Silylmethyl-substituted cyclopropyl and other strained ring systems: cycloaddition with dipolarophiles

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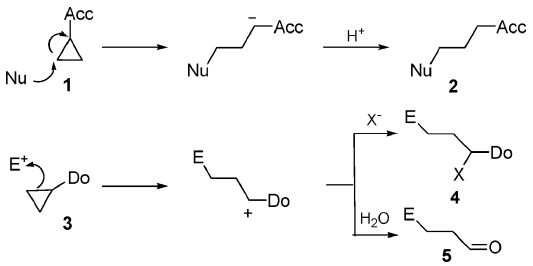
Small ring compounds represent a class of versatile building blocks in organic synthesis. Three- and four-membered ring carbo- and heterocycles are regarded as unique functional groups. Lewis acid-assisted cycloaddition of cyclopropanes, aziridines and azetidines substituted by vicinal electron-donor and electron-acceptor groups takes place in a regio- and stereocontrolled fashion. Trialkylsilylmethyl is an interesting donor substituent. In this *feature article*, we provide an overview of the cycloaddition of different dipolarophiles to silylmethyl-substituted small ring compounds and discuss their possible applications in synthesis.

Introduction

Cyclopropane is a useful synthetic intermediate because of its ready accessibility and good reactivity.[1] It is considered to be equivalent to a double bond but with one extra carbon to its advantage. The reactivity pattern is influenced by its substituents, in general, and the nature of the substituents, in particular.[1a] Different substituents force the cyclopropane ring to opt different reaction pathways. For instance, a vinyl substituent brings about $C_3 \rightarrow C_5$ ring enlargement[1b] and an electron-deficient substituent enlarges it into a four-membered ring entity. Further, the regio- and stereoselectivities of the reactions of cyclopropane are heavily dependent on the nature of the substituents. Thus, the substituents on cyclopropane fine tune both its reactivity and selectivity. The cyclopropane ring could be directed to react selectively with either an electrophile or a nucleophile by properly choosing the substituent on it. An acceptor cyclopropane such as **1** (Scheme 1) acts as a homo-Michael system and it is attacked by nucleophiles to result in **2**. Conversely, a donor cyclopropane such as **3** is attacked by electrophiles to give either **4** or **5**, depending upon the nature of the donor substituent. Thus, cyclopropanes bearing donor substituents act as homo-enolate equivalents.



Scheme 1 Ring opening of donor- and acceptor-substituted cyclopropanes.

The synthetic scope of a cyclopropane is dramatically enhanced when it is substituted with both a donor and an acceptor substituent as it is now equipped with what is considered a dual activation. The advantage of such a donor–acceptor substituted cyclopropane is two fold: (a) the cyclopropane ring cleaves under mild conditions, and (b) it results in products with two new synthetically useful functional groups. There are two modes possible for the placement of both the donor and the acceptor substituent. The geminally substituted cyclopropane **6** (Fig. 1) has limited scope as it

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Veejendra K. Yadav

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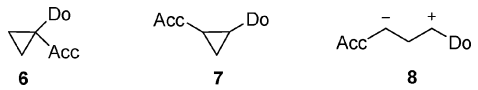


Fig. 1

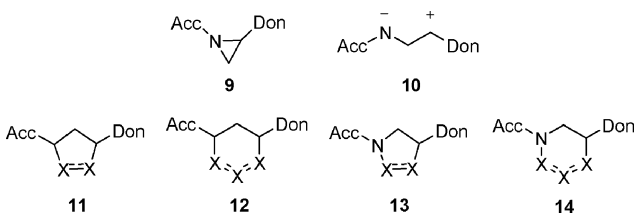


Fig. 2

undergoes mainly $C_3 \rightarrow C_4$ and $C_3 \rightarrow C_5$ ring expansion.[1c] The vicinally substituted cyclopropane **7** is a potential synthon as it combines both the homo-Michael and the homo-enolate characters depicted in **8** and, thus, it can add on to both nucleophiles and electrophiles.

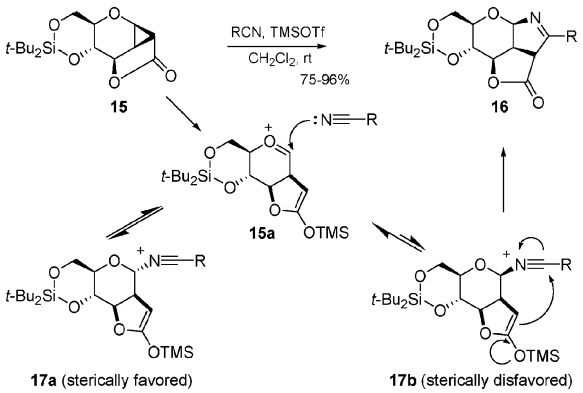
The vicinal donor–acceptor substituted aziridine **9** (Fig. 2) serves as the 1,3-dipolar synthon **10**. One of the most important synthetic applications of activated cyclopropanes and aziridines has been in the areas of formal [3 + 2] and [3 + 3] dipolar cycloadditions. The special feature of the 1,3-dipolar synthons **8** and **10** is their ability to react first either with a nucleophile at the positive end of the 1,3-dipole or an electrophile can capture its negative end. The formal [3 + 2] and [3 + 3] cycloadditions of **8** and **10** with multiple bond systems afford five- and six-membered ring carbo- and heterocycles of the general structures **11–14**.

We describe below the previously known reactions of small ring systems substituted by donor substituents other than the silylmethyl group to give a general picture of the chemistry of these small molecules first. This is followed by a detailed discussion of the chemistry of the latter to allow one to build an appreciation for retaining silicon in the product.

Lewis acid-catalyzed formal [3 + 2] and [3 + 3] cycloadditions of acceptor-substituted cyclopropanes bearing donor groups other than the silylmethyl function

Formal [3 + 2] and [3 + 3] cycloadditions of donor–acceptor substituted cyclopropanes bearing alkoxy, silyloxy and aryl groups as the donor substituents have been studied extensively. Alkylthio, arylthio and amino substituents are among the less studied donor substituents. The acceptor groups applied in the majority of instances are carbonyl and sulfonyl substituents.[2] Yu and Pagenkopf have reported a TMSOTf-promoted [3 + 2] cycloaddition of the glycal-derived cyclopropane **15** with aliphatic, aromatic, and α,β-unsaturated nitriles to generate 3,4-dihydro-2*H*-pyrroles **16** (Scheme 2).[3a] The reactions were highly stereoselective, providing a single diastereomer. The mechanism involves a [3 + 2] polar cycloaddition of the nitrile to **15**.

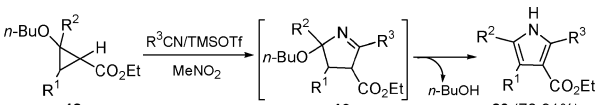
Lewis acid activates the ester group through coordination, a σ_{C-C} breaks and the 1,3-dipole **15a** is generated. Nucleophilic attack of the nitrile onto the oxonium ion following an intramolecular nucleophilic capture of the so-formed nitrilium ion by the enolate results in the formation of the observed



Scheme 2

product. Steric approach control favors attack on the α-face to generate **17a**. However, the electrophilic linear nitrilium ion is too distant to attack from the enolate. In contrast, the sterically disfavored intermediate **17b** can be trapped by the enolate to give the observed product. The efficient and stereoselective assembly of carbohydrate-derived densely functionalized amine-containing heterocycles is an attractive area of investigation due to the wide occurrence of these skeletons in pharmacologically significant natural and synthetic materials.

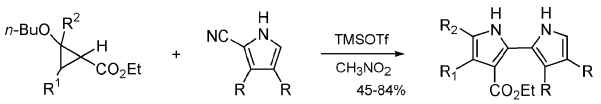
Yu and Pagenkopf have extended the above methodology to the synthesis of highly substituted pyrroles.[3b,4] Cyclopropanes of the general structure **18** underwent smooth ring opening in the presence of TMSOTf in nitromethane and reacted further with nitriles to offer the substituted pyrroles **20** (eqn (1)). The transformation follows a three-step cascade: [3 + 2] dipolar cycloaddition, elimination of *n*-BuOH, and tautomerization. The solvent played a vital role. The use of nitromethane in place of chloroform suppressed the formation of γ-ketoesters, the side products, by its inherent stabilizing effect on the oxocarbenium ion.



R^1 = Me, R^2 = H, R^3 = Me; R^1 = Et, R^2 = *n*-Pr, R^3 = Me; R^1 = Et, R^2 = Et, R^3 = Ph

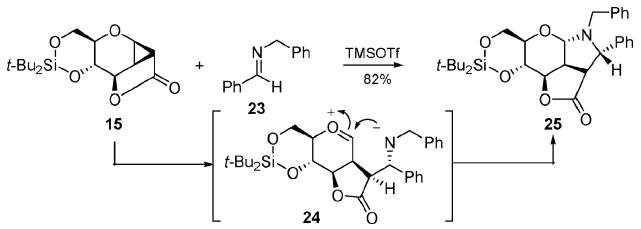
(1)

Reaction of the above dipole with 2-cyanopyrroles **21** led to a convenient access to the non-symmetrical bipyrroles **22** in moderate to good yields (eqn (2)).[3c] Remarkably, protection of the pyrrole nitrogen was not necessary. This pyrrole synthesis offers several advantages over other methods, including absolute regiocontrol (which is seldom possible through condensation protocols), high yields, simple purification and diverse substitution patterns.



(2)

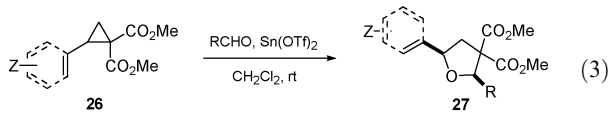
Yu and Pagenkopf have reacted electron-deficient dipolarophiles also in a formal [3 + 2] cycloaddition of the



Scheme 3

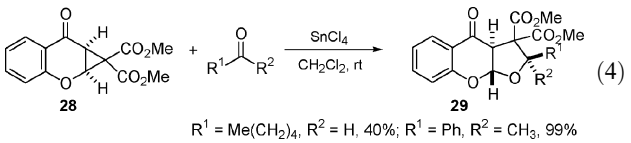
glycal-derived donor–acceptor substituted cyclopropane **15**.[3d,5] TMSOTf-mediated cycloaddition of the imine **23** to **15** furnished the pyrrolidine derivative **25**. The reaction proceeds through the oxonium species **24** (Scheme 3).

