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Recent advances in the syntheses, transformations and applications of 1,1-dihalocyclopropanes

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Gem-dihalocyclopropanes have wide-spread applications in organic synthesis due to their versatile chemistry. They can serve as substrates for a large range of useful materials such as natural products, alkaloids, cyclopropanes, heterocycles, aromatic ring systems etc. Normally the dihalocyclopropanes are prepared by the addition of dihalocarbene to alkene; but due to the great synthetic efficacy of *gem*-dihalocyclopropanes a number of methods have been developed for their synthesis. Generally *gem*-dihalocyclopropanes exist as strained cyclic system with astonishing kinetic stability. They are capable of undergoing transformations leading to a variety of products which have potential applications in various synthetic organic chemistry fields.

1. Introduction

Gem-dihalocyclopropanes play a significant role in organic synthesis.[1] Inter alia, they serve as precursors for the synthesis of cyclopropanes, monohalocyclopropanes, heterocyclic ring systems, allenes, bi-, tri- and tetra-cyclic ring systems. The ready availability and high reactivity of dihalocyclopropanes make them important substrates in organic synthesis. A peculiar feature of *gem*-dihalocyclopropane is its remarkable kinetic stability in the presence of ring strain.

Gustavson was the first one to mention dihalocyclopropanes.[2] As already stated, due to excellent reactivity and applications, *gem*-dihalocyclopropanes occupy a very special position in organic synthesis. The numerous publications in the area of synthesis and transformation of *gem*-dihalocyclopropanes during the last decade attest to their importance in organic chemistry. Literature reports show that almost all combinations of dihalocyclopropanes have been synthesized. Doering and Hoffmann described the first method for the preparation of dihalocyclopropanes in 1954.[3] Owing to the synthetic utility of dihalocyclopropanes a number of methods have been devised for their preparation; however, the phase transfer catalysed (PTC) protocol developed by Makosza in 1969 is the most popular one.[4]

The *gem*-dihalocyclopropanes are usually prepared by the action of dihalocarbene with an alkene. They are widely used in the synthesis of natural products, biologically active materials and pharmacologically useful substrates.

This review will focus on the different methods for the synthesis of *gem*-dihalocyclopropanes, the kinetics, structural and computational studies on the formation of dihalocyclopropanes as well as the transformation of the latter into different synthetically useful substrates. A number of reviews on the chemistry of dihalocyclopropanes and their applications are available.[5,6] The most recent reviews written in this area cover literature up to 2003.[7,8,9] The present review covers literature from 2003-2015.

2.Phase transfer catalysis in the synthesis of *gem*-dihalocyclopropanes

Although a number of methods are available for dihalocyclopropanation, the cycloaddition reaction between different alkenes and dihalocarbenes under phase transfer catalysis (PTC) is the most convenient method. The advantages of this protocol include simplicity, ambient experimental conditions, enhanced rate of reaction, higher yields of products and low cost of the reagents.

The *gem*-dihalocyclopropanes are easily accessible entities in organic synthesis and thus have substantial potential as effective precursors in synthetic chemistry. *Gem*-dichlorocyclopropyl derivatives of limonene, terpinolene and γ-terpinene were synthesized using NaOH and benzyltriethyl ammonium chloride (TEBAC) in $CHCl_3$ at room temperature affording monocyclopropanated products in good yields (**Scheme 1**).[10]

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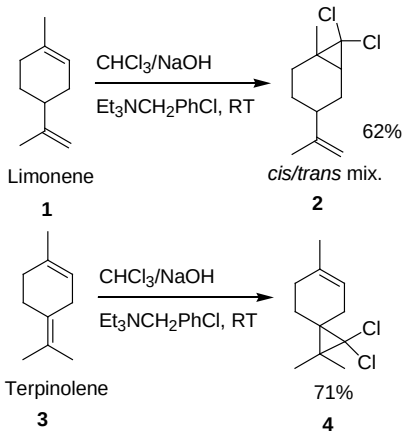
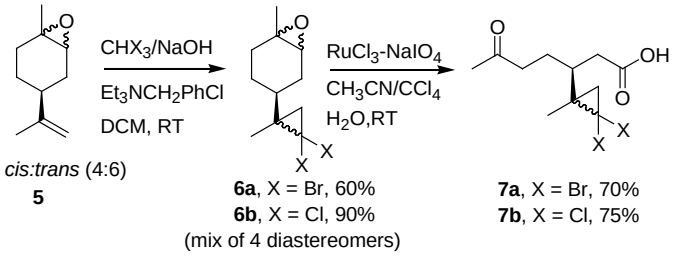
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x



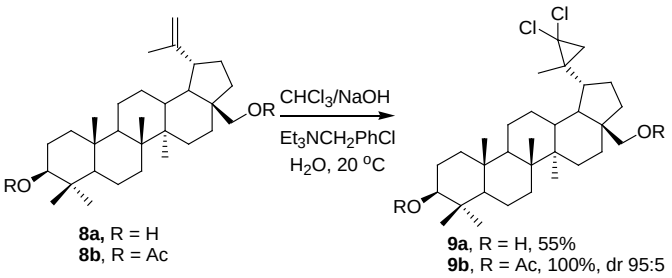
Scheme 1. Dichlorocyclopropanation of terpenes

An improved route for the synthesis of chiral dihalocyclopropanes from (*S*)-limonene oxide was also developed (**Scheme 2**).[11] First the double bond of limonene oxide **5** was dihalocyclopropanated under phase transfer conditions. The oxirane ring of the resulting product **6** was cleaved oxidatively using $RuCl_3$-$NaIO_4$ catalytic system; crystallization of the product led to the respective diastereomers of the dihalocyclopropane ring system **7**.



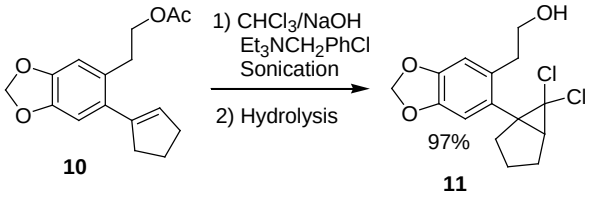
Scheme 2. Synthesis of chiral 3-(2,2-dichloro-1-methylcyclopropyl)-6-oxo-heptanoic acid

The preparation of *gem*-dihalocyclopropane derivatives of some triterpenoids of lupan series under PTC was reported.[12] The lupan triterpenoid betulin **8a** on treatment with dichlorocarbene generated from $CHCl_3$ and NaOH under PTC conditions afforded the dichlorocyclopropane derivative **9a** in 55% yield along with some side products (**Scheme 3**). However, the diacetate of betulin **8b** under similar reaction conditions afforded quantitative yield of the product **9b** with high diastereoselectivity (95:5). The corresponding dibromocyclopropane derivative could not be isolated in pure form.



