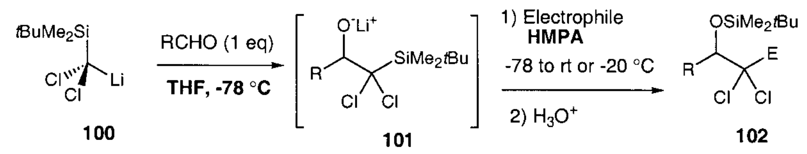
Scheme 20. Intermolecular bis-alkylation of silyldihalomethyllithium reagent.

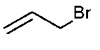
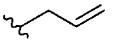
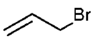
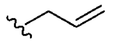
Intramolecular alkylations that follow the [1,3] silyl migration event have been reported as methods to generate cyclic compounds. The application of this strategy entails the addition of a bis-electrophile to the silyl-substituted carbanion, and requires selective addition to one of two electrophilic sites as the initial step. Lithiated silylthioacetals **89**, for example, react with bromoalkyl isocyanates **90a,b** via chemoselective addition to the isocyanate carbon, followed by [1,3] silyl migration and intramolecular alkylative ring closure to afford γ- and δ-lactams **94** after acidic workup (Scheme 19).[28] No competing siloxy elimination to afford the corresponding ketenimines was reported. Following protection of the amide nitrogen of lactams **94**, conversion of the thioacetals to carbonyl groups was also achieved, providing the corresponding α-oxolactams.

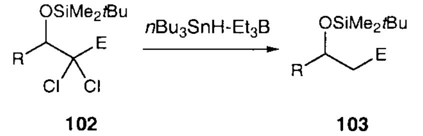
Intermolecular alkylations of stabilized silyl migration-generated carbanions have also been reported. Oshima and co-workers demonstrated a valuable application of 1,3-silyl migrations based on the *tert*-butyldimethylsilyldihalomethyllithium reagent **95** (Scheme 20).[29] Addition of benzaldehyde (2.4 equiv.) to **95** in a DME/THF (2:1) solvent system at −78°C provided 1,3-diol monosilyl ether **98** (72%) and silyl ether **99** (22%). Following initial alkylation of **95** with the first equivalent of benzaldehyde, the mechanism presumably proceeds via silyl migration from lithium alkoxide **96** to generate a carbanion (**97**) that is subsequently alkylated or protonated. Further trials of this sequence demonstrated that the distribution of the products (1:1 adduct to 1:2 adduct) is highly dependent on the substituents present on the silyl group. In all cases, the absence of products derived from Peterson reaction is surprising, since alkene formation is the major pathway observed with the related anions $Me_3SiC(Li)(SR)_2$[30] and $Me_3SiCH(Li)Cl$.[31] Although no hypothesis was presented to explain this difference, it seems likely that the added stabilization afforded by the second halide group disfavors the elimination pathway and allows the alkylation to dominate.

Further studies with the dichloro analog **100** led to the critical discovery that the rate of the silyl migration step was highly solvent dependent. Specifically, the migration of

Table 1. Solvent controlled unsymmetrical bis-alkylation of silyl dihalomethyllithium reagent



R	Electrophile	E	yield of **102** (%)
Ph	MeI	Me	71
Ph			70
PhCH=CH	MeI	Me	74
n-Pr			40
4-MeO-C_6H_4	PhCHO	PhCH(OH)	83
PhCH=CH	PhCHO	PhCH(OH)	73
n-Bu	PhCHO	PhCH(OH)	45



Scheme 21. Reduction of dichloro products.

silicon from carbon to oxygen in adduct **101**, derived from equimolar mixtures of **100** and various aldehydes, was suppressed in THF at −78°C. Addition of HMPA to the reaction mixture, however, triggered rapid carbon to oxygen silyl migration to produce a carbanion that could be efficiently trapped with a second electrophile (Table 1). This observation provided a convenient method to ensure complete consumption of the initial aldehyde prior to the silyl migration, thereby preventing the formation of symmetrically bis-alkylated products related to **98**. Dichloride products **102** were easily reduced by *n*-$Bu_3SnH–Et_3B$ to the corresponding methylene compounds **103** (Scheme 21). Thus, *tert*-butyldimethylsilyldichloromethyllithium serves as a synthon of methylene dianion that can be bis-alkylated with two *different* electrophiles in a single reaction flask.

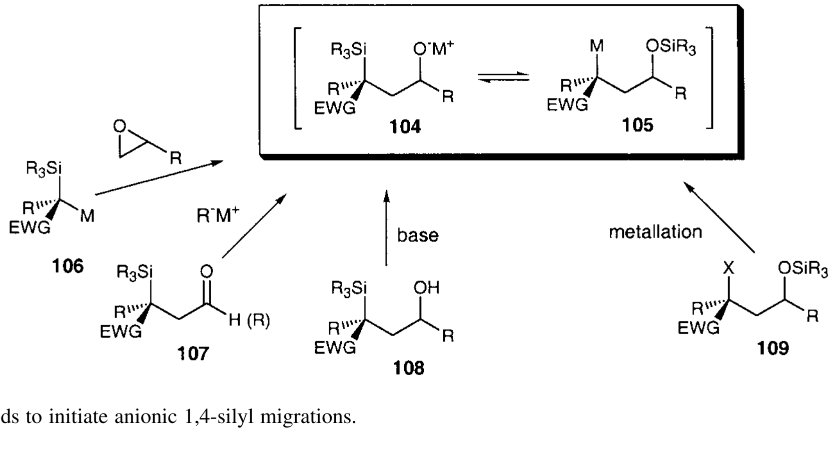
5. [1,4] Silyl migrations

A variety of applications involving anionic [1,4] silyl migrations have recently been reported, with both carbon to oxygen and oxygen to carbon migrations proving useful in synthetic contexts. In addition to the development of methods to control the direction and rate of the silyl migration, the utility of the reversible 1,4-silyl migrations can be attributed to the absence of competing side reactions and the wealth of methods available to generate the requisite anionic precursors. As shown in Scheme 22, the appropriate γ-silyl alkoxides **104** are readily available by nucleophilic opening of epoxide rings with α-silyl metallated reagents bearing an EWG (**106**), by organometallic addition to β-silyl aldehydes or ketones **107**, or by deprotonation of γ-silyl carbinols **108**. Alternatively, anionic silyl ethers **105** are generated by metallation of the appropriate precursors such as **109**.

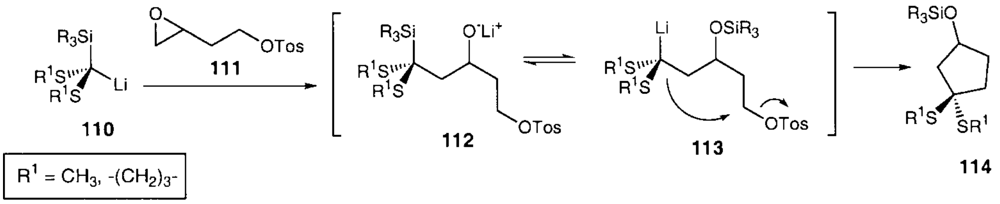
5.1. Brook rearrangements (*C* to *O* silyl migration)

5.1.1. Silyl migration/intramolecular alkylation. Tandem nucleophilic addition–1,4-silyl migration–intramolecular alkylations provide an effective method for the one-pot synthesis of functionalized cyclic products. A common strategy for this sequence is the nucleophilic ring opening of epoxides with stabilized, silyl-substituted alkyllithium reagents, followed by the 1,4-silyl migration and an intramolecular S_N2 displacement to form the new cyclic product. If the final leaving group is appended to the epoxide, this strategy necessitates that initial nucleophilic attack occurs chemoselectively at the unsubstituted terminus of the epoxide moiety rather than at the leaving group.