Pohlhaus and Johnson have reported a one-step protocol for the preparation of 2,5-disubstituted tetrahydrofurans **27** in high yields with the diastereoselectivity as high as 100 : 1 from the reaction of the donor–acceptor substituted cyclopropane **26** with aldehydes (eqn (3)).[6a]



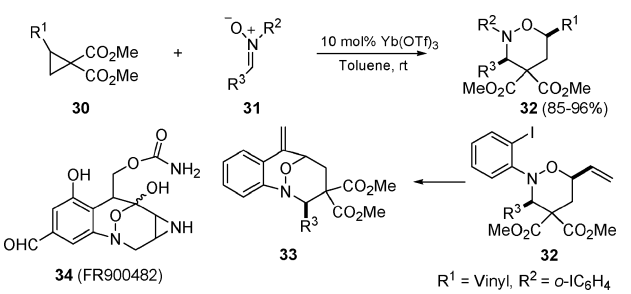
(3)

The *cis*-diastereoselectivity was shown to be easily controlled by an appropriate choice of the donor substituent and also by the aldehyde employed as the dipolarophile. The straightforward preparation of tetrahydrofurans is an important issue, owing to its repetitive occurrence in many natural products including the polyether antibiotics.[7] Sugita *et al*. have also developed a novel method for the synthesis of highly substituted aromatic ring-fused tetrahydrofuran derivatives.[8] Cyclopropanes of the general structure **28** reacted with carbonyl compounds under $SnCl_4$-catalysis to generate **29** with $>50:1$ diastereoselectivity (eqn (4)).

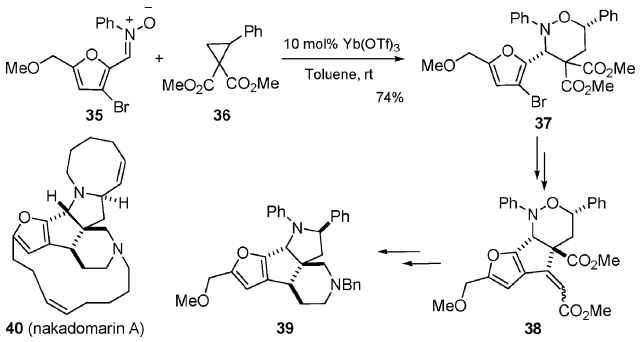


(4)

Young and Kerr have developed a novel route for the synthesis of tetrahydro-1,2-oxazines.[9] Cyclopropanes of the general structure **30** were reacted with the nitrones **31** under $Yb(OTf)_3$ catalysis to generate **32** in high yields with virtually complete 3,6-*cis*-diastereoselectivity (Scheme 4). This protocol was used in a two-step preparation of the congeners of the antitumor, antibiotic natural product FR900482, **34**.[10]



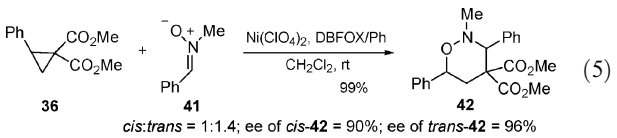
Scheme 4



Scheme 5

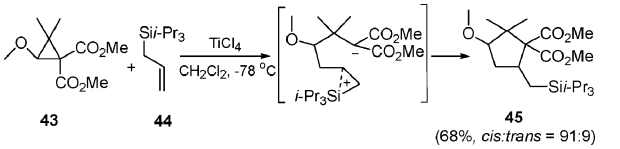
Kerr *et al*. have employed this methodology for the synthesis of the tetracyclic core of nakadomarin A, **40**, (Scheme 5).[11] The tetrahydrooxazine derivative **37** was formed with virtually complete *cis* diastereoselectivity from the combination of the nitrone **35** and the cyclopropane **36**. The ring cleavage in **38** and, again, ring closure with inversion of stereochemistry resulted in the preparation of the pyrrolidine derivative **39** that is present in nakadomarin A.

Sibi and co-workers have studied enantioselective addition of the nitrone **41** to donor–acceptor substituted cyclopropane **36** for the preparation of optically pure tetrahydro-1,2-oxazine **42** (eqn (5)).[12] Nickel perchlorate and (*R*,*R*)-4,6-dibenzofurandiyl-2,2′-bis-4-phenyloxazoline (DBFOX/Ph) gave the product with excellent enantioselectivity. The diastereoselectivity was, however, low. The low diastereoselectivity under chiral $Ni(ClO_4)_2$–DBFOX/Ph catalysis contrasts the strong *cis* selectivity registered with the achiral $Yb(OTf)_3$.



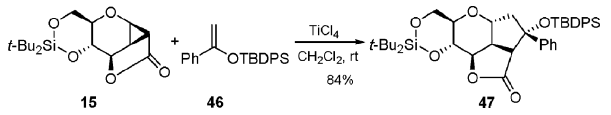
(5)

Sugita and co-workers have reacted allylsilanes with donor–acceptor substituted cyclopropanes to construct cyclopentane derivatives (eqn (6)).[13] The dicarboxylate **43** reacted with $TiCl_4$ and allyl triisopropylsilane **44** to furnish the [3 + 2] cycloadduct **45** with 91 : 9 *cis*-selectivity. The nucleophilic attack of allylsilane at the positive end of the 1,3-dipole followed by an intramolecular nucleophilic capture of the silicon-stabilized carbocation by the enolate results in the formation of the observed cyclopentane species **45**.



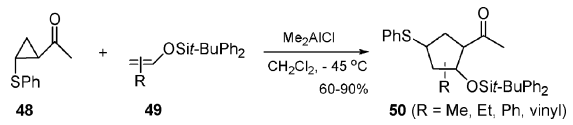
(6)

Yu and Pagenkopf have studied [3 + 2] cycloaddition of the glycal-derived donor–acceptor substituted cyclopropane **15** with silyl enol ethers.[3d] In the presence of $TiCl_4$, **15** reacted with the silyl enol ether **46** to provide **47** as the sole isolable product in good yield (eqn (7)).



(7)

Kuwajima and co-workers[14] have reported Me_2AlCl-mediated formal [3 + 2] cycloaddition of methyl 2-phenylthiocyclopropyl ketone **48** and silyl enol ethers **49** to generate functionalized cyclopentanes **50** in 60–90% yield (eqn (8)). The diastereoselectivity, however, varied from one example to the other. The reaction of **51** with the silylketene acetal **52** in the presence of $TiCl_4$, however, did not stop at cyclopentane formation. Spontaneous elimination of MeOH furnished the cyclopentenone **53** in 28–75% yield (eqn (9)).[15]



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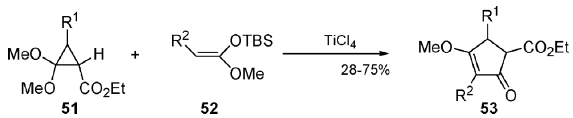
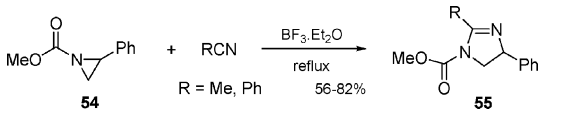


(9)

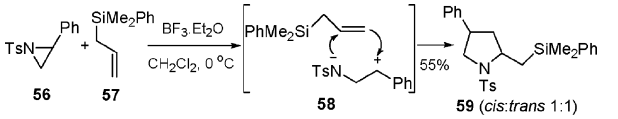
Lewis acid catalyzed formal [3 + 2] cycloaddition of activated aziridines

Lewis acid catalyzed [3 + 2] cycloaddition of aziridines bearing a vicinal phenyl group as the donor substituent has been studied extensively. The acceptor group applied in the majority of instances is a sulfone substituent on the nitrogen. Hiyama *et al.* have reported $BF_3{\cdot}Et_2O$-promoted [3 + 2] cycloaddition of 1-methoxycarbonyl-2-phenylaziridine **54** with nitriles to generate the 2-imidazolines **55** (eqn (10)).[16] However, the reaction conditions were harsh and higher amounts of nitriles were used. 2-Imidazolines are useful intermediates for the synthesis of molecules with significant pharmacological activities. For instance, the imidazoline derivatives such as midaglizole, deriglidole, and efaroxan are highly active antihyperglycemic agents.[17]



(10)

Mann and co-workers have reported the reaction of *N*-tosyl phenylaziridine **56** with the allylsilane **57** in the presence of $BF_3{\cdot}Et_2O$ to afford the pyrrolidine derivative **59** as a 1 : 1 isomeric mixture.[18a] The formation of the pyrrolidine ring is the result of a non-concerted [3 + 2] cycloaddition. The nucleophilic attack of allylsilane at the positive end of the dipole **58** and the subsequent intramolecular nucleophilic capture of the silicon-stabilized cation by the negatively charged nitrogen results in the formation of **59** (eqn (11)). This methodology was employed in the synthesis of azaoxa[3.2.0]-derivatives.[18b] Formal [3 + 2] cycloaddition of the *N*-tosyl phenylaziridine **56** to dihydropyran **60** in the presence of $BF_3{\cdot}Et_2O$ produced the two cycloadducts **61a** and **61b** in a 1 : 1 ratio in high yields (eqn (12)). The reaction of **56** with unactivated olefins **62** under $BF_3{\cdot}Et_2O$ conditions afforded the spiropyrrolidines **64** (eqn (13)).[18c] The π-bond attacks the benzylic position to generate the stable carbocation **63** which ring closes with the amide function. Spiropyrrolidines are present in the core of several biologically active alkaloids such as cylindricines A–K, FR901483, and lepadiformine.[19]



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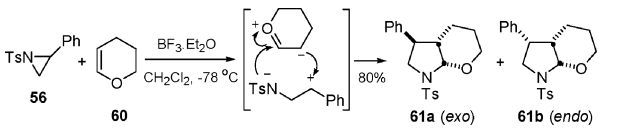

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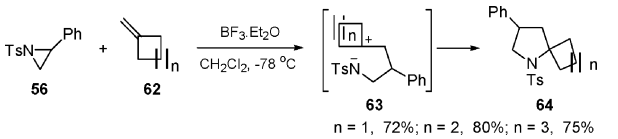
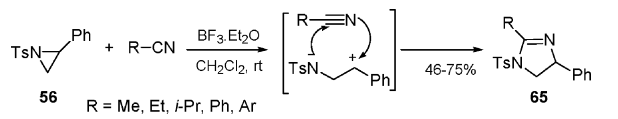


(13)

Singh and co-workers have also studied the reactions of various nitriles with **56** under $BF_3{\cdot}Et_2O$ conditions and reported the formation of 4,5-dihydro-1*H*-imidazoles **65** (eqn (14)).[20] The reaction conditions employed by these investigators were milder than those used previously by Hiyama and co-workers. Yadav and co-workers have reported a catalytic version of *N*-tosyl phenylaziridine cycloaddition to activated alkenes in the presence of $Sc(OTf)_3$ at ambient temperature to generate the pyrrolidine derivative **67** in high yield as a 1 : 1 isomeric mixture (eqn (15)).[21]



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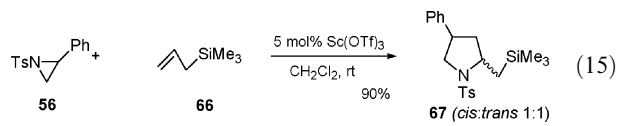

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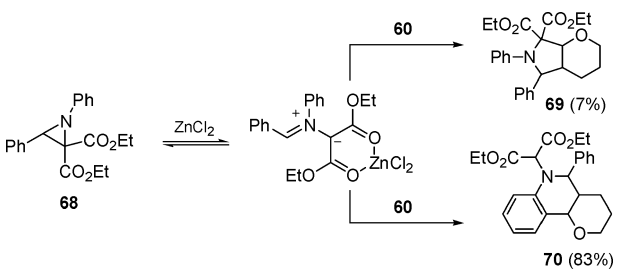


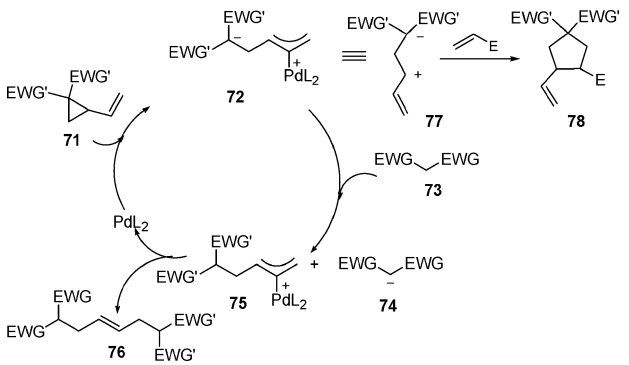
Scheme 6

Pohlhaus *et al*. have reported a Lewis acid-promoted σ_{C-C} bond cleavage in aziridines.[6b] $ZnCl_2$-promoted cycloaddition of the aziridine **68** to dihydropyran **60** produced the [3 + 2] adduct **69** in only 7% yield. The major product was the [4 + 2] adduct **70** that was formed by Mannich addition followed by intramolecular Friedel–Crafts alkylation (Scheme 6).