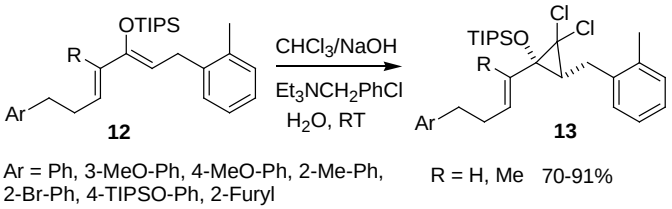
Scheme 3. Dichlorocyclopropanation of betulin and its diacetate by PTC

In the total synthesis of erythrina alkaloid frame-work, Banwell *et al*. utilized the dichlorocyclopropanation of 2-(5-cyclopentenylbenzo[*d*][1,3]dioxol-6-yl)ethyl acetate **10** under phase transfer catalysis as the key step in excellent yield (**Scheme** 4).[13]



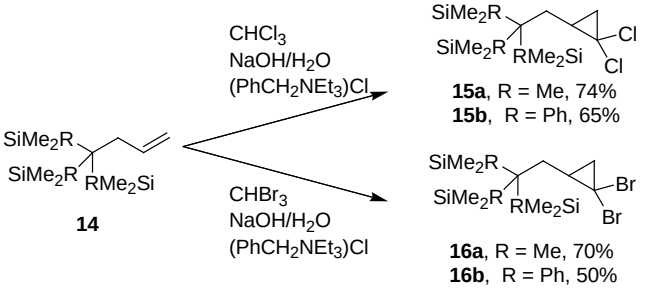
Scheme 4. Dichlorocyclopropanation of 2-(5-cyclopentenylbenzo[*d*][1,3]dioxol-6-yl)ethyl acetate

In order to obtain the *gem*-dichlorocyclopropane of 2-isopropylsiloxydienes **12** with absolute regioselectivity, West and Grant used phase transfer catalysis on various aryl substituted TIPS enol ethers which afforded good yields of the product (**Scheme 5**).[14]



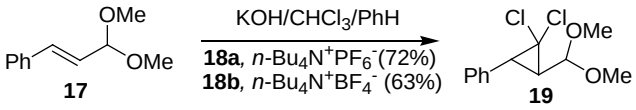
Scheme 5. Phase transfer catalyzed *gem*-dichlorocyclopropanation of 2-isopropylsiloxydienes

Organosilanes are very frequently used as protecting groups in organic synthesis. Majority of such protecting agents contain bulky alkyl substituents that impart unusual stability. But such steric hindrance has no effect in dihalocyclopropanation of silyl substituted alkenes (**Scheme 6**).[15]



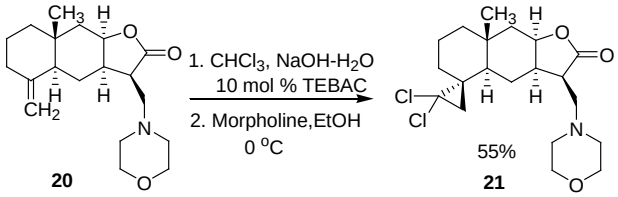
Scheme 6. Synthesis of trialkylsilane substituted dihalocyclopropanes

The commonly used catalyst for phase transfer catalysis is the tetraalkylammonium salt bearing chloride anion, which is usually lost irreversibly during the isolation of the product. But a successful method for the preparation of *gem*-dichlorocyclopropane with a recoverable phase transfer catalyst was reported in 2008 (**Scheme 7**).[16] The tetraalkylammonium salts bearing PF_6^- **18a** or BF_4^- **18b** anions were found to be recoverable. This reusable nature of catalyst is attributed to the incorporation of fluoride anion. The salt containing fluorinated anions are non-flammable, non-volatile and stable, and act as a very good solvent for inorganic, organic and organometallic species. The *n*-Bu_4NPF_6 phase transfer catalyst was utilized in the dichlorocyclopropanation of a variety of olefins, which afforded very good yields of the product.



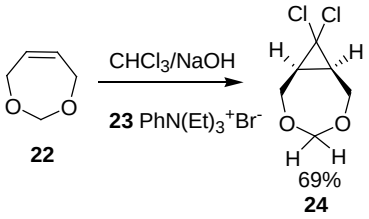
Scheme 7. Dichlorocyclopropanation using recoverable PTC

The dichlorocyclopropanation of morpholine substituted lactone **20** was achieved in moderate yields by treating it with dichlorocarbene generated from chloroform in the presence of NaOH and phase transfer catalyst (**Scheme 8**).[17]



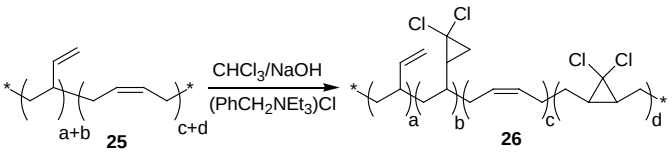
Scheme 8. Dihalocyclopropanation of morpholine substituted lactone by PTC

An improved method for the preparation of *cis-gem*-dichlorocyclopropane derivatives in which phenyltriethylammonium bromide **23** was used as a successful phase transfer catalyst was disclosed (**Scheme 9**).[18]



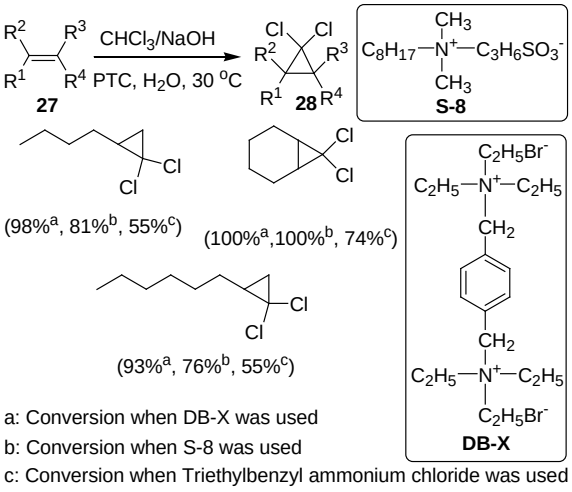
Scheme 9. Synthesis of 8,8-dichloro-3,5-dioxa-bicyclo[5.1.0]octane

Syndiotactic polybuta-1,2-diene **25** upon reaction with chloroform in the presence of NaOH and a phase transfer catalyst gave *gem*-dichlorocyclopropane functionalized polymer (**Scheme 10**).[19] The incorporation of dihalocyclopropane rings to the polymer increased the mechanical properties of the latter.[20]



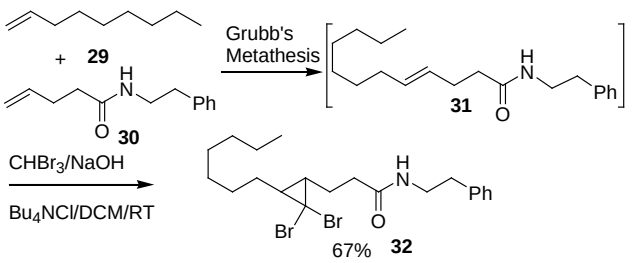
Scheme 10. Synthesis of dichlorocyclopropane substituted syndiotactic polybuta-1,2-diene

For the preparation of *gem*-dichlorocyclopropanes, the phase transfer catalysts 4-(dimethyloctylammonium)propansultan (**S-8**) and 1,4-bis(triethylmethylammonium)benzene dibromide (**DB-X**) were synthesized and employed (**Scheme 11**).[21] These PTCs led to quantitative conversion and found to be far superior to the standard catalyst, the benzyl triethyl ammonium bromide. A slightly higher conversion was shown by DB-X in comparison with **S-8**. Dienes gave a mixture of mono and bis cyclopropanation products.