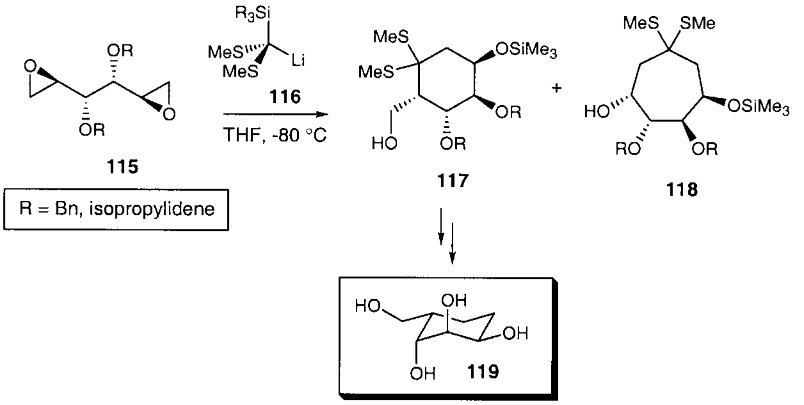
Schaumann and co-workers have utilized this strategy in the development of a formal [4+1] synthesis of substituted cyclopentanols (Scheme 23).[32] The reaction proceeds via nucleophilic attack of silyl-substituted thioacetal **110** on epoxyhomoallyl tosylate **111**, followed by a 1,4-carbon to oxygen silyl migration (**112** to **113**) and intramolecular displacement of the tosylate group. Secondary tosylates could be accommodated in this process with only a minor reduction in yield. In contrast, extension of the carbon chain of **111** as an attempted method for the formation of the corresponding cyclohexanols and cycloheptanols was only partially successful, as competing formation of furans and acyclic products, respectively, could not be completely suppressed.[33]



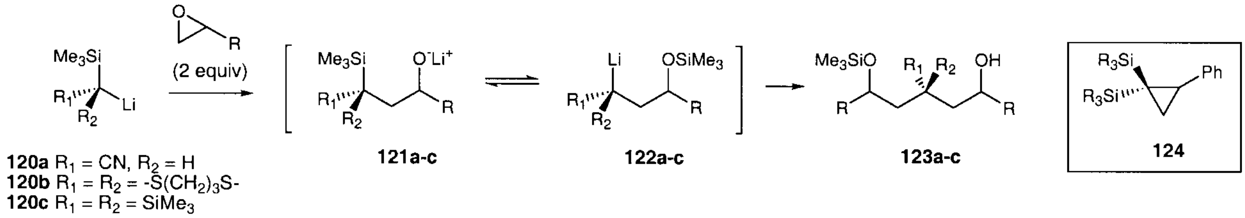
Scheme 22. Synthetic methods to initiate anionic 1,4-silyl migrations.



Scheme 23. Formal [4+1] cycloaddition approach to cyclopentanol ring systems.



Scheme 24. The use of bis-epoxides for the asymmetric synthesis of carbocycles.



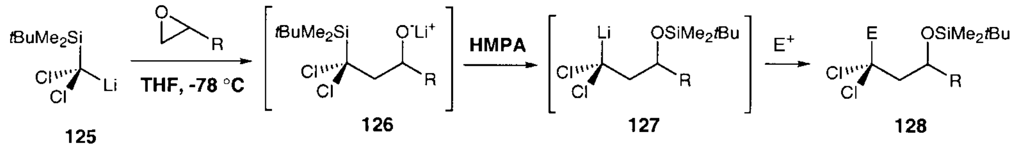
Scheme 25. Symmetrical bis-alkylations of silyl-stabilized carbanions.

In an extension of this strategy, Schaumann and co-workers utilized bis-epoxides for the asymmetric synthesis of highly oxygenated carbocycles (Scheme 24).[34] For example, carbohydrate-derived bis-epoxides **115** underwent smooth ring opening and silyl migration when treated with lithiated silyl dithioacetal **116**. Competitive 6-*exo*-tet and 7-*endo*-tet cyclizations of the resultant carbanions produced mixtures of cyclohexanes **117** and cycloheptanes **118**, respectively. Although the selectivity of the ring closure step was only moderate, the protocol provided a novel method for converting readily available sugars into highly functionalized carbocycles. For example, desulfurization of cyclohexane product **117** afforded 4-*epi*-validatol (**119**) in seven steps and 6% overall yield from D-mannitol. A closely related strategy reported by Le Merrer et al. employed bis-epoxides and 2-silylated-1,3-dithianes as the dianion synthon in a concise route to carbasugars.[35] Cyclization to both six- and seven-membered rings was also observed in this study, although product ratios could be partially controlled through the choice of protecting groups present on the starting materials.

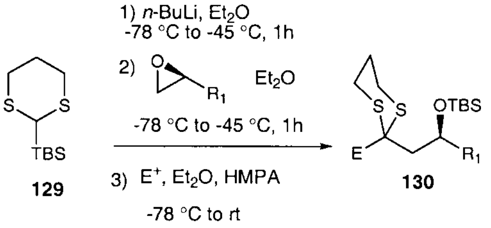
5.1.2. Silyl migration/intermolecular alkylation.

Several examples of tandem nucleophilic addition–1,4-silyl migration–intermolecular alkylations have been reported, starting from stabilized α-silyl carbanions. The general strategy, depicted in Scheme 25, entails addition of 2 equiv. of an epoxide to the stabilized carbanion, and results in the formation of symmetrically bis-alkylated acyclic products such as **123**. Matsuda et al., for example, reported that the γ-trimethylsiloxynitriles **123a** were obtained in good yield via the addition of 2 equiv. of various epoxides (R=Me, Et, Ph) to THF solutions of trimethylsilylacetonitrile anion at −78°C, followed by warming to room temperature and stirring for 14 h.[36] Tietze et al. utilized THF solutions containing 12-crown-4 to couple the lithium anion of 2-trimethylsilyl-1,3-dithiane (**120b**) with 2 equiv. of styrene oxide to obtain **123b** in a process requiring 2 days.[37] The related coupling of styrene oxide was also accomplished through the use of tris(trimethylsilyl)methyllithium (**120c**), although in this case, the intramolecular nucleophilic displacement of the silyloxy moiety was also observed, providing cyclopropane **124** as well as the acyclic product **123c**.[38]

The shortcoming associated with all of these examples is the inability to control the timing of the silyl migration. Under the reported reaction conditions, the initial epoxide ring opening appears to represent the rate-determining step, with subsequent silyl migration occurring more rapidly. The carbanion **122** is therefore generated prior to the consumption of one full equivalent of starting epoxide. This precludes an efficient bis-alkylation with two *different* epoxides, as the competitive alkylation of carbanions **120**



Scheme 26. Unsymmetrical bis-alkylations via solvent controlled silyl migrations.