Vinylcyclopropanes

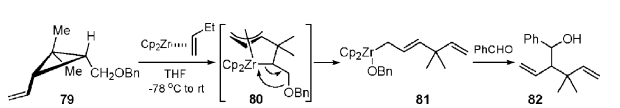
The exploration of vinylcyclopropanes for application to organic synthesis has been an area of intense research that has been reviewed previously.[22] However, to put the present review in a broader perspective, some salient features of this class of compounds are given below.

The ring cleavage of vinylcyclopropanes was viewed to have much synthetic potential should the regiochemistry of nucleophilic attack be controlled. Burgess achieved regiospecific conjugate addition of active methylene compounds to activated vinylcyclopropanes under neutral conditions.[23] The Pd(0) complex was envisaged to cleave the σ_{C1-C2} bond in **71** to form the zwitterionic π-allyl intermediate **72** (Scheme 7). Deprotonation of an active methylene species **73** generated the corresponding stabilized enolate **74** that added to the π-allyl terminus to result in the observed product. The complex **72** can also react with electron-deficient olefins.[24] Shimizu *et al*. have synthesized the cyclopentanes **78** by [3 + 2] cycloaddition of the zwitterion **72** to activated alkenes.[25]



Scheme 7

Hanzawa *et al*. have achieved regioselective bond scission using Cp_2Zr under the influence of a substituent that had critical steric effect on the direction of the Cp_2Zr approaching the vinylcyclopropane **79** (eqn (16)).[26] The allylzirconium species **80** reacted with PhCHO to generate **82**. Kataoka *et al*. have explored the transformation of 1-acceptor-1-sulfenyl-substituted 2-vinylcyclopropanes **83** (eqn (17)).[27] The treatment of **83** with sulfonic acids such as *p*-TsOH and CF_3SO_3H in a nonpolar solvent caused a rapid σ_{C1-C2} bond scission that was followed primarily by a 1,5-sulfenyl shift, as shown in **84**, to result in **85**.



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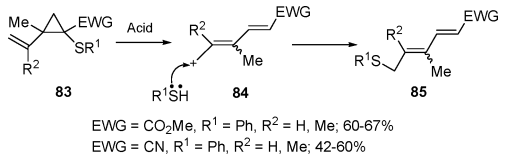
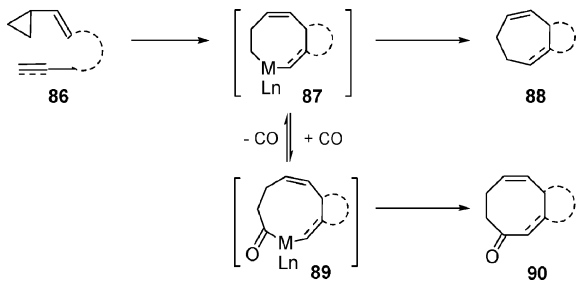


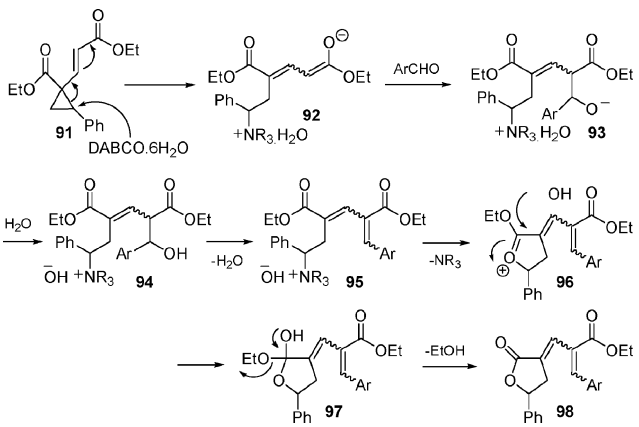
(17)

Wender *et al*. have reported the first study of a transition metal-catalyzed [5 + 2] cycloaddition of alkenes and vinylcyclopropanes (**86** → **88**) in 70–94% yields.[28a] This study was extended to the first examples of [5 + 2 + 1] cycloaddition of vinylcyclopropanes, alkynes and CO, leading to the formation of eight-membered rings (**86** → **90**) in 48–97% yields (Scheme 8).[28b]



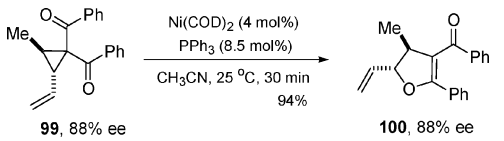
Scheme 8

Du and Wang have reacted the activated vinylcyclopropane **91** with substituted arylaldehydes to finally afford the α-methylene γ-butyrolactones **98** in the presence of DABCO. This tandem domino process, as shown in Scheme 9, took place in aqueous medium. It was presumably initiated by the ring opening of cyclopropane by the nucleophilic addition of DABCO.[29]

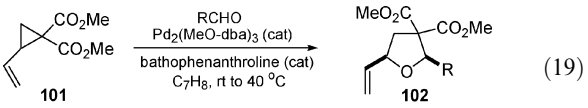


Scheme 9

Johnson and co-workers have developed a Ni(0)-catalyzed rearrangement of 1-acyl-2-vinylcyclopropane **99** to the dihydrofuran **100** (eqn (18)).[30a] They have also developed a palladium(0)-catalyzed cycloaddition of the malonate-derived vinylcyclopropane **101** with aldehydes to afford the *cis*-2,5-disubstituted tetrahydrofuran **102** (eqn (19)).[30b]



(18)



(19)

yield 53-100%, dr up to 98:2

Silicon-assisted ring opening of cyclopropanes

The trimethylsilylmethyl function is an interesting donor substituent because of some unique properties associated with the silicon such as (a) its relatively low electronegativity compared to carbon, and (b) its ability to expand its valency under specific circumstances. These properties enable silicon to stabilize a positive charge on the β carbon, a subject of much mechanistic, synthetic, and theoretical investigation.[31] Its magnitude has been calculated to be ~38 kcal mol^{-1}. The mode of stabilization could be through either hyperconjugation without significant movement in the transition state (TS) as in **103** or the internal neighbouring group participation to form the siliranium cation **104** in which the pentavalency of silicon is allowed by its d orbital (Fig. 3).[32]

The silicon-assisted ring opening of cyclopropane derivatives has been utilized by Chan and Fleming in the synthesis of substituted olefins.[33d] Dubois *et al.* have studied extensively the ring opening of cyclopropanes assisted by a trimethylsilylmethyl substituent.[33] In these cases, the silicon function was lost and the reactions resulted in substituted olefins. In the initial studies, different (cyclopropylmethyl)trimethylsilanes such as **105** were sulfonated with trimethylsilylchlorosulfonate to obtain the trimethylsilyl monosulfonate **106** which, on subsequent treatment with water, gave the sulfonic acid **107** (Scheme 10).[33e] Electrophilic attack of I_2 or ICl on (cyclopropylmethyl)trimethylsilane resulted in ring cleavage to give 4-iodo-1-butene **108**.[33c] However, Br_2, being more reactive to double bonds, added further to give 1,2-dibromobutane **109**. The $AlCl_3$-promoted acylation of **105** with RCOCl gave a mixture of **110–112**. With almost all the acyl halides studied except the α,β-unsaturated acyl halides, the β,γ-unsaturated ketone **111** was the major product.[33b]

Ryu and co-workers have studied the electrophilic ring opening of a variety of substituted (cyclopropylmethyl)trimethylsilanes **113** with $SnCl_4$, BBr_3, and $BHBr_2$.[34] $SnCl_4$-assisted ring

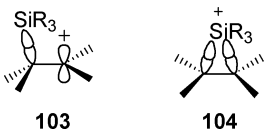
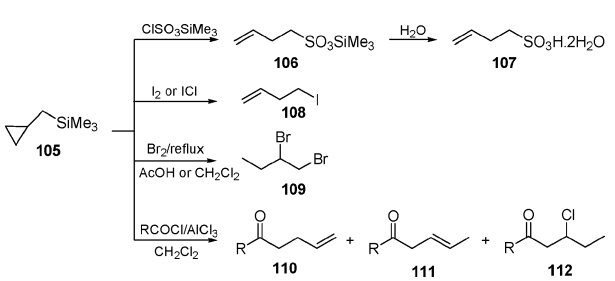
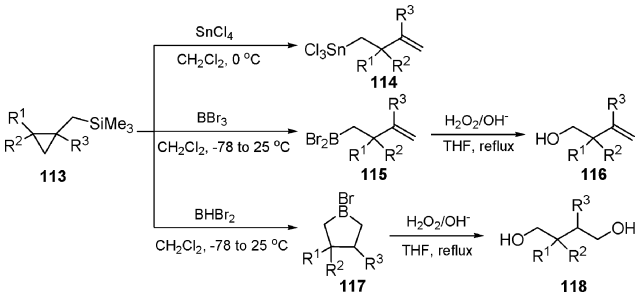


Fig. 3 Stabilization of a β-carbocation by silicon.



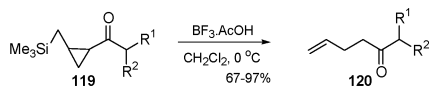
Scheme 10



Scheme 11

cleavage was highly regioselective as it resulted in the formation of the homoallylic trichlorostannanes, **114**.[34b] Likewise, the electrophilic attacks involving BBr_3 and $BHBr_2$ were also site-selective and took place at the least substituted cyclopropane ring carbon.[34a] Homoallylboranes **115** and boracyclopentanes **117** obtained from the respective reactions with BBr_3 and $BHBr_2$ were easily converted into homoallylic alcohols **116** and 1,4-diols **118**, respectively, by oxidation with alkaline H_2O_2 (Scheme 11).