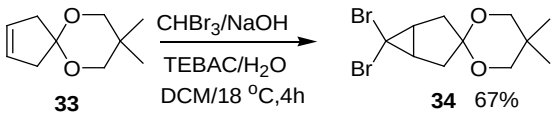
Scheme 11. Dichlorocyclopropanation of olefins using S-8 or DB-X

There are a vast number of natural products that contain cyclopropane framework. Sometimes the dihalocyclopropane derivatives are essential as reactive intermediate for the synthesis of naturally occurring compounds. The phase transfer catalysis is the most easily adaptable method in such cases. In the preparation of (+/-) grenadamide, use of dibromocarbene for cyclopropanation under phase transfer catalysis was employed (**Scheme 12**).[22]



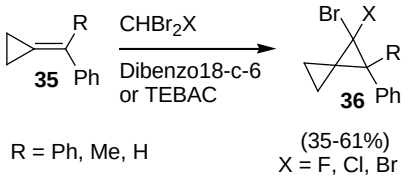
Scheme 12. Synthesis of 3-(2,2-dibromo-3-heptyl-cyclopropyl)-N-phenethylpropanamide

Banwell and coworkers utilized dibromocyclopropanation of ketal protected cyclopentenone **33** in an attempted synthesis of the alkaloid Tazettine (**Scheme 13**).[23]



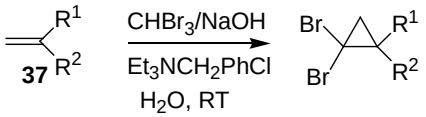
Scheme 13. Synthesis of *gem*-dibromocyclopropane derivative of protected cyclopentenone

The synthesis of dihalospiropentanes **36** by the cyclopropanation of alkylidenecyclopropanes **35** under phase transfer condition is reported (**Scheme 14**).[24] Here, dibenzo-18-crown-6 was used as the phase transfer catalyst for the generation of bromofluorospiropentane, TEBAC for bromochlorocyclopropane and KO^{t}Bu for dibromocyclopropane derivatives, respectively.



Scheme 14. Synthesis of *gem*-dihalospiropentanes using crown ether/TEBAC as PTC

Similarly the preparation of 2,2-dibromocyclopropane-1-carboxylic acid esters was achieved using phase transfer catalysis.[25] The dibromocarbene prepared *in situ* from bromoform under phase transfer condition was reacted with di-*tert*-butyl methylene malonate to afford the 2,2-dibromocyclopropane-1,1-dicarboxylic acid di-*tert*-butyl ester **38a** (**Scheme 15**). Similar substrates gave excellent yields of the product.



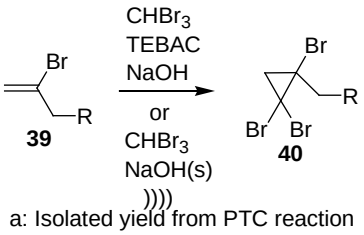
38a, R^1 = COO^{t}Bu, R^2 = COO^{t}Bu, 27%

38b, R^1 = COOEt, R^2 = OC(Me$_2$)OMe, 95%

38c, R^1 = COOEt, R^2 = CH$_2$OTHP, 79%

Scheme 15. Phase transfer catalyzed synthesis of 2,2-dibromocyclopropane-1-carboxylic acid esters

The synthesis of 1,1,2-tribromocyclopropanes **40** was achieved under both PTC and ultrasonic conditions (**Scheme 16**).[26] Here the yield of the isolated products obtained *via* PTC and ultrasonic irradiation are comparable.

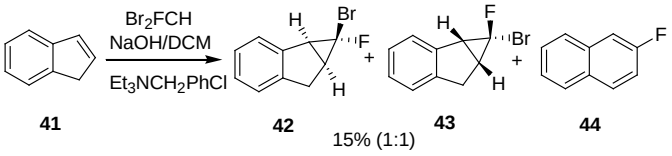


a: Isolated yield from PTC reaction

b: Isolated yield from ultrasonication

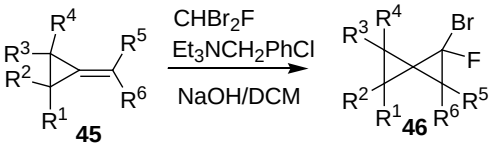
Scheme 16. Synthesis of 1,1,2-tribromocyclopropane under PTC or Ultrasonication

The mixed dihalocyclpropanes of adenine, guanine and purine derivatives were also prepared *via* phase transfer catalysis.[27] The synthesis of *gem*-bromofluorocyclopropylindene was reported from bromofluorocarbene generated by treating dibromofluoromethane with NaOH and benzyltriethylammoniumchloride affording a racemic mixture in low yields (**Scheme 17**).[28] The low yield of the product is attributed to the formation of two unstable diastereomers of bromofluorocyclopropyl analogue, which are converted to 2-fluoronaphthalene **44** by ring expansion and bromide ion expulsion.



Scheme 17. Generation of bromofluorocyclopropyl derivative from indene

In a similar fashion *gem*-bromofluorospiropentane **46** was prepared from the respective methylenecyclopropane by the addition of bromofluorocarbene using phase transfer catalysis (**Scheme 18**).[29]



46a, R^1,R^2,R^3,R^4,R^5,R^6 = H, 64%

46b, R^1 =Ph, R^2,R^3,R^4,R^5,R^6 = H, 52%

46c, R^1 =R^2 = -(CH$_2$)$_2$-,R^3,R^4,R^5,R^6 = H, 59%

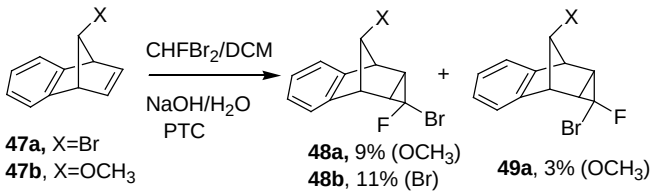
46d, R^1 =R^2 = -(CH$_2$)$_3$-,R^3,R^4,R^5,R^6 = H, 65%

46e, R^1 =R^2 = -(CH$_2$)$_5$-,R^3,R^4,R^5,R^6 = H, 92%

46f, R^1 =R^3 = -(CH$_2$)$_6$-,R^2,R^4,R^5,R^6 = H, 39%

Scheme 18. Synthesis of bromofluorospiropentanes

The bromofluorocyclopropane derivative of bromo- **47a** or methoxybenzonorbornadiene **47b** was obtained in low yields by the addition of bromofluorocarbene generated from dibromofluoromethane in the presence of NaOH and suitable phase transfer catalyst (**Scheme 19**).[30]

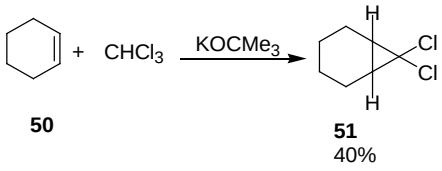


Scheme 19. Synthesis of both *endo* and *exo* bromofluorocyclopropyl derivative of benzonorbornadiene

3. Non PTC methods of synthesis of *gem*-dihalocyclopropanes

3.1 Synthesis of *gem*-dichlorocyclopropanes

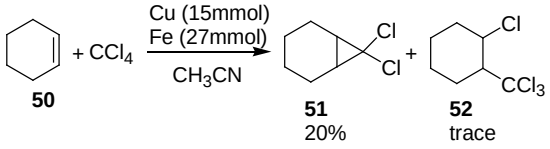
The first reported dichlorocyclopropane, a bicyclic compound **51**, was synthesized by the addition of dichlorocarbene to cyclohexene.[3] The reactive dichlorocarbene species was generated *in situ* from chloroform by treatment with potassium *t*-butoxide (**Scheme 20**).