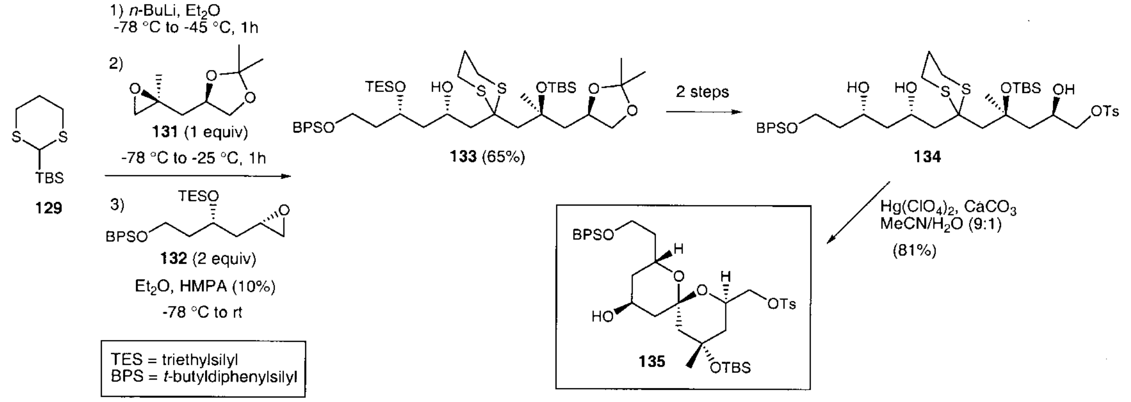
Scheme 27. Unsymmetrical bis-alkylations of silyl dithianes.

and **122** would result in the formation of mixtures of symmetrically and unsymmetrically substituted products.

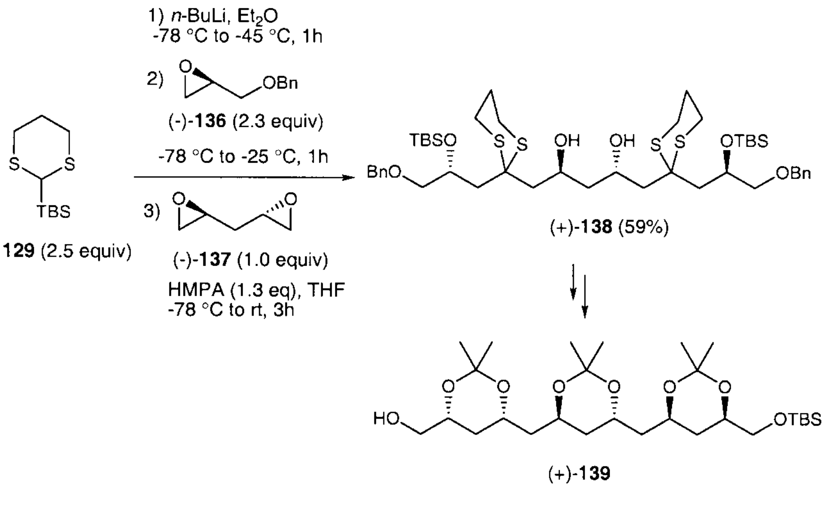
As discussed earlier in this report, Oshima and co-workers demonstrated that the rate of 1,3-silyl migrations was highly solvent dependent.[29] In conjunction with these studies, it was also observed that the choice of solvent was effective in controlling the rate of the 1,4-silyl migration in adducts **126**, generated by addition of *tert*-butyldimethylsilyldichloromethyllithium **125** to epoxides (Scheme 26). In Et_2O, for example, silyl migration was completely suppressed, whereas in THF the migration was initiated upon warming the solution from −78 to −40°C. Addition of HMPA was again effective in promoting rapid silyl migration even at −78°C, thus providing a practical method for one-pot unsymmetrical bis-alkylations of **125** with an epoxide and a second electrophile.

Further development of the solvent-controlled Brook rearrangement process has been reported by Smith and co-workers, utilizing 2-*tert*-butyldimethylsilyl-1,3-dithianes (**129**) as linchpins in one-pot multicomponent coupling sequences.[39–42] The protocol, illustrated in Scheme 27, involves initial metallation of **129** and alkylation with 1 equiv. of an epoxide in Et_2O. Upon complete consumption of the epoxide, addition of HMPA or DMPU plus a second electrophile results in rapid Brook rearrangement and alkylation, thus providing unsymmetrically bis-alkylated products **130** in good yields.[39]

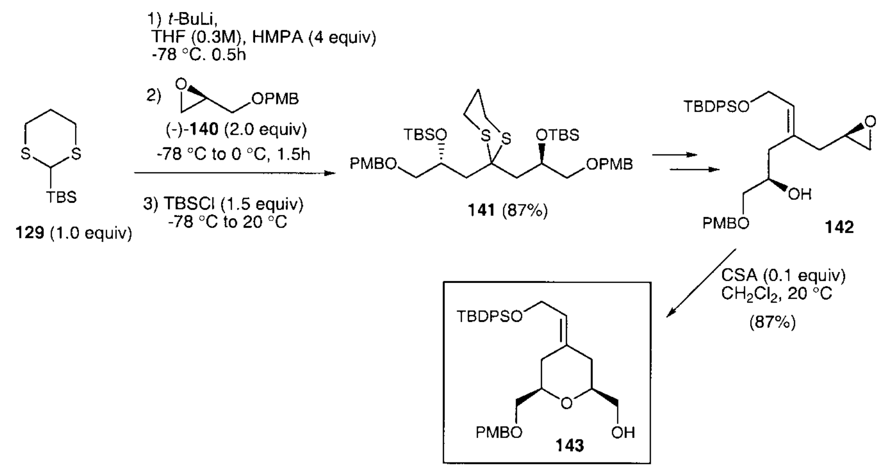
The synthetic appeal of this process is heightened by the versatility of the dithiane moiety, which serves as a masked carbonyl group. An example of this concept is provided by the elaboration of triol **134**, which is efficiently produced by bis-alkylation of **129** with chiral epoxides **131** and **132**, followed by routine protecting group manipulation (Scheme 28). Treatment of **134** with mercuric perchlorate in aqueous acetonitrile effected hydrolysis of the dithiane moiety with concurrent spiroketalization to afford **135**, thus providing an expeditious route to the AB spiroketal ring system of the spongistatin antitumor agents.[40] This strategy was also



Scheme 28. Application of the unsymmetrical dithiane bis-alkylation to the synthesis of spiroketals.



Scheme 29. Application of dithiane bis-alkylation to the stereodefined synthesis of 1,3-polyols.



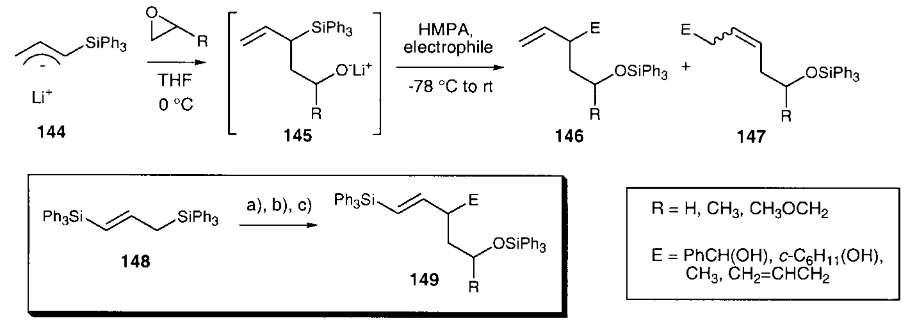
Scheme 30. Application of symmetrical dithiane bis-alkylation in the construction of a bryostatin subtarget.

successfully applied in the synthesis of the CD spiroketal ring system.[41]

In conjunction with the silyl migration-mediated bis-alkylation protocol, the Smith group has also exploited the conversion of a dithiane moiety to a hydroxy group in an approach to stereodefined 1,3-polyol systems (Scheme 29).[42] Treatment of lithiated dithiane **129** (2.5 equiv.) with (−)-benzyl glycidyl ether ((−)-**136**, 2.3 equiv.) in Et_2O solvent effected the initial alkylation, and was followed by addition of diepoxide (−)-**137** (1.0 equiv.) in an HMPA/THF solvent system to trigger carbon to oxygen silyl migration and subsequent alkylation. The C_2-symmetric diol (+)-**138** was obtained in good yield, demonstrating the efficiency of this one-flask, five-component coupling tactic. Removal of the dithiane group and hydroxyl-directed *syn*-reduction[43] of the resultant ketones represented the key steps in the elaboration of (+)-**138** to trisacetonide (+)-**139**, an intermediate previously reported by Schreiber and coworkers in their synthesis of (+)-mycoticin A.[44]