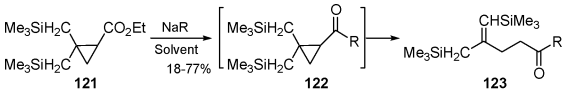
Only scant reports are available for the ring opening of donor–acceptor substituted cyclopropanes possessing a trimethylsilylmethyl group as the donor function. Vicinal donor–acceptor substituted cyclopropyl ketones **119** underwent smooth ring opening under Lewis acidic conditions to generate **120** (eqn (20)).[35] This methodology was applied to the formal syntheses of *cis*-jasmone and dihydrojasmone.



(20)

R^1 = H, R^2 = SO_2Ph; R^1 = *n*-C_5H_{11}, R^2 = H; R^1 = Me, R^2 = SO_2Ph; R^1 = Ph, R^2 = H

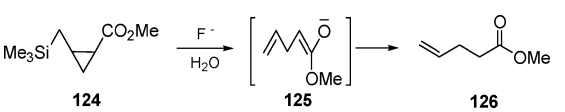
Nucleophilic displacement on the ester function of **121** with the sodium salt of a sulfone under basic conditions in solvents such as DME, DMSO and THF showed an unusual ring opening to afford 2-substituted 1,3-bis(trimethylsilyl)propenes **123** (eqn (21)).[36] The rapid ring opening occurred presumably from the corresponding acylated derivative **122**. This was attributed to the severe destabilizing steric interaction between the acyl substituent and the trimethylsilylmethyl group *syn* to it.



(21)

R = CH_2SO_2Ph, CH_2SO_2Me, $CH(SO_2Ph)CH_2CHCHCH_2CH_3$

Fluoride ion-promoted cleavage of methyl (2-trimethylsilylmethyl)cyclopropylcarboxylate **124** was studied by Reichelt and Reissig.[37] The enolate **125** gave methyl 4-pentenoate **126** on being quenched with water (eqn (22)). It is to be noted that no α-methylated methyl 4-pentenoate was formed from a quench of the reaction by MeI.



(22)

1-Acylimidazole **127** serves as the 1,2-dipole **128** (Fig. 4). It adds to diethyl maleate and ethyl 2-ethoxycarbonyl-2,4-hexadienoate to give substituted cyclobutanones **129** and

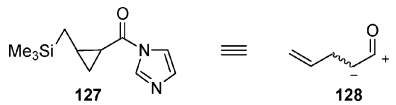
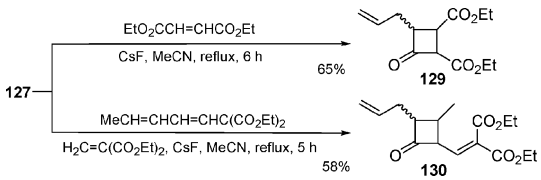


Fig. 4



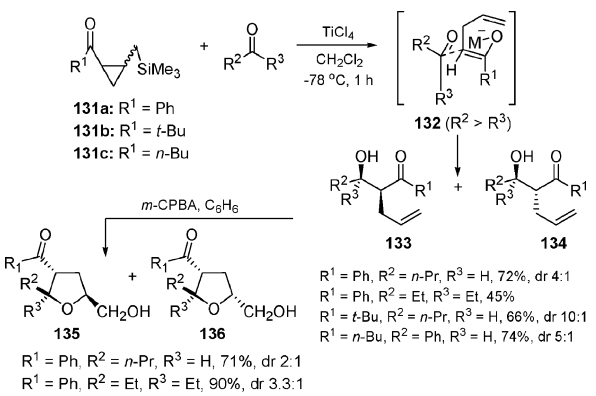
Scheme 12

130, respectively, on ring opening with CsF (Scheme 12).[38] The success of this reaction is due probably to the electrophilic 1-acylimidazole moiety, which assists the ring opening, and the leaving ability of the imidazole group that generates a positively charged carbonyl carbon.

Diastereoselective aldol reactions of the enolates generated from vicinally substituted trimethylsilylmethyl cyclopropyl ketones

Cyclopropanes bearing vicinal trimethylsilylmethyl and electron-attracting groups undergo ring-opening on treatment with reagents such as CsF,[38] $BF_3{\cdot}OEt_2$,[38] $BF_3{\cdot}AcOH$[35] and TBAF[37] or under nucleophilic conditions.[36] Surprisingly, sufficient effort was not made to trap the intermediate enolate to make the overall reaction synthetically useful. Only the γ,δ-unsaturated carbonyl compounds were obtained. Attempts to trap the enolate formed from the TBAF-induced ring opening of methyl (2-trimethylsilylmethyl)cyclopropylcarboxylate with MeI were unsuccessful.[37]

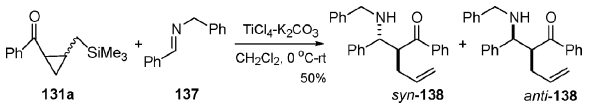
Since the aldol reaction is a powerful tool for constructing σ_{C-C} bonds in a stereoselective manner,[39] we studied the reactions of the cyclopropane derivatives **131a–c** (Scheme 13) with carbonyl compounds under Lewis acid conditions.[40] The related reactions of substituted cyclopropanes bearing stronger donor substituents such as the alkoxy and siloxy groups are known in the literature.[8,41] The aldol products **133** and **134** were obtained in good yields with high *syn* selectivity. The reactions were sluggish with ketones at −78 °C and required warming to 25 °C to obtain the products in decent yields.[42] A more than 2-fold increase in the *syn* selectivity was observed with the *tert*-butyl ketone **131b**. The enhancement in the *syn* selectivity indicated predominant involvement of the (*Z*)-enolate.[43] The closed chair transition state **132** was implicated to explain the predominant *syn* selectivity. The synthetic utility of this protocol was demonstrated by the easy transformation of selected aldol products into 2-tetrahydrofuranylmethanol derivatives **135** and **136** under oxidative conditions.[44]



Scheme 13

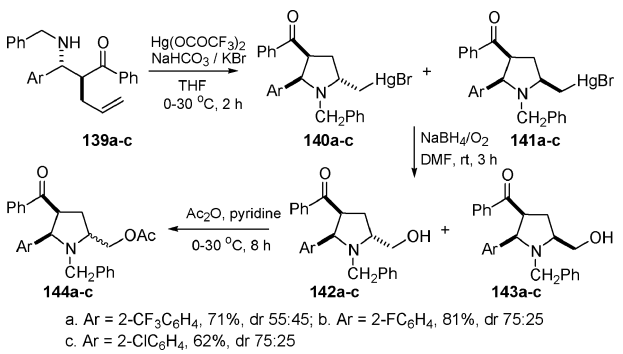
Imino-aldol reaction of the enolate generated from vicinally substituted trimethylsilylmethyl cyclopropyl ketones

Pyrrolidines are important heterocycles for their frequent occurrence in biologically active compounds[5,45] and as valuable synthetic intermediates[46] and organocatalysts.[47] We have explored the reaction of **131a** with imines and conversion of the so-generated imino-aldols into pyrrolidine derivatives.[48a] For instance, **131a** reacted with the imine **137** in the presence of $TiCl_4$ and K_2CO_3 to generate *syn*-**138** and *anti*-**138** as a 4 : 1 diastereomeric mixture in 50% yield (eqn (23)).



(23)

The substituent on the imine-nitrogen influenced the reaction strongly. The *N*-sulfonyl imine was not a good substrate. Under the optimized conditions, *N*-*p*-methoxy benzylimine reacted with **131a** to afford the desired imino-aldol product in 41% yield as a 77 : 23 diastereomeric mixture. The *N*-benzyl imine, therefore, offered the optimal result. The benzylimines of different aromatic aldehydes were, therefore, successfully reacted with **131a**. The utility of the above imino-aldol protocol was demonstrated by the cyclization of several imino-aldol products into pyrrolidine derivatives following a literature protocol (Scheme 14).[48b]



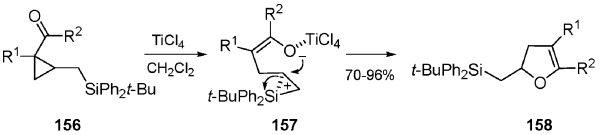
Scheme 14

An expedient entry to substituted dihydrofurans

In all the cases except the alkylative ring opening of **121**, the carbon–silicon bond is cleaved to effect ring opening. Furthermore, the ring opening without the extrusion of the silicon occurred only because of the steric encumbrance caused by the bulky acyl substituent and the trimethylsilylmethyl group *syn* to it. Such a restricted scope of the ring opening is due to the extrusion of the important silicon group that could have allowed further synthetic manipulations. Hence, need arose to effect the ring opening without the extrusion of silicon. In doing so, the ring opened species will have the features of a homo-Michael system and an enolate equivalent, as in **145**, that may be expected to undergo either an intramolecular cyclization through the enolate carbon to give a cyclobutane derivative **146** involving 1,2-silyl migration or an intramolecular cyclization of the enolate oxyanion on the siliranium ion to generate the dihydrofuran **147** or the dihydropyran **148**, or both. The reaction of the dipole **145** with electrophiles such as carbonyls and Michael acceptors may be expected to result in the species **149–152**. The reaction involves an initial intermolecular attack of the enolate on the electrophile preceding an intramolecular ring closure (Scheme 15).

One way to achieve the above objective was the placement of bulky substituents on the silicon, as these would shield the silicon from attack by nucleophiles. When one or more of the methyl groups in allyltrimethylsilane **153** are replaced by bulky groups such as isopropyl, phenyl, and *tert*-butyl, it may be expected to behave as either the 1,3-dipole **154** that will form from 1,2-migration of the silicon function or the 1,2-dipole **155** that does not require any migration (Fig. 5).

Cyclopropanes bearing two electron-attracting groups, as in **156**, underwent facile regioselective ring opening to furnish the substituted dihydrofurans **158** in high yields (eqn (24)).[49a,50] The formation of the dihydrofuran proceeds presumably through the 5-*exo*-*trig* cyclization of the titanium enolate **157** on the silicon-stabilized carbocation that is formed from ring opening. The carbon–silicon bond is not cleaved, and it is preserved in the product for further manipulation into useful functional groups, including OH, for subsequent synthetic exploitation.[51] No ring cleavage was observed even on stirring for a prolonged time at room temperature when the cyclopropane ring had a single ester function. This may be due to the insufficient activation of the ring by a single ester function. Contrary to this, a single phenyl ketone brought about the ring cleavage smoothly. However, the resultant enolate did not cyclize onto the incipient carbocation to give the corresponding dihydrofuran.