Scheme 20. Preparation of *gem*-dichlorocyclopropane from cyclohexene and chloroform

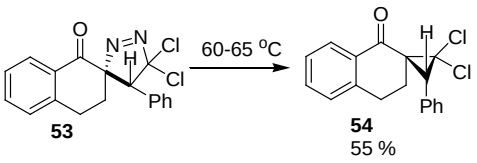
Generally *gem*-dichlorocyclopropanes were obtained by the addition between dichlorocarbene and a suitable alkene. However, during the past twenty years a number of other methods also emerged for their synthesis; the important ones are briefly described below.

A very efficient method for the generation of *gem*-dichlorocyclopropanes was introduced by the activation of CCl_4 using bimetallic Fe/Cu or Ni/Cu couple in acetonitrile (**Scheme 21**).[31] The mechanistic analysis showed that the reactive species involved in the *gem*-dichloromethylation of nucleophilic alkene is a carbenoid.



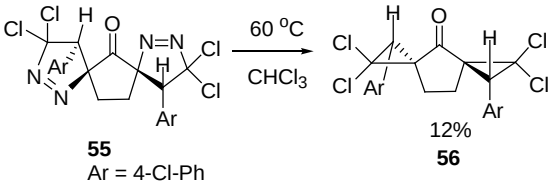
Scheme 21. Dichlorocyclopropanation of cyclohexene via bimetallic Fe/Cu couple

The synthesis of 2'-phenyl-1',1'-dichlorospiro(1,2,3,4-tetrahydronaphthalene-2,3'-cyclopropan)-1-one **54** was reported from 4'-phenyl-3',3'-dichlorospiro[1,2,3,4-tetrahydronaphthalene-2,5'-(1'-pyrazoline)]-1-one **53** by heating at 60-65 ^{o}C (**Scheme 22**).[32] On heating, N_2 is eliminated from the spirocyclic 3-chloro-1-pyrazoline leading to a spirocyclic *gem*-dichlorocyclopropane.



Scheme 22. Synthesis of 2'-phenyl-1',1'-dichlorospiro(1,2,3,4-tetrahydronaphthalene-2,3'-cyclopropan)-1-one

The same protocol was also used for the preparation of 1,1,6,6-tetrachloro-2,7-bis(4-chlorophenyl)dispiro[2.1.2.2]nonan-4-one **56** in low yields (**Scheme 23**).[33]

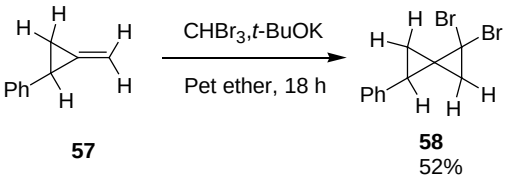


Scheme 23. Synthesis of 1,1,6,6-tetrachloro-2,7-bis(4-chlorophenyl)dispiro[2.1.2.2]nonan-4-one.

3.2 Synthesis of *gem*-dibromocyclopropanes

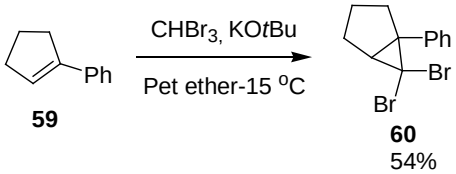
The reactivity of *gem*-dibromocyclopropanes is higher than that of *gem*-dichlorocyclopropanes. Therefore the synthesis of *gem*-dibromocyclopropanes has great significance in organic synthesis.

The original Doering-Hoffmann method utilizing bromoform and potassium tertiary butoxide was used for the generation of cyclopropane-substituted *gem*-dibromocyclopropanes **58**.[34] The carbene that evolved undergoes [1+2] cycloaddition to methylenecyclopropane **57** leading to the spiroyclic system having *gem*-dibromocyclopropyl attachment (**Scheme 24**).



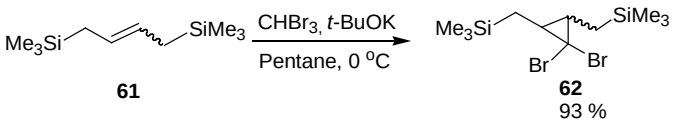
Scheme 24. Synthesis of spirocyclic dibromocyclopropane

The group of Christl also used the Doering-Hoffmann method for the preparation of dibromophenylbicyclohexane **60** (**Scheme 25**).[35]



Scheme 25. Synthesis of dibromophenylbicyclohexane from 1-phenylcyclopentene

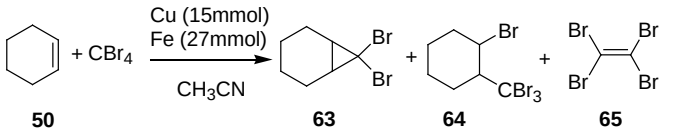
The same technique was also used for the generation of allyldisilane substituted *gem*-dibromocyclopropanes **62** (**Scheme 26**).[36]



61 **62** 93 %

Scheme 26. Dibromocarbene addition to 2,3-dimethyl-1,4-bis(trimethylsilyl)-but-2-ene

The protocol using bimetallic Fe/Cu or Ni/Cu catalyst in acetonitrile (*vide infra*) was also used for the generation of dibromocarbene from CBr_4 (**Scheme 27**).[28] This provides a non toxic and inexpensive method for the preparation of *gem*-dibromocyclopropanes **63**, *albeit* in low yields.

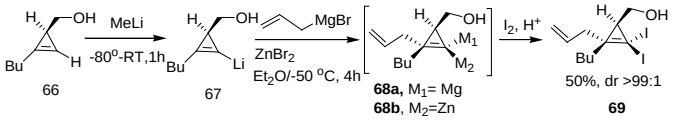


50 **63** 25% **64** traces **65** 40 %

Scheme 27. Dibromocyclopropanation of cyclohexene by CBr_4 activation via bimetallic Fe/Cu couple

3.3 Synthesis of *gem*-diiodocyclopropanes

There are only a few reports on the synthesis of *gem*-diiodocyclopropanes, presumably due to their unstable nature. The reaction of bismetallated cyclopropane species with iodine afforded *gem*-diiodocyclopropanes.[37] The allyl metallation of cyclopropenyllithium **67** gave bismetallated cyclopropane moiety **68** which on further reaction with I_2 under acidic conditions afforded the corresponding diiodocyclopropane **69** (**Scheme 28**). The bismetallated cyclopropyl species is a stable intermediate, but the exact nature of the intermediate is not clear yet (Mg, Zn or Zn, Zn).