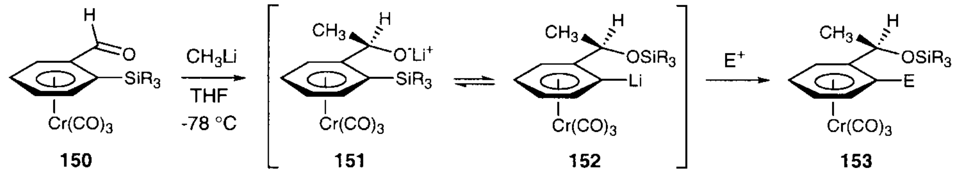
Another bis-alkylation example highlighting the utility of the dithiane moiety was recently implemented by Hale et al. as a key step in the construction of a B-ring synthon of the bryostatin antitumor macrolides (Scheme 30).[45] Addition of 2 equiv. of homochiral epoxide **140** to lithiated dithiane **129** in an HMPA/THF solvent system was followed by in situ trapping of the resultant alkoxide with TBSCl to afford the C_2-symmetric product **141** in excellent yield. Although solvent control of the silyl migration is unnecessary in this symmetrical coupling reaction, the inclusion of HMPA is still beneficial for enhancing the rate of the otherwise sluggish silyl migration. After unmasking the dithiane moiety, the corresponding C_2-symmetrical ketone was successfully converted to epoxy-alcohol **142**, followed by an acid-catalyzed intramolecular Williamson etherification reaction to complete the synthesis of the desired subtarget **143**.

Solvent effects were also found to be critical in tandem bond-forming reactions with silyl-substituted propenyllithium reagents (Scheme 31).[46] Treatment of 1-triphenylsilyl-2-propenyllithium (**144**) with epoxides in THF resulted in initial formation of alkoxides **145**. Addition of HMPA along with a second electrophile promoted 1,4-silyl migration and alkylation of the resultant allylic carbanion. Regioselectivity of this second alkylation was low, however, affording mixtures of the monosilyl ethers **146** and **147**. This problem was alleviated through the use of 1,3-bis(triphenylsilyl)-1-propene (**148**) as starting material. Following lithiation, epoxide ring opening, and silyl migration, alkylation with aldehydes provided the 1,4-diol derivatives **149** almost exclusively. Importantly, the initial step required a mixed solvent system (THF:ether=1:2) for the procedure to be effective. In THF, even in the absence of HMPA, the rate of silyl migration was competitive with epoxide ring opening. This resulted in premature generation of the carbanion intermediate, which subsequently attacked



a) *n*-BuLi, Et_2O/THF (2:1); b) epoxide, THF 0 °C; c) E^+, HMPA, -78 °C to rt

Scheme 31. Silyl migration-mediated bis-alkylations of propenyllithiums.



Scheme 32. Silyl migration-mediated bis-alkylations of arene chromium tricarbonyl complexes.

remaining starting material to afford complex reaction mixtures.

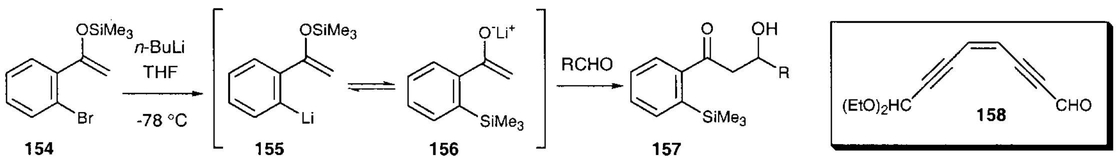
A 1,4-silyl migration-mediated bis-alkylation of silyl-substituted arene chromium tricarbonyl complexes was recently reported (Scheme 32).[47] Addition of methyllithium to THF solutions of arene chromium tricarbonyl complex **150** at −78°C generates alkoxide **151** and promotes carbon to oxygen silyl migration at temperatures below 0°C. The resultant aryl anion **152** can be efficiently trapped by a variety of electrophiles to afford bis-alkylation products **153**. In this sequence, the chromium tricarbonyl moiety not only provides sufficient electronic stabilization of aryl anion to facilitate carbon to oxygen silyl migration, but also controls the stereoselectivity of the initial alkylation step. The products **153**, which contain planar chirality, are thus obtained with good diastereoselectivity.

5.2. Retro-Brook rearrangements (*O* to *C* silyl migrations)

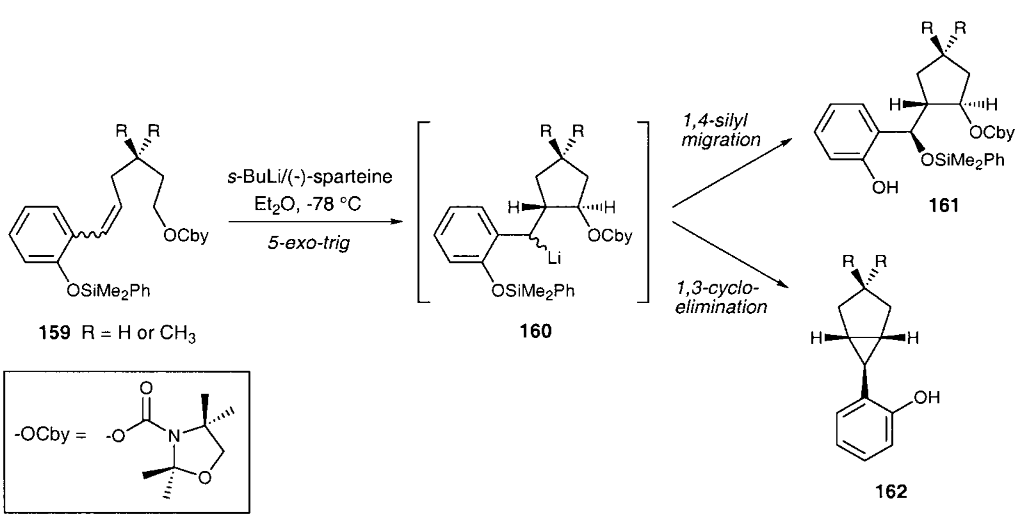
Synthetic applications of 1,4-silyl migrations in the oxygen to carbon direction have also been reported. Provided the silyl migration is a reversible and kinetically rapid process, shifting the equilibrium away from the silyl ether requires the generation of a carbanion that is thermodynamically unstable relative to the corresponding alkoxide anion. Since they are likely to be highly reactive, the consideration of competitive reaction pathways available to such carbanions is essential in the planning of tandem bond-forming sequences.

Fallis and co-workers observed that the aryl anion **155**, generated from metal–halogen exchange of *o*-bromoacetophenone trimethylsilyl enol ether (**154**) in THF at −78°C, rapidly underwent [1,4] oxygen to carbon silyl migration (Scheme 33).[48] The resultant enolate anion **156** participated in aldol reactions to afford β-hydroxy ketones **157** in good yield. Notably, attempted aldol condensation of the potassium enolate derived from *o*-bromoacetophenone with unstable aldehyde **158** provided only 12% of the desired adduct, whereas the silyl migration protocol, when performed in the presence of anhydrous cerium trichloride, increased the yield to 72%.