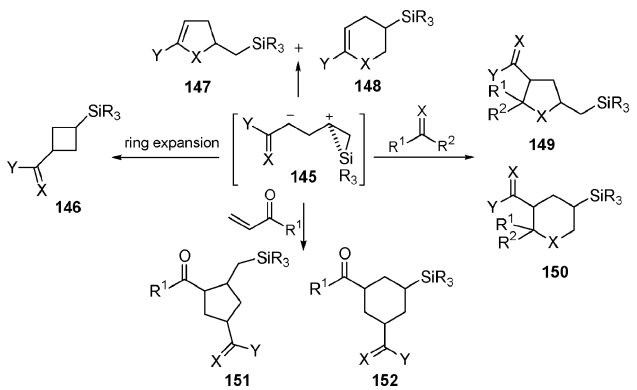
156 157 158

$R^1 = CO_2Me$, $R^2 = OMe$; $R^1 = COMe$, $R^2 = Me$; $R^1 = CO_2Et$, $R^2 = Me$; $R^1 = SO_2Ph$, $R^2 = OEt$

(24)

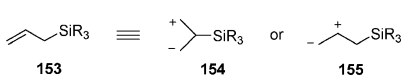
To examine the role of the silicon substituents, we have reacted dimethyl (2-triisopropylsilylmethyl)cyclopropyl-1,1-dicarboxylate **159** (Scheme 16) bearing the comparatively less bulky triisopropyl function with $TiCl_4$.[49b] It did not give the expected dihydrofuran, instead it gave a mixture of the α-allylated dimethylmalonate **162** and the α,β-unsaturated diester **164** in 26% and 54% yields, respectively. The formation of **162** was explained by the elimination of the silicon function on attack by chloride ion. The formation of **164** was delineated from a D_2O-quench experiment to involve hydride migration from the carbon γ to the silicon to the β-carbocation (path *b*) *via* **163**. The triisopropylsilyl function had thus favored predominant elimination.

The above cyclopropane derivative **165** bearing the less bulky phenyldimethylsilyl function was also subjected to $TiCl_4$-promoted ring opening. It furnished dimethyl α-allyl malonate quantitatively by the complete extrusion of the phenyldimethylsilyl function. These experiments indicated the importance of the bulky *tert*-butyldiphenylsilyl substituent in the formation of dihydrofurans. Since the enolate generated from the phenyl ketone **166a** (Scheme 17) on treatment with $TiCl_4$ did not cyclize intramolecularly to a dihydrofuran derivative, it offered a decent opportunity to explore its reactions with external electrophiles. On reaction with butyraldehyde, the tetrahydrofuran derivative **167** was obtained as a



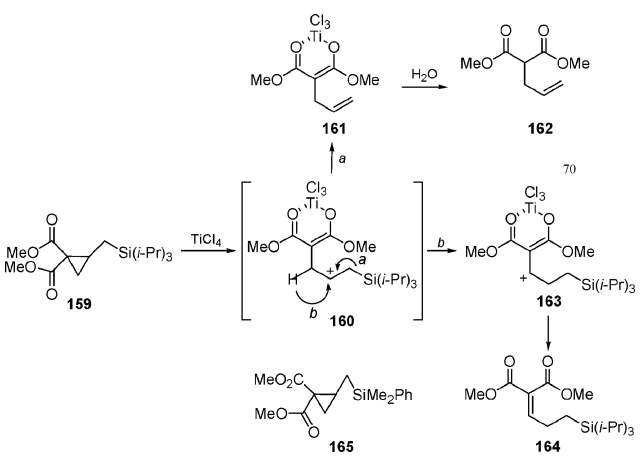
147 148 149 150 151 152 145 146

Scheme 15



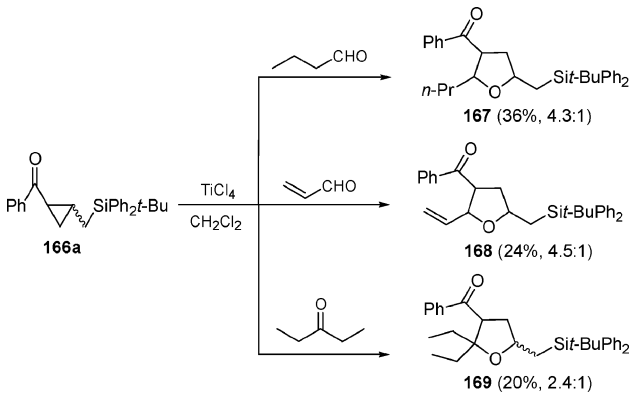
153 154 155

Fig. 5



159 160 161 162 163 164 165

Scheme 16



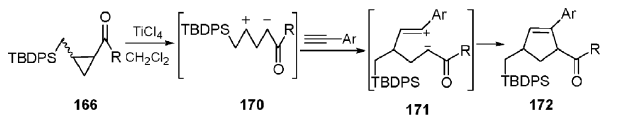
Scheme 17

4.3 : 1 diastereomeric mixture in 36% yield.[49b] Likewise, the reaction with acrolein furnished a 4.5 : 1 diastereomeric mixture of the tetrahydrofuran derivative **168** in 24% yield. The said enolate reacted with ketones as well: a diastereomeric mixture of **169** in 20% yield was obtained on reaction with 3-pentanone.

Formal [3 + 2] and [3 + 3] additions of acceptor-substituted cyclopropylmethylsilanes

Arylacetylenes

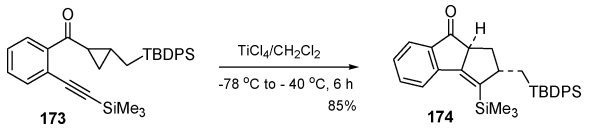
In the first ever application of arylacetylenes as dipolarophiles for formal [3 + 2] additions to donor–acceptor substituted cyclopropanes in the presence of Lewis acids, we reacted the cyclopropyl ketones **166a–c** bearing a vicinal *tert*-butyldiphenylsilylmethyl group to generate substituted cyclopentenes in a single step.[52a] The previously reported additions of acetylenes were carried out with hetero-1,3-dipoles to construct heterocycles.[52b–d] The reaction outlined in eqn (25) entails initial attack of the terminal acetylenic carbon at the positive end of the 1,3-dipole **170**. The enolate intercepts the resultant vinyl cation, as in **171**, and the cyclopentene skeleton **172** is formed.



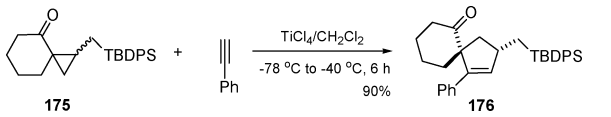
(25)

Arylacetylenes bearing electron-donating groups reacted better than those having electron-withdrawing groups. A *p*-methoxy substituent caused extensive migration of the olefinic linkage under the reaction conditions. This was ascertained to be acid-catalyzed as it could be prevented completely by conducting the reaction in the presence of suspended K_2CO_3. All the reactions were *cis*-selective. Simple alkylacetylenes, such as 1-decyne and benzylpropargyl ether, did not react.

The intramolecular variant also proceeded very well. The reaction of *trans*-**173** furnished **174** in 85% yield (eqn (26)). The hydrogen at the ring junction was determined to be *cis* to the silylmethyl substituent based on NOE measurements. Spiro ring systems, which are present in a large number of natural products, often constitute challenging synthetic targets.[53] Both the *trans*-**175** and *cis*-**175** (formed as a 3 : 1 mixture) reacted smoothly with phenylacetylene to generate **176** as the sole product in 90% yield (eqn (27)).



(26)



(27)

The cyclopentene skeleton is the key motif in the preparation of numerous biologically active materials of natural and synthetic origin.[54] For instance, carbonucleosides have been the focus of recent investigation in the development of new antiviral and antitumor therapeutic agents.[55] In a large search for new antiviral agents, particularly those used for the treatment of HIV, both carbovir **177** and abacavir **178** have been demonstrated to possess inhibitory activity.[56] The adenosine analogues aristeromycin **179** and neplanocin A **180** are also strong antiviral agents as they inhibit the cellular enzyme *S*-adenosyl homocysteine hydrolase (Fig. 6). In addition, neplanocin A has been shown to possess anticancer activity against leukemia.[57]

The fused tricyclic skeleton is present in several important molecules, *e.g.*, taiwaniaquinols **181**[58] and hamigerans (**182a** and **182b**).[59] The [4,5]-spiro carbocycles are structures of

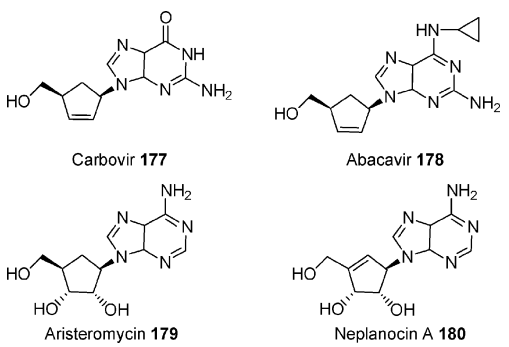


Fig. 6

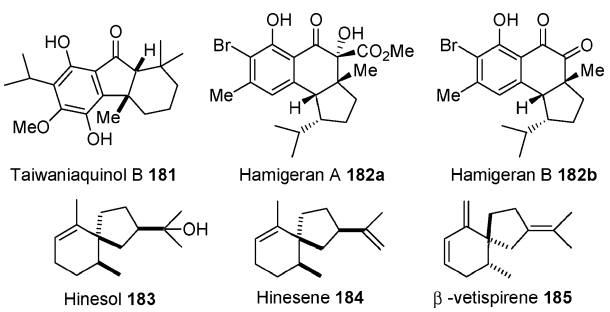
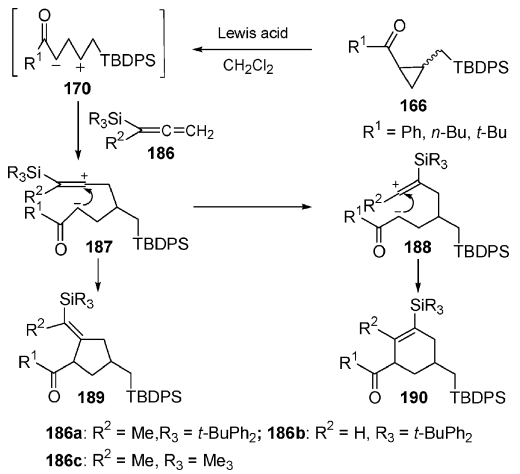


Fig. 7

broad pharmaceutical interest. Spirovetivanes such as hinesol **183**,[60] hinesene **184**[61] and β-vetispirene **185**,[62] for instance, are a group of spiro[4,5]decane sesquiterpenes (Fig. 7).

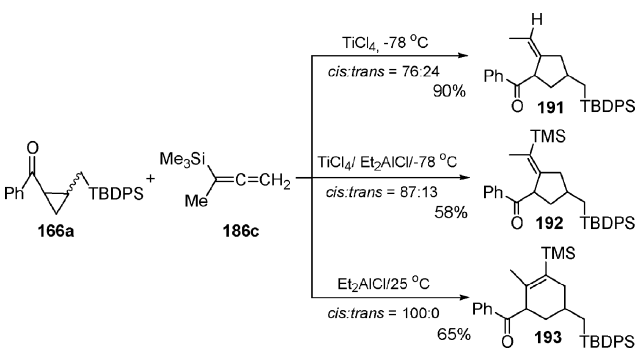
Allenylsilanes

Lewis acid promoted reactions of allenylsilanes with 1,2- and 1,3-dipoles provide easy access to five- and six-membered carbo- and heterocyclic rings wherein the allenylsilane functions as the synthetic equivalent of silyl-substituted 1,2- and 1,3-dipoles, respectively.[63] In principle, the donor–acceptor substituted cyclopropane **166** (Scheme 18) can react with an allenylsilane **186** under Lewis acid conditions to generate the vinyl cation **187** which could rearrange to the vinyl cation **188**, entailing 1,2-silicon migration, should the latter be competitively stable. Subsequent intramolecular capture of the cations **187** and **188** by the enolate may then result in the formation of the five- and six-membered carbocycles **189** and **190** through [3 + 2] and [3 + 3] cycloadditions, respectively. The olefin geometry in **189** is likely to be controlled by the steric effects arising from the substituents in both the allenylsilane and enolate and also by the stereoelectronic effects arising from the allenyl silicon during ring closure.[63b]



Scheme 18

The phenyl ketone **166a** underwent smooth ring opening with $TiCl_4$ in CH_2Cl_2 at −78 °C and the resultant enolate reacted further with the allenylsilane **186c** to afford the [3 + 2] adduct **191** (Scheme 19). The allenyl trimethylsilicon was, however, lost. Use of Et_2AlCl along with $TiCl_4$ (1.3 mol equiv. each) prevented this loss and **192** was isolated in 58% yield.