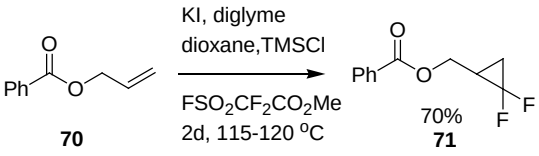


66 67 **68a,** M_1= Mg **68b**, M_2=Zn 50%, dr >99:1 **69**

Scheme 28. Synthesis of *gem*-diiodocyclopropane from bismetallated cyclopropane

3.4 Synthesis of *gem*-difluorocyclopropanes

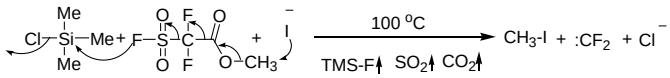
Introduction of fluorine atom to cyclopropane ring profoundly enhances its chemical and structural profiles. The efficacy of drugs containing fluorine is found to be high due to enhanced activity, bioavailability and retarded drug metabolism. It is noteworthy that a number of reviews dealing with the synthesis and applications of difluorocyclopropanes are available.[6,9,38] The first report on the synthesis of *gem*-difluorocyclopropane was published in 1970 by Sargeant.[39] Recently a very efficient method for the generation of difluorocarbene was introduced using methyl-2,2-difluoro-2-(fluorosulfonyl)acetate (**MDFA**) as the difluorocarbene source.[40] Trimethylsilylchloride (TMSCl) was used as a trapping agent for fluoride anion generated from demethylated **MDFA** (**Scheme 29**).



70 70% **71**

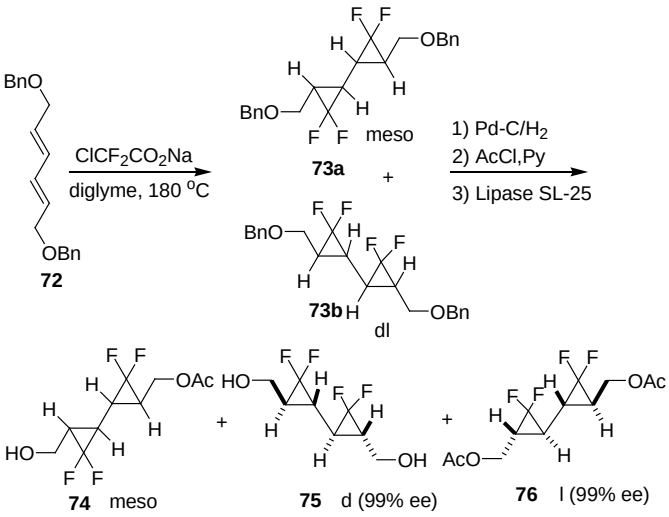
Scheme 29. Synthesis of 2,2-difluoro cyclopropylmethyl benzoate

The optimized reaction condition for the carbene generation involved treating MDFA with KI and TMSCl at 100 °C (**Scheme 30**).



Scheme 30. Formation of difluorocarbene from MDFA

An efficient protocol for the synthesis of liquid crystalline molecules having chiral bis *gem*-difluorocyclopropane skeleton using sodium chlorodifluoroacetate as the carbene source for difluorocyclopropanation has been reported (**Scheme 31**).[41] Thus (*E,E*) 1,6-bis benzyloxyhexa-2,4-diene **72** on treatment with difluorocarbene generated *in situ* by the pyrolysis of sodium chlorodifluoroacetate afforded the corresponding bis *gem*-difluorocyclopropane as a mixture of *meso* **73a** and *dl* pair **73b** in equal amounts. The diacetate of the mixture on lipase catalyzed resolution afforded the isomers in excellent enantiomeric purity.

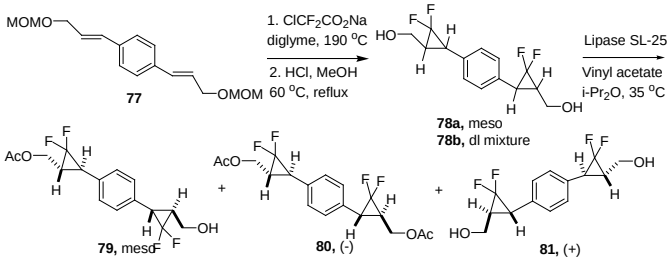


72 **73a** + **73b** **74** meso **75** d (99% ee) **76** l (99% ee)

Scheme 31. Synthesis of chiral difluorocylopropane derivative from benzylated *trans*-2,4-hexanediol

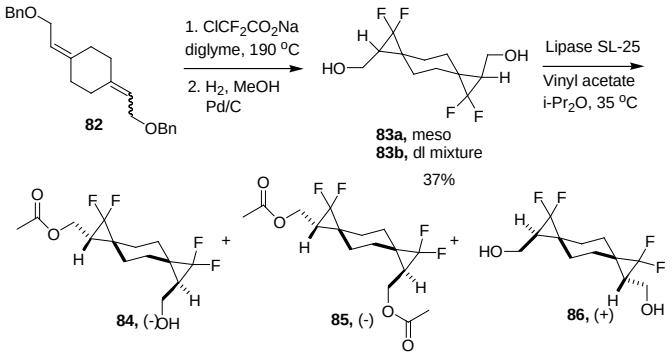
The protocol was extended to other systems and used to resolve the chiral *gem*-difluorocyclopropane isomers by chiral enzymatic strategy.[42] The pyrolysis of sodium chlorodifluoroacetate generated diflurocarbene which was added to bis-(methoxymethyl-propenyl)-benzene **77**. The

product was obtained as a mixture of *meso* **78a** and *dl*-form **78b**. The optical resolution of the product was achieved with lipase SL-25 (**Scheme 32**).



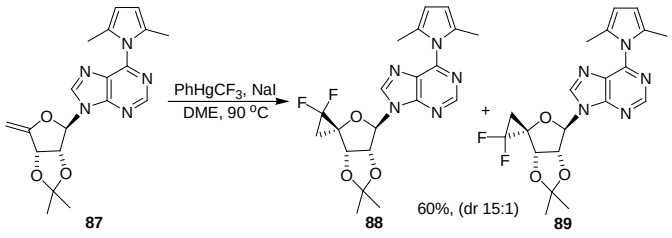
Scheme 32. Synthesis of chiral *gem*-difluorocyclopropane analogue of bis-(methoxymethyl-propenyl)-benzene

The same strategy for generating difluorocarbene has also been used for the difluorocyclopropanation of dibenzyl ether system to afford tetrafluoro derivative of 2,8-bis(hydroxymethyl)decane (**Scheme 33**).[43]



Scheme 33. Synthesis and optical resolution of spiro type bis *gem*-difluorocyclopropane using lipase SL-25

A mixture of $PhHgCF_3$ and NaI was used as a source for difluorocarbene[44] and utilized in the synthesis of difluorocyclopropane analogue of uridine, cytidine[45] and adenosine derivatives (**Scheme 34**).[46] Later another method was developed for the preparation of *gem*-difluorocyclopropane derivative of guanine.[47] Here $ClCF_2CO_2Na$ was used as the difluorocarbene source in the presence of diglyme at 190 °C. The *gem*-difluorocyclopropane substituted guanine derivative showed anti-HIV and anti-herpes activity.