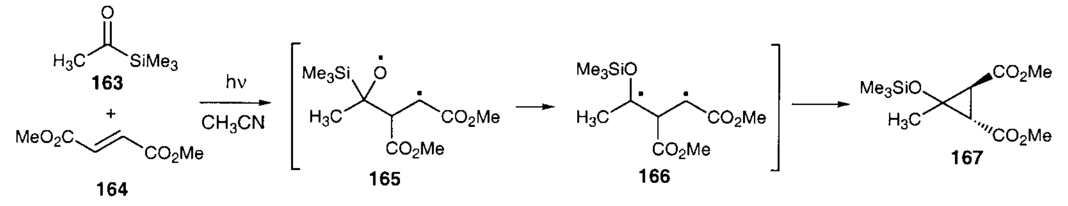
An oxygen to carbon [1,4] silyl migration has also been reported as the termination step in a highly stereoselective tandem bond-forming sequence reported by the Hoppe



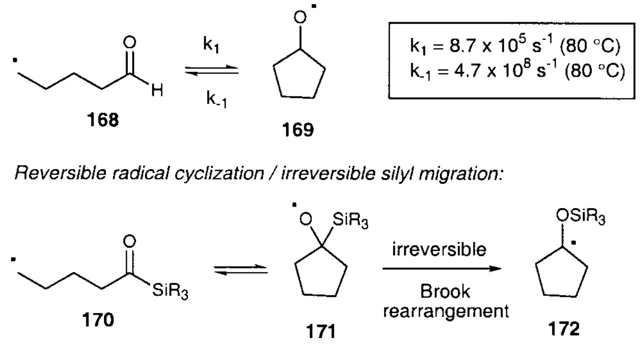
Scheme 33. Tandem 1,4-silyl migration–aldol condensation sequence.



Scheme 34. 1,4-Oxygen to carbon silyl migrations in stereoselective tandem reactions.



Scheme 35. Proposed radical silyl migration-mediated cyclopropanation reaction.



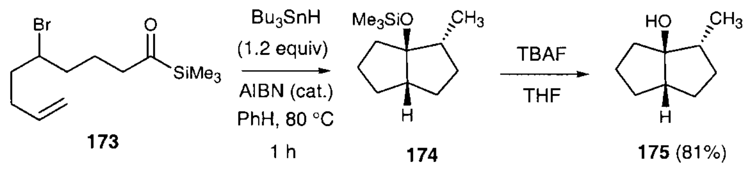
Scheme 36. Silyl migration-mediated radical cyclization strategy.

group (Scheme 34).[49] Chiral non-racemic Li–carbanion pairs are accessible through the enantioselective deprotonation of alkyl carbamate **159** with *s*-BuLi/(−)-sparteine in Et_2O at −78°C. Subsequent 5-*exo*-trig cyclization and silyl migration proceeds upon warming the solution to −40°C for several hours, affording **161** in good yield and extremely high enantioselectivity (>98:2), along with a minor amount of **162**, the product of 1,3-cycloelimination of the intermediate carbanion **160**. The intramolecular 1,4-oxygen to carbon migration, which is thermodynamically driven by formation of the stabilized phenoxide anion, must be kinetically faster than the 1,3-cycloelimination process, since the undesired bicyclic product **162** is formed quantitatively in the absence of the silyl group. Significantly, the relative and absolute configuration of cyclized product **161** is independent of the geometry of alkene **159**. To explain this observation, the authors suggest that the mechanism proceeds via a mixture of the configurationally labile epimers of **160**, with silyl migration with stereoretention favored from a single epimer due to steric interactions.

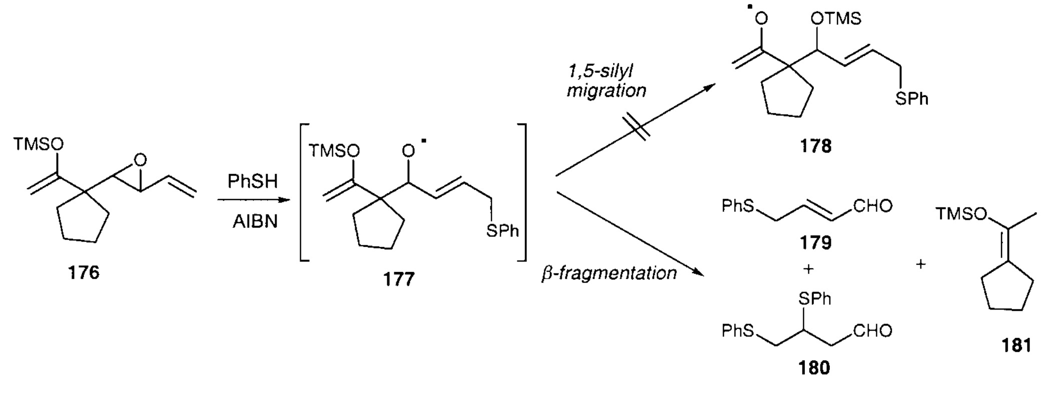
6. Radical silyl migrations

Silyl migrations of radical species have also been observed, although these have not been explored as extensively as anionic migrations. A radical [1,2] Brook rearrangement **165** to **166** was first proposed in 1981 by Dalton and Bourque as an explanation for the photochemically induced formation of cyclopropanes such as **167** from the corresponding acylsilanes and electron-poor olefins (Scheme 35).[50] Further evidence for related intramolecular 1,2-radical silyl migration pathways has been provided by ESR spectroscopy[51] and ab initio calculations.[52]

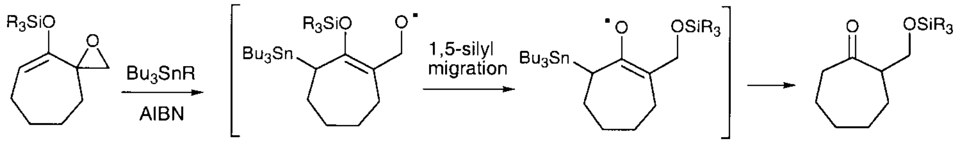
Although radical silyl migrations are suggested to share many of the same characteristics as their anionic counterparts, the reversibility of the radical Brook rearrangement has not been demonstrated. Tsai and co-workers recognized that this feature could be beneficial in the formation of carbocyclic ring systems (Scheme 36).[53] Specifically, radical cyclizations to carbonyl groups (**168** to **169**) are



Scheme 37. Silyl migration-mediated radical bicyclization reaction.



Scheme 38. Competitive β-fragmentations of alkoxy radicals.



182 183 184 185

Scheme 39. 1,5-Oxygen to oxygen radical silyl migration.

reversible, and the predominance of the acyclic form **168** at equilibrium often prevents isolation of the closed ring system **169**. However, ring closure **170** to **171** followed by the thermodynamically favorable radical Brook rearrangement **171** to **172** would provide an effective method to trap the cyclic product. This idea was reduced to practice by the Tsai group,[53a] who demonstrated that the resultant α-silyloxy radicals also participate in additional bond-forming reactions.[53b] As depicted in Scheme 37, radical cyclization and silyl migration of precursor acylsilane **173** was followed by a second cyclization onto the pendant olefin moiety. Subsequent removal of the silyl group was performed in situ, providing a one-pot method for the stereoselective synthesis of bicyclic carbinol **175** in good yield.