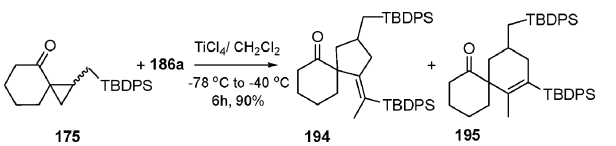
Scheme 19

The loss of the trimethylsilyl group under the $TiCl_4$ conditions was due presumably to protodesilylation caused by the HCl that may have formed from the hydrolysis of $TiCl_4$ by adventitious moisture. Since Et_2AlCl is an efficient proton scavenger,[64] its usage terminated the protodesilylation channel completely. Et_2AlCl alone as Lewis acid also worked at 25 °C. Interestingly, only the [3 + 3] adduct **193** was formed and the allenyl trimethylsilicon was retained in the product to equip it with the synthetically versatile vinylsilane motif.[65]

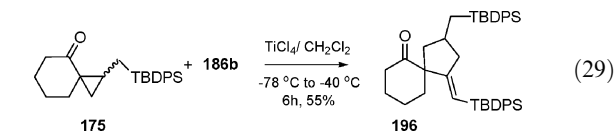
$TiCl_4$ as Lewis acid resulted in an intractable mixture of several products at 25 °C. The reaction with the TBDPS-containing allenylsilane **186a** at −78 °C generated a 1.7 : 1 mixture of [3 + 2] and [3 + 3] adducts. This ratio changed to 1 : 3 when the reaction was conducted at −20 °C. This result, taken together with the complete silicon migration at 25 °C using Et_2AlCl, indicated that the 1,2-migration of silicon was temperature-dependent, higher temperature favoring the same.

In partial support of the reaction proceeding through discrete vinyl cations as outlined in Scheme 18, the reaction of the unsubstituted allenylsilane **186b** was studied. The transition state corresponding to **188** will be expected to be higher in energy than the transition state corresponding to **187** due to the less substituted nature of the cationic center in the former. One will, therefore, expect the [3 + 2] adduct to be formed in preference to the [3 + 3] adduct, irrespective of the reaction temperature and the Lewis acid. This was indeed the case.

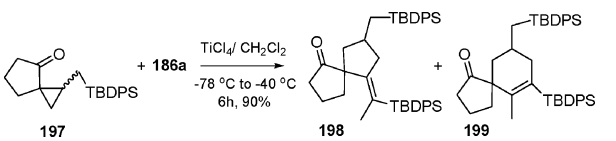
The [4,4]-, [4,5]- and [5,5]-spiro skeletons were also generated in good to excellent yields. Both *trans*-**175** and *cis*-**175** reacted separately with the allenylsilane **186a** to generate a 2 : 1 mixture of **194** and **195**, each as a single diastereomer (eqn (28)), and with the allenylsilane **186b** to generate **196** exclusively, again as a single diastereomer (eqn (29)). Likewise, *trans*-**197** and *cis*-**197** reacted with the allenylsilane **186a** and generated a 1 : 1 mixture of **198** and **199**, each as a single diastereomer (eqn (30)).



(28)



(29)

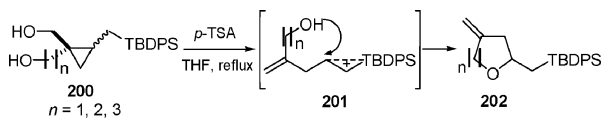


(30)

Thus, vicinal *tert*-butyldiphenylsilylmethyl substituted cyclopropyl ketones react with allenyl silanes to form five- and six-membered carbocycles with high regio- and stereocontrol. This protocol has potential for application in the synthesis of carbocyclic natural products and carbocyclic nucleosides.[66]

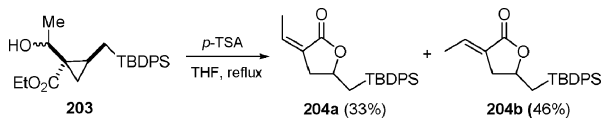
Silicon-assisted ring opening of cyclopropyl carbinols

Among the known ring cleavage reactions of cyclopropanes, the acid-promoted cleavage of cyclopropyl carbinols has been studied extensively from theoretical and synthetic viewpoints.[67] The initially formed cyclopropyl carbinyl cation can undergo either ring expansion to give a cyclobutyl cation[68] or ring cleavage to result in a homoallyl cation[69] to relieve the ring strain. Vicinal phenyl and alkoxy-containing cyclopropyl carbinols have been studied extensively as these groups facilitate the ring opening by stabilizing the resulting carbocation, which could be trapped by nucleophiles for further synthetic manipulations.[70] In an extension of the protocol for the synthesis of substituted dihydrofurans without the extrusion of the silicon function, we have studied the ring cleavage of cyclopropyl carbinols bearing a vicinal *tert*-butyldiphenylsilylmethyl substituent to trap, intramolecularly, the resultant carbocations with heteroatoms.[71] The cyclopropyl carbinols **200** (n = 1–3) underwent smooth ring cleavage on treatment with *p*-TSA in THF at reflux to furnish the γ-methylene oxacycles **202** (eqn (31)).[72]



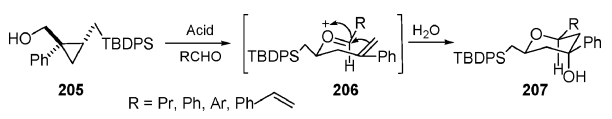
(31)

To exploit the above methodology further, the substrate **203**, which bears one hydroxy and one ester function, was reacted to generate the α-ethylidene-γ-lactones **204a** and **204b** (eqn (32)) in a combined 79% yield.[73]



(32)

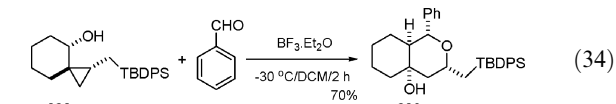
Prins cyclization is a versatile method for the construction of a tetrahydropyran ring.[74] However, the major drawback of this reaction is its competition with the oxonia-Cope rearrangement. We wished to trap the homoallyl cation formed on acid treatment of the cyclopropyl carbinol **205** with a carbonyl function.[75a] The subsequent intramolecular nucleophilic capture of the oxonium ion **206** by the *in situ* formed olefin generated a single multiply-substituted tetrahydropyran **207** stereoselectively (eqn (33)). The oxonia-Cope rearrangement was completely suppressed.



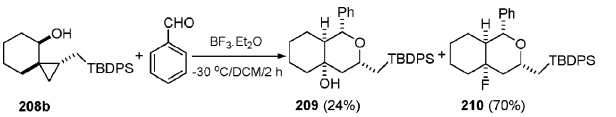
(33)

The reaction introduced three stereogenic centers in the product. The high stereoselectivity observed is due possibly to the bulky silylmethyl group that occupied the equatorial position in the six-membered cyclic transition state and the nucleophilic capture of the aryl-substituted cation that proceeded from the stereoelectronically favored axial direction.[75b] The use of trifluoroacetic acid gave a single product. $BF_3{\cdot}Et_2O$, however, yielded a mixture of two regioisomeric olefins by the exclusive deprotonation of the benzylic cation. The reactions proceeded smoothly with ketones as well to generate the desired products in good yields.[76]

To assess the contribution of the phenyl group in the final ring closure and also to further expand the scope of the methodology to diverse ring systems, we have studied the reactions of **208a** and **208b**. The species **208a** reacted with benzaldehyde and furnished **209** as a single isomer in 70% yield (eqn (34)). The reaction had proceeded with high stereoselectivity and four new stereogenic centers were generated. The isomer **208b** gave a 1 : 3 mixture of the above **209** in 24% yield and the fluoro species **210** in 70% yield under similar conditions (eqn (35)). The inversion of configuration of the alcohol stereocenter was apparently the cause of the formation of **210** as the major product. However, its incidence on product distribution between **209** and **210** and, particularly, the formation of **210** was not understood.



(34)



(35)

The tetrahydropyran ring is featured in a variety of biologically active natural products, marine toxins and pheromones[77] such as bryostatin **211**, (−)-centrolobine **212**, mucocin **213**, catechols 1 (**214a**) and 2 (**214b**), apicularen A (**215a**) and B (**215b**), and ratjadone A **216** (Fig. 8). A 2,4,6-trisubstituted tetrahydropyran ring was constructed by the Prins cyclization of a silicon-stabilized homoallyl cation formed from a cyclopropyl carbinol that was vicinally substituted by a silylmethyl function.[75a] We have replaced the silylmethyl function by a *p*-methoxyphenyl substituent as the donor group and achieved

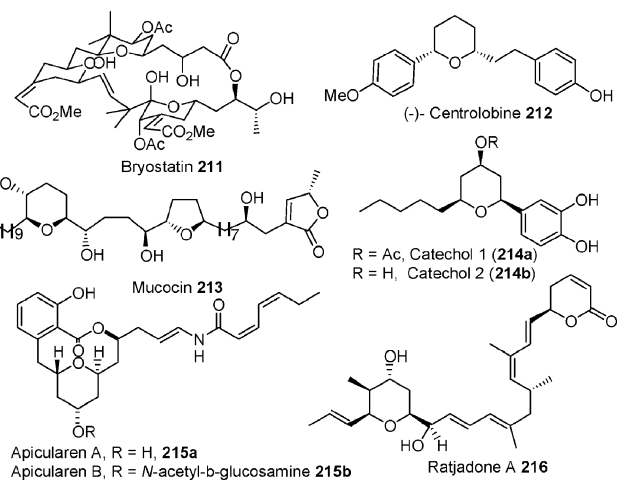
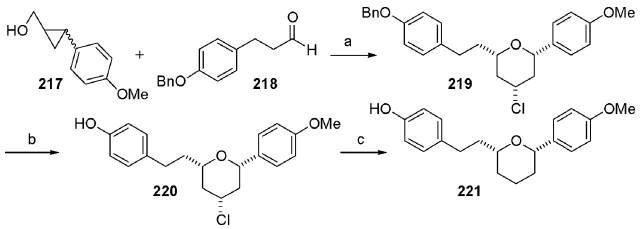