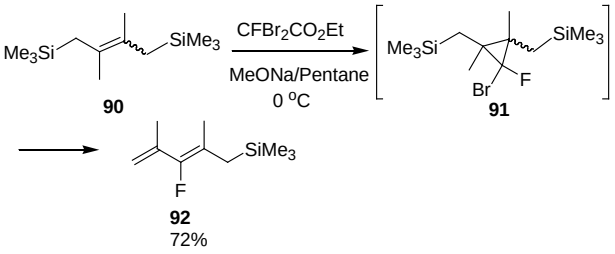


Scheme 34. Synthesis of difluoro cyclopropane analogue of adenine derivative

3.5 Synthesis of mixed *gem*-dihalocyclopropanes

The first report on mixed *gem*-dihalocyclopropane was published in 1957 by Parham.[48] The synthesis involved the reaction between indene and dichlorobromomethane in the presence of potassium-*t*-butoxide.

An excellent method for the *in situ* generation of disilane-substituted bromofluorocyclopropanes was also reported.[36] Here substituted allyldisilanes **90** on addition with bromofluorocarbene generated from ethylbromofluoroacetate and sodium methylate afforded silylated fluoropentadiene **92** via spontaneous ring opening of an unstable *gem*-bromofluorocyclopentane **91** (**Scheme 35**).



Scheme 35. *In situ* generation of disilane-substituted bromofluorocyclopropanes

4. Mechanism

Dihalocyclopropane has attracted the attention of both experimental and theoretical chemists because of its special structural and chemical properties. There are a few reports on the computational calculations of dihalocyclopropane synthesis and its reactivity, and these are discussed below.

4.1 Kinetic Studies

The reaction rate for electrocatalytic reduction of dihalocyclopropanes was determined in the presence of transition metal salen complexes and the results of these kinetic studies showed that electron transfer occur *via* the inner sphere mechanism.[49] Wang and co-workers found that the rate of dichlorocyclopropanation of 1,7-octadiene follow a pseudo first order under phase transfer conditions with high or low alkaline concentration.[50,51] For phase transfer catalysts of same anion, a smaller quaternary ammonium cation showed larger reactivity and the reason for this behaviour was attributed to the interfacial reaction mechanism where the reaction rate is highly dependent on the concentration of the catalyst at the interface. The kinetics of cyclopropanation of styrene under phase transfer catalysis was investigated and the results showed that formation of a film in a liquid-liquid system and formation of a crust of a product on the surface of the solid reactant in solid-liquid system make significant contribution to the observed kinetics.[52] The kinetics of chain chlorination of cyclopropanes was also studied.[53] The absolute and relative rate constants were measured and computationally confirmed. The reactivities and ring opening of difluorocyclopropylmethyl tosylate was studied by experimental and DFT calculation methods suggesting the involvement of cationic species in the reaction.[54]

4.2 Theoretical Calculations

The first quasi-classical trajectory calculation using quantum mechanical energies and forces was generated by Venus and Gaussian programmes which gave detailed insight into the dynamics of carbenes and their cycloaddition to alkenes.[55] All the reactive trajectories follow the non-linear approach proposed by Moore[56] and Hoffmann.[57] The reaction of $:CCl_2$ with ethylene occurs in a concerted fashion with time gap between bond formation of the two bonds of 50fs while that of $:CF_2$ with ethylene is complex with bi-exponential decay of the biradical species formed from the first bond formation.

Craig and co-workers calculated the harmonic and anharmonic fundamental frequencies of 1,2-difluorocyclopropane and its isotopomers using the Gaussian 03, B3LYP and MP2 models.[58] They also calculated the IR and Raman spectral data of the same using B3LYP/cc-p VTZ quantum chemical model and Gaussian 03 software.[59] Borden *et al.* used (4/4)CASSCF and CASPTZ calculations to understand the enthalpy of activation for the rearrangement of 2,2,3,3-tetrafluoromethylenecyclopropane to 1-(difluoromethylene)-2,2-difluorocyclopropane.[60] The ring opening reaction of lithium bromocyclopropylidinoids to allenes was also investigated computationally.[61] *Gem*-dihalocyclopropanes effectively act as a mechanophore for polymers.[62] The mechanochemical properties of dihalocyclopropane substituted polymers and its force induced stereochemistry was scrutinized by *ab-initio* calculations. A detailed study on the electronic and geometrical properties of various dihalocyclopropane derivatives was carried out with the aid of photoelectron (PE) spectroscopy.[63]

4.3 Structural Studies

Generally, the structural studies of the compounds containing halogens were done by ^1H, ^{13}C NMR and X-ray diffraction analyses. Since the halogenated species have high dipole moment and magnetic sensitivity, line broadening occurs. A detailed spectral study of chloro and bromo analogues of 2,2-dihalo-1-propylcyclopropanecarboxylic acids and 1,1-dihalo-2-phenyl cyclopropane derivatives was reported by Sydnes *et al*.[64] They also investigated the photochemical debromination products *via* a detailed ^1H NMR study of the mono brominated products. The structural analysis of polyfunctionalized *gem*-dihalocyclopropanes was carried out by X-ray diffraction and the absolute configuration (1'S, 3R) was established by refinement of the Flack parameter.[11]

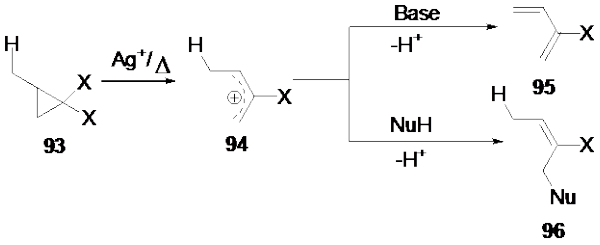
A detailed structural analysis of the product obtained by the reaction of costunolide lactone with dihalocarbene under phase transfer catalysis revealed that mono, bis and tris dihalocyclopropane adducts were formed in the reaction.[65] The structure of dimerization product of carbenes, which were produced by the reaction of methyllithium with 3,3-dibromo-2,7,7-trimethyl-tricyclo[4.1.1.0]octane, was confirmed by Balci and co-workers.[66] The Chemically Induced Dynamic Nuclear Polarization (CIDNP) studies of dehalogenated products of substituted dibromocyclopropanes were carried out which indicated that the reaction was fast and complete within minutes and then only the CIDNP was observable.[67]

The π-facial selectivity of the dihalocyclopropanation of conformationally heterogeneous 2-substituted 4,7-dihydro-1,3-dioxepines was studied and the results revealed that π-facial solvation of substrates enhanced *endo*-addition of dihalocarbene on the side of the distant alkyl substituent.[68]

5. Transformations of *gem*-dihalocyclopropanes

Gem-dihalocyclopropane derivatives are useful synthetic intermediates because they can be readily transformed into cyclic, acyclic, heterocyclic and macrocyclic compounds including natural product precursors. It is noteworthy that *gem*-dihalocyclopropanes easily undergo carbonylation, dehalogenation and annulation leading to a wide variety of interesting and useful substrates.

Even though *gem*-dihalocyclopropanes are strained ring systems, they possess considerable kinetic stability.[69] *Gem*-dihalocyclopropanes **93** generate a π-allyl carbocation **94** by silver salt or heat assisted electrocyclic ring opening reaction. This cation was found to be an effective intermediate for the synthesis of a number of natural products. The fate of the allyl cation depends on the reaction conditions used for its generation (**Scheme 36**). If the reaction is carried out under basic condition, deprotonation of the cation occurs resulting in 2-halo-1,3-butadiene **95**. On the other hand if nucleophiles are added to the reaction mixture, they intercept the cation leading to allyl systems **96**.