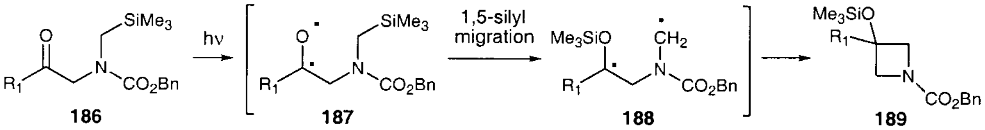
Although ESR studies demonstrate that [1,2] radical Brook rearrangements are extraordinarily rapid,[51] higher order radical silyl migrations appear to be slower, such that H atom abstractions and β-fragmentations become competitive pathways. For example, β-fragmentation of alkoxy radical **177**, which generates the observed products **179–181**, was more facile than the corresponding 1,5-oxygen to oxygen silyl migration, perhaps since the β-fragmentation product is a stabilized allylic radical (Scheme 38).[54]

In contrast, stannyl radical addition to epoxide **182** generates alkoxy radical **183**, for which β-fragmentation is less favorable (Scheme 39). In this case, the 1,5-silyl migration to **184** is the predominant pathway. The stannyl group is lost upon chromatographic purification, providing products **185** in good yield. Intramolecular trapping of the enolate radical **184** with alkenes was also demonstrated, generating regio- and stereoisomeric mixtures of bicyclic compounds.

One example of a radical 1,5-carbon to oxygen silyl migration has been reported (Scheme 40).[55] Irradiation of silylamido-ketones **186** produced azetidines **189** through a Norrish type II pathway involving 1,5-silyl migration to the carbonyl oxygen followed by diradical coupling. In contrast to the silylamide analogs, silylalkyl ketones react by 1,5-H atom migration to produce methyl ketones and vinylsilane. The competitive balance between H and Si migration is further demonstrated by photolysis of silylethylphthalimide **190** to yield benzazepindione **195** (Scheme 41). Careful studies revealed that a 1,5-H migration pathway was followed in acetonitrile, whereas 1,5-silyl migration predominated in H_2O–MeCN solvent mixtures.

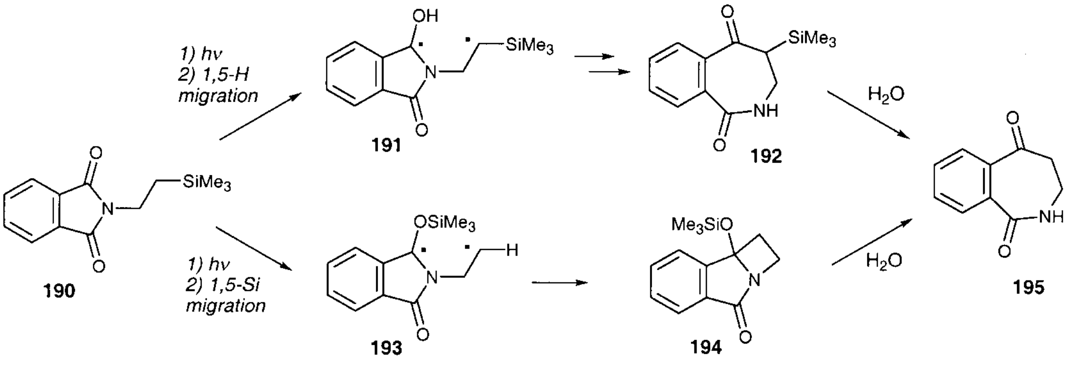
7. Aza-Brook rearrangements

In contrast to the wide variety of Brook and retro-Brook rearrangements that have been observed, reports involving the analogous migration of silyl groups between carbon and nitrogen atoms have been extremely scarce. Part of the reason for this disparity is undoubtedly due to the relative



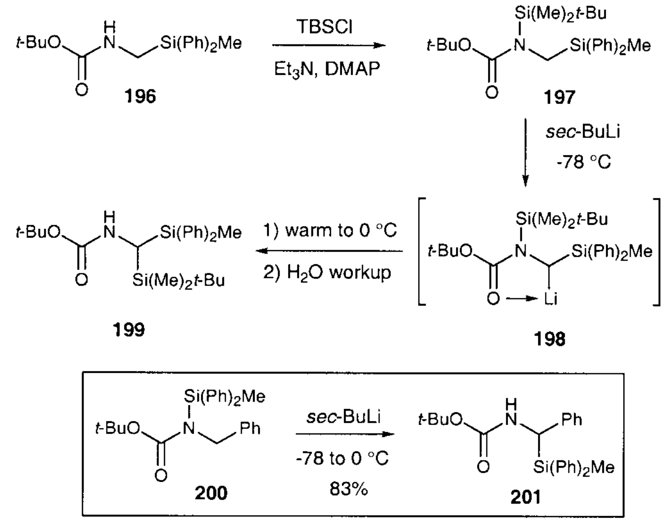
186 187 188 189

Scheme 40. Radical silyl migration-mediated formation of azetidines.



191 192 190 193 194 195

Scheme 41. Competitive 1,5-Si and H migration.

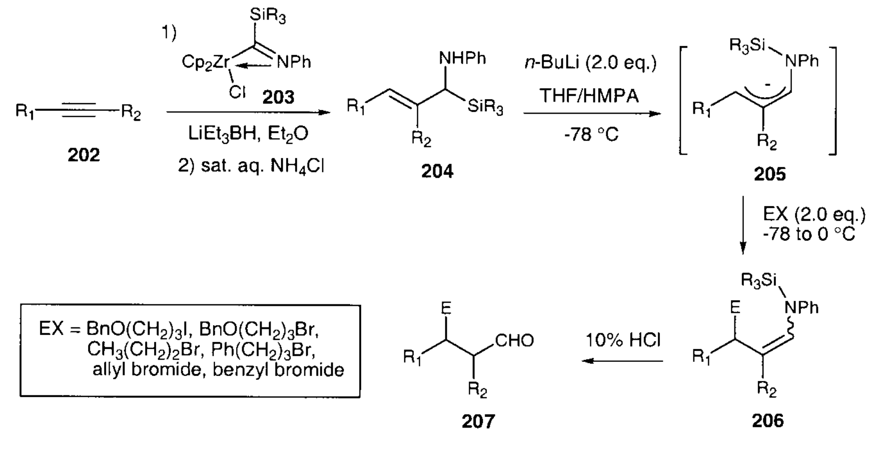


Scheme 42. 1,2-Aza-Brook rearrangements.

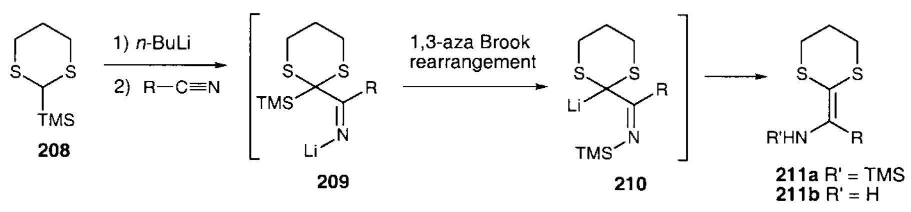
lack of general methods for the synthesis of the α-, β-, and γ-silyl substituted amine precursors required for carbon to nitrogen silyl migrations. In addition, since the strength of the N—Si bond is much less than the corresponding O—Si bond, one may assume that the decreased thermodynamic driving force precludes *C* to *N* silyl migrations in some cases.

Notably, one reported method for the synthesis of α-silylamines makes use of a retro [1,2] aza-Brook rearrangement (Scheme 42).[56] The Boc-protected aminosilane **196** was readily silylated on the amide nitrogen to afford **197**. Subsequent treatment with *sec*-butyllithium gave a bright yellow anion, presumably **198**. Upon warming this solution to 0°C, migration of the silyl group was observed to afford α-silylamine **199** in good yield after workup. Similar reactivity was reported for Boc-derived benzylamine **200**, suggesting the method may provide a general method for α-silylamine synthesis.