Fig. 8



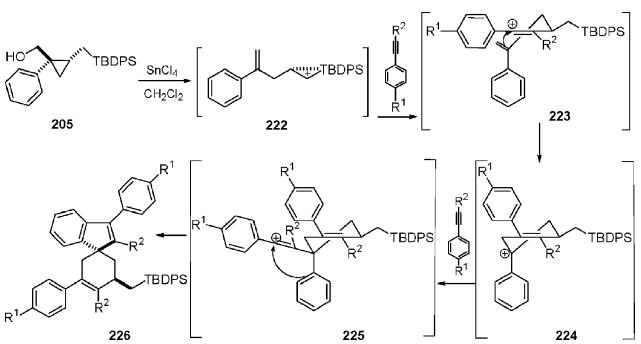
Scheme 20 Reagents: a. $SnCl_4$, CH_2Cl_2, −78 °C, 80%; b. H_2, cat. Pd/C, MeOH, 95%; c. nBu_3SnH, AIBN, toluene, reflux, 90%.

a concise synthesis of racemic centrolobine (**217** → **221**), as shown in Scheme 20.[78]

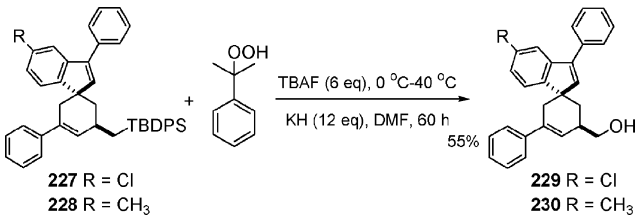
Tandem reactions play a vital role in organic synthesis because they lead to the formation of two or more carbon–carbon bonds without adding additional reagents and catalysts.[79] The tandem intermolecular cation–olefin cyclization[80a] has advantages over the intramolecular cation–olefin cyclization[80b–e] because one has the choice to manipulate both the reactants. We have studied a novel tandem intermolecular cation–arylacetylene cyclization for the synthesis of substituted indene derivatives from vicinal silylmethyl-substituted cyclopropylcarbinols. The silicon-stabilized cation **222**, generated from **205** on treatment with $SnCl_4$, reacted with different arylacetylenes to generate indene derivatives in reasonably good yields (Scheme 21).

The intramolecular nucleophilic attack by the *in situ* formed olefin on the aryl-stabilized vinyl cation resulted in another aryl-stabilized cation, **223** → **224**. This cation reacted further with one more equivalent of the arylacetylene to generate yet another aryl-stabilized vinyl cation **225** that finally underwent intramolecular Friedel–Crafts alkenylation to terminate the reaction in **226**.[81] The reaction generated four new σ_{C-C} bonds, two new stereogenic centers, including one quaternary, and led to the formation of two new rings. The high stereoselectivity of the reaction is indeed remarkable; the bulky silylmethyl group occupied the equatorial position in the cyclic six-membered transition state and the second arylacetylene entered exclusively from the equatorial site.

The oxidative cleavage of the σ_{C-Si} bond into alcohol was achieved conveniently by the employment of a slightly modified version of the literature protocol[51d] that was originally used for the cleavage of a carbon–$SiPhMe_2$ bond. The substrates **227** and **228** were conveniently transformed into **229** and **230**, respectively, as shown in Scheme 22.



Scheme 21



Scheme 22

Substituted indene derivatives are useful compounds that serve as building blocks for functional materials[82a–c] and pharmaceutical compounds such as oxytocin antagonists,[82d] antiproliferative agents,[82e] estrogen receptor modulators,[82f] and an h5-HT6 serotonin receptor.[82g] Consequently, many methods have been developed for the assembly of the indene skeleton.[83] Vicinal silylmethyl substituted cyclopropyl carbinols undergo tandem intermolecular cation–arylacetylene cyclization to generate indene derivatives. The halogen derivatives are likely to serve as strategic substrates for organometal-promoted reactions such as Suzuki–Miyura and Sonogashira couplings for further elaborations leading to fine tuning of the photoluminescence behavior that are eminent of indenes.[84]

Organic light-emitting diodes (OLEDs) are a subject of intense investigation due to their potential application in flat-panel displays and solid-state lighting.[85] Substituted indene derivatives are known for blue light emission.[82a] The photoluminescence properties of **227**–**230** were studied in hexane as solvent.[51a] While compounds **227** and **228** did not show any fluorescent properties, the related alcohols **229** and **230** emitted in the near blue light region[86] with 15% and 7% quantum yields, respectively (Table 1). It therefore appears that the fluorescence from the indene skeleton in **227** and **228** was quenched by the TBDPS group.

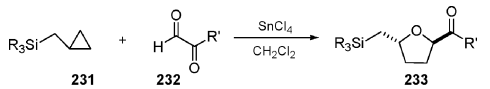
Table 1 Photoluminescence study of selected indene derivatives

Substrate	λ_{max}abs/nm	λ_{max}em/nm	Φ_{rel}[a] (%)
227	224	284	3
228	226, 248	285	1
229	229	284, 371	15
230	231, 281	285, 351	7

[a] Quantum yields were measured using L-tryptophan as the standard.

[3 + 2] dipolar cycloaddition of 2-silylmethylcyclopropyl ketones with aldehydes and ketones leading to tetrahydrofurans

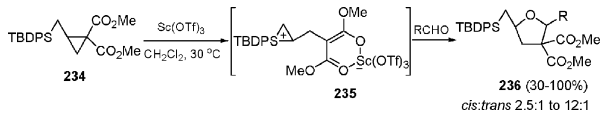
The dipolar addition of carbonyl species to cyclopropanes represents a powerful and convergent entry to compounds of this class. Akiyama *et al.* have reported $SnCl_4$-catalyzed [3 + 2] addition of cyclopropylmethylsilanes **231** with α-ketoaldehydes **232** to afford 2-silylmethyl-substituted tetrahydrofurans **233** in high yields (eqn (36)).[87] The relative stereochemistry of the product was dependent on the reaction temperature; the *trans*- and *cis*-tetrahydrofurans were formed selectively at 0 °C and −78 °C, respectively.



R = *i*-Pr, R' = Ph, 83%; R = *i*-Pr, R' = 2-Furyl, 90%
R = $(i\text{-Pr})_2$Ph, R' = Ph, 84%; R = $(t\text{-Bu})Ph_2$, R' = Ph, 69%

(36)

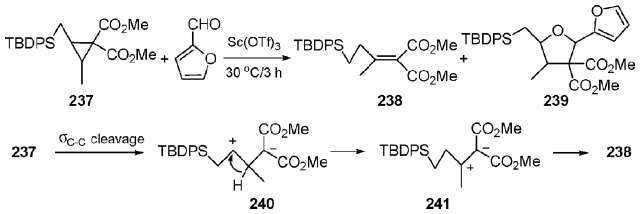
We envisioned the interception of the *in situ* generated 1,3-dipole with a carbonyl species to generate highly substituted tetrahydrofurans.[88] When **234** was reacted with different aldehydes at ambient temperature in the presence of a catalytic amount of $Sc(OTf)_3$, the tetrahydrofuran **236** was formed in 30–100% yield as a diastereomeric mixture (eqn (37)). Spiro skeletons were generated in good yield from the reaction with cyclic ketones. Acyclic ketones did not react under $Sc(OTf)_3$ catalysis. However, a catalytic amount of $SnCl_4$ proved efficient and the acyclic ketones too, including the alkyl aryl ketones, reacted well.



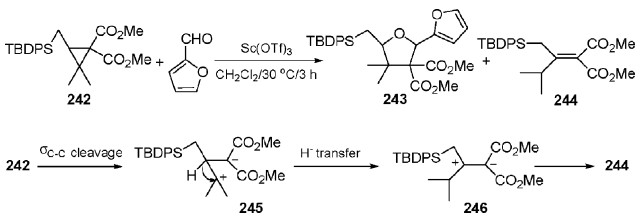
(37)

The tolerance of the reaction to the substituents on the cyclopropane ring was examined from the reactions of **237** and **242** with furfural to generate all-carbon-substituted tetrahydrofurans. The reaction of **237** with furfural generated methyl 5-*tert*-butyldiphenylsilyl-2-carbomethoxy-3-methyl-2-pentenoate, **238**, as the main product in 85% yield along with the planned tetrahydrofuran derivative **239** in 5% yield (Scheme 23). 1,2-Hydride transfer from the methyl-bearing carbon to the silylmethyl-substituted carbon in the 1,3-dipole **240** was considered to account the formation of the major product.

In order to prevent the above hydride shift, the substrate **242** (Scheme 24) was studied. The reaction with furfural furnished the desired product **243** in moderate yield (60%) with 14 : 1 *trans* diastereoselectivity along with the pentenoate



Scheme 23

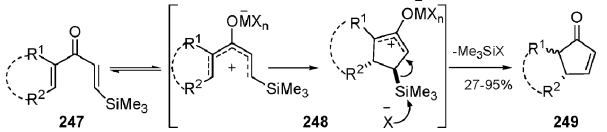


Scheme 24

244 in 28% yield. The pentenoate was considered tentatively to arise from the cleavage of the alternate cyclopropane bond followed by 1,2-hydride transfer as shown in **245**.

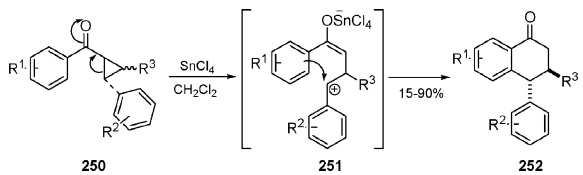
Homo-Nazarov cyclization of donor–acceptor substituted cyclopropanes

Acid-catalyzed transformation of divinyl ketones to 2-cyclopentenones is known as the Nazarov cyclization.[89] The major limitation of the Nazarov cyclization was the uncertainty related to the position of the double bond in the product which was addressed utilizing the β-effect of silicon. Denmark and co-workers demonstrated a β-silyl group that acted as a spectator until the crucial electrocyclization at which point it was stereoelectronically aligned to direct collapse of the cation (eqn (38)).[90]



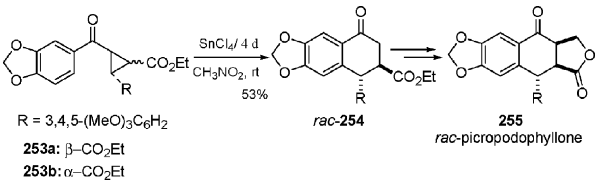
(38)

The acid-catalyzed ring closure of heteroaryl vinyl ketones to cyclopentanones fused with heteroaromatic rings is known as heteroaromatic Nazarov cyclization.[91,92] An electron-withdrawing group present at the position 2 or 3 of the heterocyclic ring does not allow its Friedel–Crafts alkylation by the initially formed cation due to deactivation of the ring.[93] To facilitate this transformation, one needs to mask the carbonyl group. Nazarov cyclization provides the requisite masking of the carbonyl group in the form of an enol/enolate. Analogous to the heteroaromatic Nazarov cyclization, an acid-induced transformation of a cyclopropyl heteroaryl ketone into cyclohexanone fused with a heteroaromatic ring may be called a heteroaromatic homo-Nazarov cyclization.[94] Murphy and Wattanasin have studied the Lewis acid-promoted cyclization of aryl cyclopropyl ketones **250** to the aryltetralones **252** (eqn (39)).[95a]



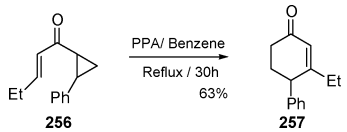
(39)

Murphy and Wattanasin have applied the above reaction to the synthesis of picropodophyllone **255** (eqn (40)).[95b] The *trans*-tetralone **254** was the sole product when the ketoester **253** was treated with $SnCl_4$ in nitromethane. The use of either epimer of **253** separately or as a mixture and the use of longer reaction times did not affect the yield. A close examination of the epimers **253a** and **253b** in $SnCl_4$–CH_3NO_2 solution at 0 °C showed that **253a** was rapidly isomerized to **253b**. However, **253b** did not isomerize to **253a**.