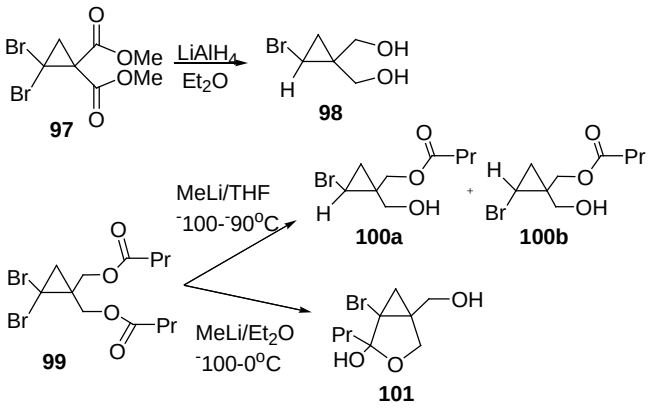
Scheme 36. Fate of π-allyl carbocation generated from *gem*-dihalocyclopropane

5.1 Reductive dehalogenation

The *gem*-dihalocyclopropanes easily undergo reductive dehalogenation reaction. The product of dehalogenation depends on the reaction conditions and the reagents used.[1] The rate of dehalogenation of carbon-halogen bond follows the order I>Br>Cl>F.

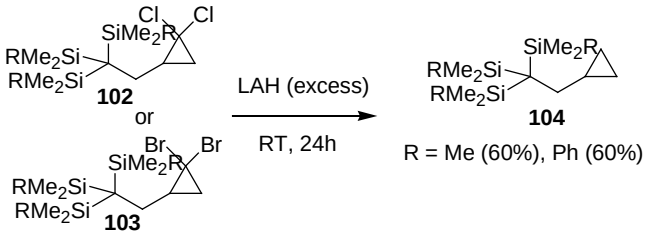
The reductive dehalogenation of 2,2-dibromocyclopropane-1,1-dicarboxylate **97** and **99** with two different reagents has been reported.[25] Results showed that reduction using lithium aluminum hydride (LAH) in diethyl ether afforded exclusively the monobromo alcohol derivative of the respective dihalocyclopropane **98** (**Scheme 37**). At the same time, reaction of a similar ester with methyl lithium in THF followed by quenching at very low temperature resulted in the formation of monobromocyclopropane as a mixture of 3:1 *cis*- **100a** and *trans*-isomers **100b**. However if the reaction

mixture was warmed to 0 °C immediately after the addition of MeLi, a hemiacetal was formed.



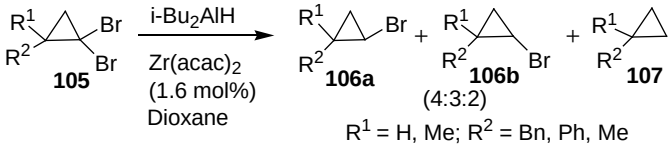
Scheme 37. Reductive dehalogenation of *gem*-dibromocyclopropane gem-dicarboxylate

The complete reductive dehalogenation of bulky silyl substituted dihalocyclopropanes was reported.[15] The results proved that there is no considerable difference in the rate of dehalogenation of dihalocyclopropanes with sterically demanding silyl substituents (**Scheme 38**). The reductive dehalogenation of dihalocyclopropanes that gave substituted cylopropanes has great significance.



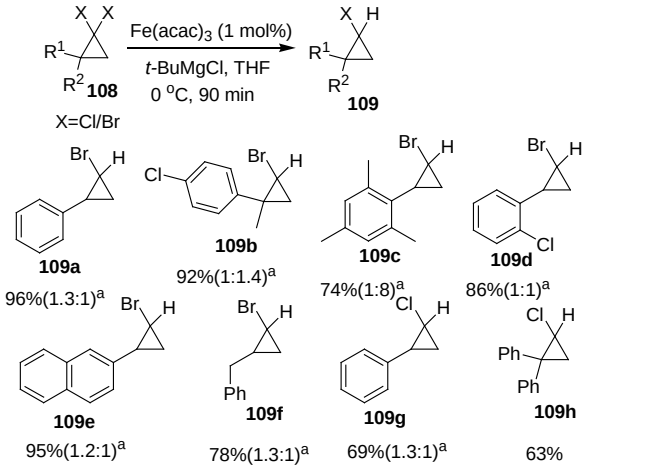
Scheme 38. Reductive dehalogenation of dihalocyclopropanes containing bulky silyl substituents using $LiAlH_4$

A catalytic method for reductive dehalogenation was described in which both aryl and alkyl dihalocyclopropanes **105** underwent dehalogenation by reaction with diisobutylaluminum hydride in the presence of catalytic amount (1.6 mol%) of $Zr(acac)_2$ (**Scheme 39**).[67] The study suggests the direct involvement of *i*-Bu group in the catalytic cycle forming an unstable complex with *i*-Bu-Zr bond.



Scheme 39. Reductive dehalogenation with diisobutylaluminum hydride and $Zr(acac)_2$

An efficient Fe-catalyzed protocol for selective monodehalogenation of dihalocyclopropanes **108** with commercially available *t*-BuMgCl is reported (**Scheme 40**).[70] Allene, which is a common by-product of usual dehalogenation of dihalocyclopropanes was not observed in the reaction. Iron-catalyst was found to be highly tolerant towards a large number of functional groups. The monohalocyclopropanes **109** obtained are potential coupling partners in transition-metal catalyzed cross-coupling reactions.

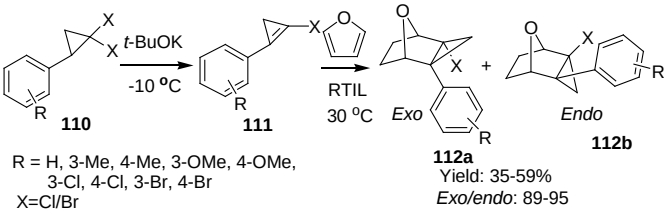


a: combined isolated yield of *cis/trans* isomers; the ratio of isomers in parenthesis

Scheme 40. Selective monodehalogenation of dihalocyclopropane derivatives

Mechanistic studies revealed that the dehalogenation follows a free radical pathway involving cyclopropyl-iron free radical species which is reduced by an iron centered hydride transfer.

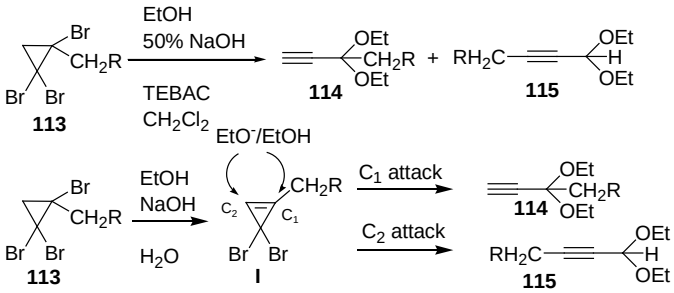
Unsubstituted cyclopropene has explosion liability, while the substituted ones are stable.[71] Consequent to the extra stability of cyclopropene accrued from halo substituent, it can act as a dienophile. Room temperature ionic liquids (RTIL) are a class of solvents that provide excellent solubility range compared to commonly existing solvents. The RTILs are capable of affecting product stereochemistry in the cycloaddition reaction between halosubstituted cyclopropene **111** and furan. 1-Aryl-2,2-dihalocyclopropanes on treatment with *t*-BuOK in hexane at -10 °C afforded 1-aryl-2-halocyclopropene. The latter underwent cycloaddition reaction with furan in RTIL at 30 °C affording mainly the *exo* isomer with less than 10% *endo* isomer (**Scheme 41**). The use of imidazolium type ionic liquids such as 1-hexyl-3-methylimidazolium $[hmin]^+$ and 1-methyl-3-octylimidazolium $[omin]^+$ increased the yield and stereoselectivity. The formation of the *exo* isomer **112a** in this reaction was attributed to the 'polarity' of the imidazolium type RTIL and to the congestion that exists between aryl ring of the cyclopropene and oxygen atom of the furan ring.