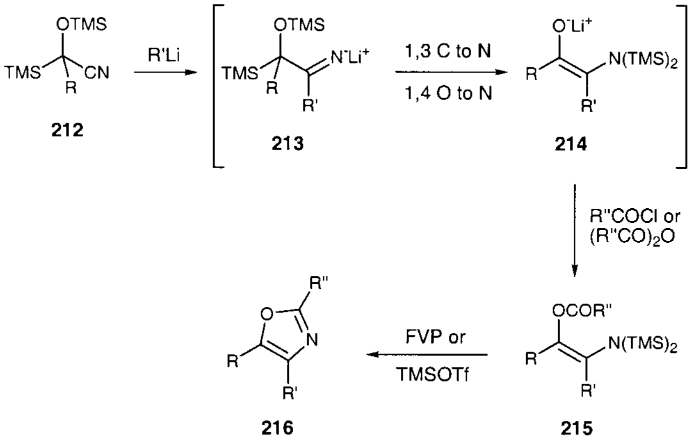
A unique synthesis of α-silylamines was utilized in conjunction with a silyl migration-mediated tandem sequence for the functionalization of alkyne precursors (Scheme 43).[57] Treatment of alkynes **202** with iminosilaacyl complex **203** in the presence of $LiEt_3BH$ afforded α-silylamines **204** in good yields through an insertion and hydrolysis sequence. Subsequent treatment of α-silylamines **204** with *n*-BuLi in a THF/HMPA solvent mixture induced 1,2-carbon to nitrogen silyl migration to afford the stabilized *N*-silylallyl anion **205**, which was alkylated exclusively at the γ-position by



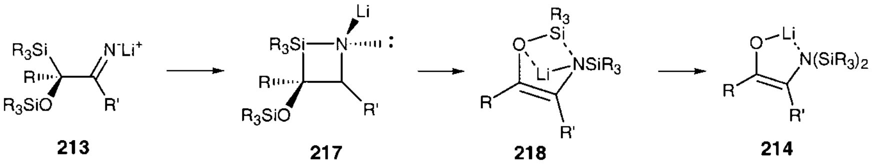
Scheme 43. Tandem aza-Brook rearrangement–alkylation process.



Scheme 44. 1,3-Aza-Brook rearrangements.



Scheme 45. Tandem silyl migrations in oxazole formation.



Scheme 46. Proposed mechanism for Z-enolate formation.

a variety of alkyl halides to afford **206**. Final acid hydrolysis affords aldehydes **207**. The overall process introduces functional groups to both carbons of the original alkyne. One is the formyl group derived from the iminosilaacyl complex and the other is an electrophile introduced by the aza-Brook rearrangement.

An example of a [1,3] aza-Brook rearrangement involving migration of silyl groups to an sp^2 hybridized nitrogen anion was reported by Bulman Page et al. (Scheme 44).[58] Lithiation of 2-trimethylsilyl-1,3-dithiane (**208**) and addition to non-enolisable nitriles afforded aminoketene dithioacetals **211b**. The proposed mechanism, involving 1,3-carbon to nitrogen silyl migration to generate the dithiane carbanion **210**, is supported by the isolation of silyl enamines **211a** if aqueous workup is omitted. Subsequent alkylations of the aminoketene dithioacetals at either the carbon or nitrogen centers were achieved, although tandem reactions were not reported.

A related [1,3] aza-Brook rearrangement has been reported in an interesting synthesis of substituted oxazoles (Scheme 45).[59] The method begins with addition of organolithium reagents to *O*-trimethylsilyl cyanohydrins **212**, which triggers sequential 1,3-carbon to nitrogen and 1,4-oxygen to nitrogen silyl migrations to afford lithium β-bis(trimethylsilyl)amino enolates **214**. Subsequent in situ acylation provides products **215**, which are isolated with exclusive *Z* stereochemistry. Cyclization of **215** to the desired oxazoles **216** was then accomplished either by flash vacuum pyrolysis or treatment with trifluoromethanesulfonate (TMSOTf) at 25°C. The preferred formation of the *Z* isomer of **215** was postulated to result from intramolecular lithium–oxygen complexation accompanying the carbon to nitrogen and/or oxygen to nitrogen silyl migrations (Scheme 46).[60]

8. Concluding remarks

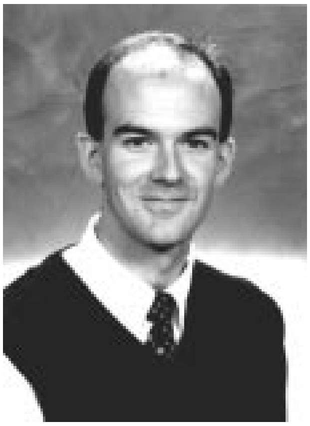
The wide variety of tandem bond-forming reactions mediated by silyl migrations outlined in this report clearly serves notice to the synthetic utility of the strategy. In an era where synthetic endeavors are increasingly judged not only by the end product, but also by the efficiency and elegance of the process,[10] it is anticipated that silyl migrations will continue to be embraced as a valuable tool. Additionally, the expanding recognition of silicon as a tool for stereochemical control in organic synthesis[61] should motivate continued development of silyl migrations in stereoselective organic transformations.

References

1. (a) Brook, A. G. *J. Am. Chem. Soc.* **1958**, *80*, 1886. (b) Brook, A. G.; Warner, C. M.; McGriksin, M. E. *J. Am. Chem. Soc.* **1959**, *81*, 981. (c) Brook, A. G.; Schwartz, N. V. *J. Am. Chem. Soc.* **1960**, *82*, 2435. (d) Brook, A. G.; Iachia, B. *J. Am. Chem. Soc.* **1961**, *83*, 827.
2. (a) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77. (b) Brook, A. G.; Bassindale, A. R. In *Rearrangements in Ground and Excited States*; De Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 2, pp 149–227. (c) Colvin, E. W. In *Silicon in Organic Synthesis*; Butterworths: London, 1981; pp 30–37.
3. Speier, J. L. *J. Am. Chem. Soc.* **1952**, *74*, 1003.
4. West, R.; Lowe, R.; Stewart, H. F.; Wright, A. *J. Am. Chem. Soc.* **1971**, *93*, 282.
5. (a) Jiang, X.; Bailey, W. F. *Organometallics* **1995**, *14*, 5704. For pertinent recent examples, see: (b) Kawashima, T.; Naganuma, K.; Okazaki, R. *Organometallics* **1998**, *17*, 367. (c) Naganuma, K.; Kawashima, T.; Okazaki, R. *Chem. Lett.* **1999**, 1139.
6. Jankowski, P.; Raubo, P.; Wicha, J. *Synlett* **1994**, 985.