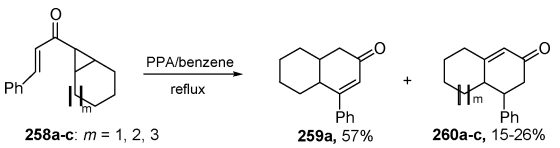


(40)

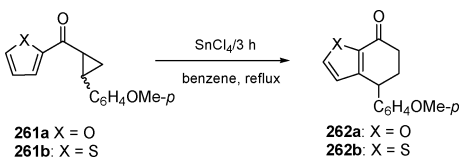
Tsuge *et al*. have studied the ring-enlargement of 1-alkenyl cyclopropyl ketones **256** (eqn (41)) and **258** (eqn (42)) in the presence of polyphosphoric acid (PPA).[94] However, the reaction was successful in limited cases only. The cyclization of **256** proceeded *via* a six-membered ring transition state to furnish **257**. The ring-fused cyclopropyl ketones **258** were similarly isomerized to the fused cyclohexanones **259** and **260** in low yields. The heteroaryl-substituted cyclopropyl ketones **261a** and **261b** were transformed into **262a** and **262b**, respectively, in excellent yields on treatment with $SnCl_4$ in benzene under reflux (eqn (43)).[96b]



(41)

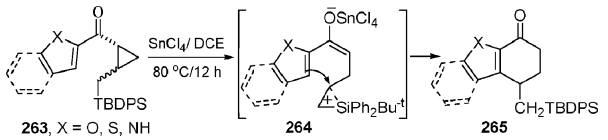


(42)



(43)

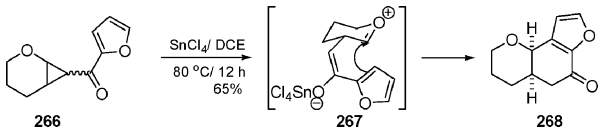
We reasoned that the silicon-stabilized cation generated from a cyclopropyl heteroaryl ketone could probably be effectively trapped, in a Friedel–Crafts manner, by the heteroaryl ring and, thus, lead to the formation of 2,3-heteroaryl-fused-4-silylmethyl-2-cyclohexanone in an overall process that is reminiscent of the homo-Nazarov cyclization. However, a reactivity issue was of much concern. The presence of a keto group at the 2-position in furan and thiophene hampers the Friedel–Crafts alkylation due to the deactivation of the ring.[93] Fortunately, the furan, thiophene and indole derivatives possessing a keto group at both the 2- and 3-positions reacted well on admixture with $SnCl_4$ in dichloroethane at 80 °C to furnish the homo-Nazarov products in high yields. A reaction prototype is shown in eqn (44).[96a] The *cis*-**263** and *trans*-**263** generated the same product **265** in identical yields when reacted separately (eqn (44)). There was no epimerization of one isomer into the other and both the isomers required the same time for complete reaction.



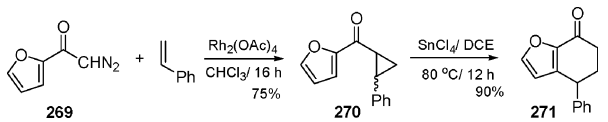
(44)

The success with 2-substituted furan and thiophene substrates is indeed noteworthy. The high temperature probably allows the 2-substituted furan and thiophene reactants to achieve the requisite transition states with near as much facility as the corresponding 3-substituted reactants. Both the 2- and 3-substituted indoles generated the desired products in excellent yields. The protection of nitrogen was not necessary.

The reactions of substrates bearing other electron-donating substituents, such as oxygen and phenyl, also proceeded well. The substrate **266** was smoothly transformed into the tricyclic product **268** (eqn (45)). Under the Lewis acid conditions, **266** is expected to generate the oxonium-enolate **267** which ring closes, under stereoelectronic control, from the axial site to result in the observed *cis* stereochemistry at the ring junction. Likewise, a 1 : 2 isomeric mixture of the cyclopropyl ketone **270** was transformed into 2,3-furano-4-phenylcyclohexanone **271** in high yield (eqn (46)).

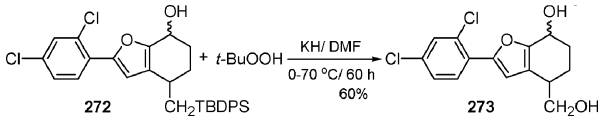


(45)



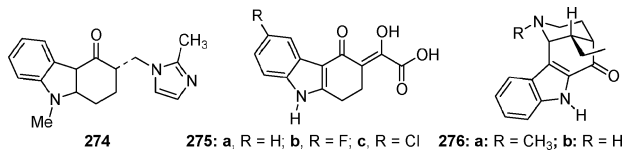
(46)

Since the silicon acts as a masked hydroxyl group, the present protocol extends the synthetic scope of the homo-Nazarov cyclization considerably. As a representative example, a 1 : 1.5 diastereomeric mixture of the alcohol **272**, obtained from the reduction of the corresponding ketone with $LiAlH_4$, was transformed into a 1 : 1.5 diastereomeric mixture of the corresponding diols **273** in 60% yield (eqn (47)). Oxidative cleavage of the σ_{C-Si} bond in the parent ketone itself was unclean under these reaction conditions.



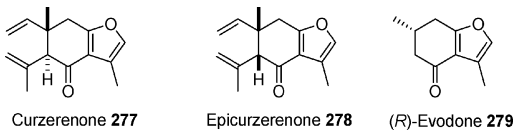
(47)

Acid-catalyzed transformation of cyclopropyl heteroaryl ketones into 2,3-heteroaryl-fused cyclohexanones can be christened homo-Nazarov cyclization. These skeletons are present in many natural products. Ondansetron **274** (Fig. 9), a 1-imidazolylmethyl substituted tetrahydrocarbazolone, is a potent 5-HT_3 receptor antagonist which is used to prevent severe vomiting caused by cancer chemotherapy and radiotherapy.[97]



274 **275: a**, R = H; **b**, R = F; **c**, R = Cl **276: a:** R = CH_3; **b:** R = H

Fig. 9



Curzerenone **277** Epicurzerenone **278** (*R*)-Evodone **279**

Fig. 10

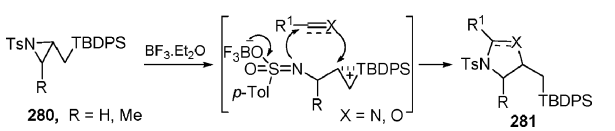
Carbazolone-containing α,γ-diketo acid analogs **275a–c** inhibit recombinant HIV integrase at 10 μM range.[98] Dasycarpidone **276a** and nordasycarpidone **276b** belong to the uleine family of alkaloids.[99]

Curzerenone **277** and epicurzerenone **278** are constituents of the drug zedoary. Xi *et al*. found that zedoary could protect hepatic cells against necrosis and degeneration as well as proliferation of fibrous tissues.[100] It is noteworthy that both exist in racemic form. (*R*)-Evodone **279**, a furanomonoterpene, is reported to exhibit strong germination inhibitory activity and stimulatory effects towards *Schizachyrium scoparium* seeds.[101] All these molecules are furan-fused substituted cyclohexanone species as shown in Fig. 10 and their syntheses could be designed using the homo-Nazarov strategy.

Silylmethyl-substituted aziridine and azetidine

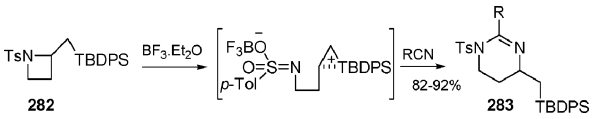
Aziridine is a versatile building block for the synthesis of many nitrogen-containing biologically active molecules.[102] It reacts with various nucleophiles, and its ability to undergo regioselective ring opening contributes immensely to its high synthetic value.[103] In particular, the cycloaddition of aziridine to dipolarophiles is a useful method for the synthesis of nitrogen-containing five- and six-membered ring molecules.[6b,18c,104]

In order to explore further the synthetic application of the *tert*-butyldiphenylsilylmethyl substituent, we considered generation of 1,3- and 1,4-dipoles from aziridine and azetidine, respectively, and their applications for formal [3 + 2] and [4 + 2] cycloadditions to nitrile and carbonyl substrates to generate five- and six-membered ring heterocycles (eqn (48) and (49)).[51b] The cycloaddition chemistry of aziridine was limited to the stabilization of the cation by an aryl substituent which has limited further usage. Since *tert*-butyldiphenylsilylmethyl is a latent CH_2OH function, the present methodology widened the synthetic scope of aziridine chemistry.



280, R = H, Me **281**

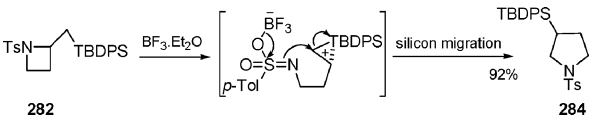
(48)



282 **283**

(49)

The cycloaddition of azetidine to dipolarophiles constitutes a powerful protocol for the formation of nitrogen-containing six-membered ring heterocycles.[105] The azetidine **282** reacted smoothly with several nitriles under $BF_3{\cdot}Et_2O$ conditions at 25 °C to generate the tetrahydropyrimidine derivatives **283**. The azetidine **282** was also rearranged to the pyrrolidine derivative **284** on admixture with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 (eqn (50)). This involved 1,2-silicon migration. 2-Imidazolines are useful intermediates for the syntheses of molecules with pharmacological activities, such as anticancer, anti-inflammatory and antidiabetic.[106] Tetrahydropyrimidines are reported to exhibit a wide range of pharmacological activities.[107] The pyrrolidine derivatives are ubiquitous among natural products as they are materials of much pharmacological interest.[5]



282 **284**

(50)

The oxidative cleavage of the σ_{C-Si} bond into a σ_{C-OH} bond was achieved by employment of the basic conditions (KH–*t*-BuOOH–DMF, 25 °C) reported previously by Smitrovich and Woerpel for a similar transformation of the smaller $PhMe_2Si$ function.[51h] For instance, 2-ethyl-5-hydroxymethyl-*N*-tosyl-1,3-oxazolidine was obtained in 60% yield from the corresponding 5-*tert*-butyldiphenylsilylmethyl derivative. It is to be noted that the sulfonamide function was inert to the reaction conditions.

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