7. Lautens, M.; Delanghe, P. H. M.; Goh, J. B.; Zhang, C. H. *J. Org. Chem.* **1995**, *60*, 4213.
8. (a) Linderman, R. J.; Ghannam, A. *J. Am. Chem. Soc.* **1990**, *112*, 2392. (b) Fleming, I.; Roberts, R. S.; Smith, S. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1215.
9. (a) Hoffmann, R.; Bruckner, R. *Chem. Ber.* **1992**, *125*, 1471. (b) Boche, F.; Opel, A.; Marsch, M.; Harms, K.; Haller, F.; Lohrenz, J. C. W. *Chem. Ber.* **1992**, *125*, 2265. (c) Hoffmann, R.; Bruckner, R. *Chem. Ber.* **1992**, *125*, 2731. (d) Hoffman, R.; Ruckert, T.; Bruckner, R. *Tetrahedron Lett.* **1993**, *34*, 297. (e) Bousbaa, J.; Ooms, F.; Krief, A. *Tetrahedron Lett.* **1997**, *38*, 7625. (f) Wang, Y.; Dolg, M. *Tetrahedron* **1999**, *55*, 12751.
10. (a) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (c) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
11. Kuwajima, I.; Kato, M.; Mori, A. *Tetrahedron Lett.* **1980**, *21*, 2745.
12. Reich, H. J.; Olson, R. E.; Clark, M. C. *J. Am. Chem. Soc.* **1980**, *102*, 1423.
13. Koreeda, M.; Koo, S. *Tetrahedron Lett.* **1990**, *31*, 831.
14. (a) Bienz, S.; Enev, V.; Huber, P. *Tetrahedron Lett.* **1994**, *35*, 1161. (b) Cunico, R. F.; Nair, S. K. *Synth. Commun.* **1996**, *26*, 803.
15. (a) Takeda, K.; Fujisawa, M.; Makino, T.; Yoshii, E.; Yamaguchi, K. *J. Am. Chem. Soc.* **1993**, *115*, 9351. (b) Takeda, K.; Nakayama, I.; Yoshii, E. *Synlett* **1994**, 178. (c) Takeda, K.; Nakajima, A.; Yoshii, E. *Synlett* **1997**, 255.
16. (a) Takeda, K.; Takeda, M.; Nakajima, A.; Yoshii, E. *J. Am. Chem. Soc.* **1995**, *117*, 6400. (b) Takeda, K.; Nakajima, A.; Yoshii, E. *Synlett* **1996**, 753. (c) Takeda, K.; Nakajima, A.; Takeda, M.; Yasushi, O.; Sato, T.; Yoshii, E.; Koizume, T.; Shiro, M. *J. Am. Chem. Soc.* **1998**, *120*, 4947. (d) Takeda, K.; Nakajima, A.; Takeda, M.; Yoshii, E. *Org. Synth.* **1999**, *76*, 199.
17. Takeda, K.; Ohtani, Y. *Org. Lett.* **1999**, *1*, 677.
18. Takeda, K.; Ubayama, H.; Sano, A.; Yoshii, E.; Koizumi, T. *Tetrahedron Lett.* **1998**, *39*, 5243.
19. Takeda, K.; Nakane, D.; Takeda, M. *Org. Lett.* **2000**, *2*, 1903.
20. Takeda, K.; Tanaka, T. *Synlett* **1999**, 705.
21. Portella, C.; Brigard, T.; Lefebvre, O.; Plantier-Royon, R. *J. Fluorine Chem.* **2000**, *101*, 193.
22. Ager, D. J. *Org. React.* **1990**, *38*, 1.
23. Trindle, C.; Hwang, J.-T.; Carey, F. A. *J. Org. Chem.* **1973**, *38*, 2664.
24. (a) Yamamoto, K.; Tomo, Y. *Tetrahedron Lett.* **1983**, *24*, 1997. (b) Yamamoto, K.; Kimura, T.; Tomo, Y. *Tetrahedron Lett.* **1984**, *25*, 2155.
25. Masnyk, M.; Wicha, J. *Tetrahedron Lett.* **1988**, *29*, 2497.
26. Raubo, P.; Wicha, J. *Tetrahedron: Asymmetry* **1996**, *7*, 763.
27. Achmatowicz, B.; Wicha, J. *Tetrahedron: Asymmetry* **1993**, *4*, 399.
28. Jung, A.; Koch, O.; Ries, M.; Schaumann, E. *Synlett* **2000**, 92.
29. (a) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1993**, *34*, 1951. (b) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron* **1996**, *52*, 503.
30. (a) Seebach, D.; Grobel, B.-T.; Beck, A. K.; Braun, M.; Geiss, K.-H. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 443. (b) Carey, F. A.; Court, A. S. *J. Org. Chem.* **1972**, *37*, 1926. (c) Jones, P. F.; Lappert, M. F.; Szary, A. C. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2272. (d) Seebach, D.; Kolb, M.; Grobel, B.-T. *Chem. Ber.* **1973**, *106*, 2277.
31. Burford, C.; Cooke, F.; Ehlinger, E.; Magnus, P. D. *J. Am. Chem. Soc.* **1977**, *99*, 4536.
32. (a) Fischer, M. R.; Kirschning, A.; Michel, T.; Schaumann, E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 217. (b) Brauer, N.; Michel, T.; Schaumann, E. *Tetrahedron* **1998**, *54*, 11481.
33. Michel, T.; Kirschning, A.; Beier, C.; Brauer, N.; Schaumann, E.; Adiwidjaja, G. *Liebigs Ann.* **1996**, 1811.
34. Brauer, N.; Dreeben, S.; Schaumann, E. *Tetrahedron Lett.* **1999**, *40*, 2921.
35. Le Merrer, Y.; Gravier-Pelletier, C.; Maton, W.; Numa, M.; Depezay, J. *Synlett* **1999**, 1322.
36. Matsuda, I.; Murata, S.; Ishii, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 26.
37. Tietze, L. F.; Geissler, H.; Gewart, J. A.; Jakobi, U. *Synlett* **1994**, 511.
38. Fleming, I.; Floyd, C. D. *J. Chem. Soc., Perkin Trans. 1* **1981**, 969.
39. Smith III, A. B.; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925.
40. Smith III, A. B.; Lin, Q.; Nakayama, K.; Boldi, A. M.; Brook, C. S.; McBriar, M. D.; Moser, W. H.; Sobukawa, M.; Zhuang, L. *Tetrahedron Lett.* **1997**, *38*, 8675.
41. Smith III, A. B.; Zhuang, L.; Brook, C. S.; Lin, Q.; Moser, W. H.; Trout, R. E. L.; Boldi, A. M. *Tetrahedron Lett.* **1997**, *38*, 8671.
42. Smith III, A. B.; Pitram, S. M. *Org. Lett.* **1999**, *1*, 2001.
43. Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.
44. Poss, C. S.; Rychnovsky, S. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 3360.
45. Hale, K. J.; Hummersone, M. G.; Bhatia, G. S. *Org. Lett.* **2000**, *2*, 2189.
46. Takaku, K.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1998**, *39*, 2575.
47. Moser, W. H.; Endsley, K. E.; Colyer, J. T. *Org. Lett.* **2000**, *2*, 717.
48. Comanita, B. M.; Woo, S.; Fallis, A. G. *Tetrahedron Lett.* **1999**, *40*, 5283.
49. Kleinfeld, S. H.; Wegelius, E.; Hoppe, D. *Helv. Chim. Acta* **1999**, *82*, 2413.
50. Dalton, J. C.; Bourque, R. A. *J. Am. Chem. Soc.* **1981**, *103*, 699.
51. Harris, J. M.; Walton, J. C.; Maillard, B.; Grelier, S.; Picard, J.-P. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2119.
52. Schiesser, C. H.; Styles, M. L. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2335.
53. (a) Tsai, Y.; Cherng, C. *Tetrahedron Lett.* **1991**, *32*, 3515. (b) Tsai, Y.; Tang, K.; Jiang, W. *Tetrahedron Lett.* **1993**, *34*, 1303.
54. Kim, S.; Do, J. Y.; Lim, K. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2517.
55. Lee, Y. J.; Lee, C. P.; Jeon, Y. T.; Mariano, P. S. *Tetrahedron Lett.* **1993**, *34*, 5855.
56. Sieburth, S. M.; Somers, J. J.; O'Hare, H. K.; Hewitt, G. W. *Appl. Organomet. Chem.* **1997**, *11*, 337.
57. Honda, T.; Mori, M. *J. Org. Chem.* **1996**, *61*, 1196.
58. Bulman Page, P. C.; van Niel, M. B.; Westwood, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 269.
59. Cunico, R. F.; Kuan, C. P. *J. Org. Chem.* **1992**, *57*, 3331.
60. Cunico, R. F.; Kuan, C. P. *J. Org. Chem.* **1990**, *55*, 4634.
61. Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.

Biographical sketch



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