Scheme 41. Dehydrohalogenation of *gem*-dihalocyclopropane with *t*-BuOK and subsequent cycloaddition with furan in RTIL

5.2 Ring opening/expansion reactions

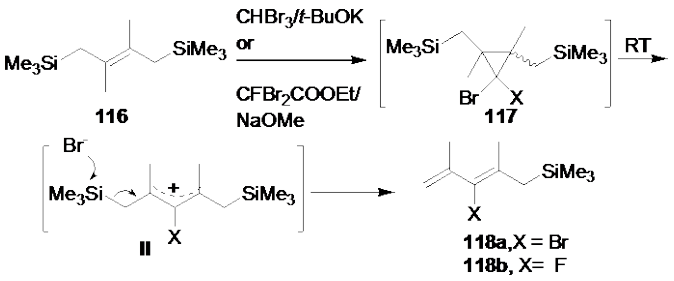
The ring opening reactions of *gem*-dihalocyclopropanes have been known for some time. A number of methods were used for the ring opening of dihalocyclopropanes. It is observed that the sequential treatment of 50% aqueous NaOH and triethylbenzylammonium chloride in the presence of EtOH on 1,1,2-tribromocyclopropane resulted in the opening of the cyclopropane ring giving the respective acetal and ketal in moderate yield (**Scheme 42**). The acetal/ketal ratio was dependent on the steric bulkiness of the substituent group attached to cyclopropane and favored the ketal formation as the bulkiness increased. Thus *i*-Pr and *t*-Bu substituted cyclopropanes afforded exclusively the acetal product when the former was treated with NaOH and TEBAC in ethanol.



Scheme 42. Ring opening of 1,1,2-tribromo-2-alkyl cyclopropane with NaOH and TEBAC in EtOH

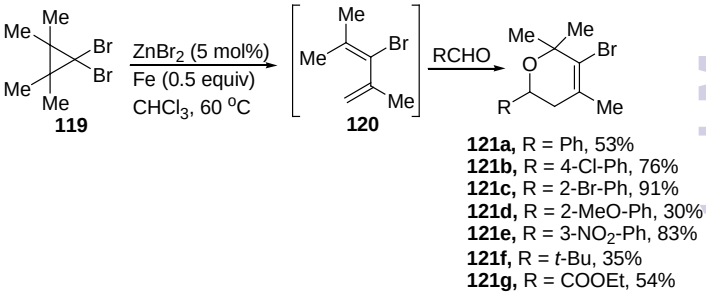
The formation of the product involves initial dehydrobromination of the tribromocyclopropane yielding a dibromocyclopropene, followed by nucleophilic attack of EtO^-/EtOH on C1 or C2 of the cyclopropene depending on the steric bulkiness of the substituent group R (**Scheme 42**).[26] Bulky group at C1 prevents attack of nucleophile at this carbon leading to the acetal product. However, if H-bonding groups are present in the substituent R, the ketal product is formed in excess presumably due to the attractive forces between the solvent (EtOH) and the substituent group compensating more than the steric factor.

Bis allylsilyl alkenes **116** on reaction with the corresponding dibromo or bromofluorocarbene afforded unstable dihalocyclopropanes **117** which then underwent ring opening at room temperature yielding bromo **118a** or fluorosilyldienes **118b** in good yields (**Scheme 43**).[36]



Scheme 43. Ring opening of silyl substituted dibromo or bromofluorocyclopropanes

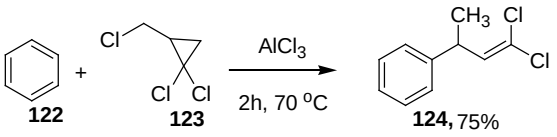
$ZnBr_2$/Fe-mediated ring opening of symmetrical and unsymmetrical *gem*-dihalocyclopropanes is reported where the ring-opening results in the formation of halo-substituted 1,3-diene **120** which undergoes hetero-Diels-Alder reaction with aldehydes, α-keto esters and electron-deficient imines affording moderate to good yields of the corresponding pyran and piperidine derivatives (**Scheme 44**).[72]



Scheme 44. Synthesis of 3,6-dihydro-2H-pyrans *via* $ZnBr_2$/Fe-mediated ring opening and hetero-Diels-Alder reaction

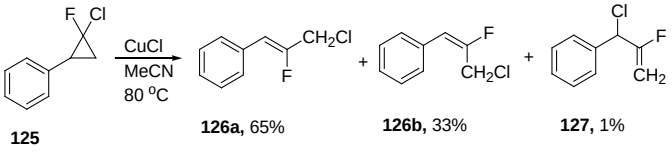
When aldehydes were replaced with imines, the corresponding tetrahydro pyridine derivatives were formed in moderate yields.

Chloromethyl *gem*-dihalocyclopropane was successfully used as an alkylating agent for benzene and toluene in presence of $AlCl_3$ leading to dihaloalkenyl derivative **124**, analogous to the Friedel-Crafts alkylation reaction (**Scheme 45**).[73]



Scheme 45. Alkylation with chloromethyl *gem*-dihalocyclopropanes in presence of $AlCl_3$

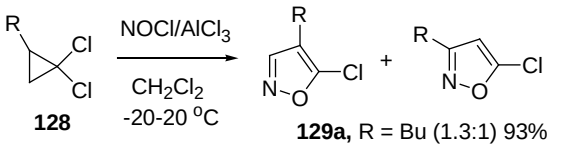
Cu(I)Cl catalyzed electrocyclic ring opening isomerization of *gem*-chlorofluorocyclopropanes **125** with phenyl-, vinyl-, alkyl- and cyclopropyl substituents is reported (**Scheme 46**).[74] The reaction when carried out in aprotic solvents led to the formation of *Z*- and *E*-chlorofluoroalkenes.



Scheme 46. Cu(I) catalyzed ring opening isomerization of substituted chlorofluorocyclopropanes

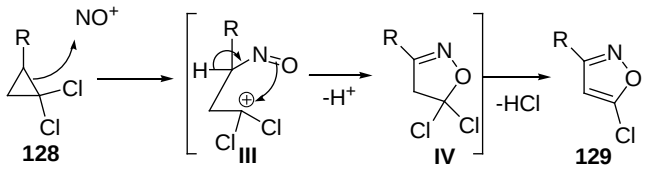
A new method for cyclopropane ring expansion using NOCl-$AlCl_3$ system is developed in which reaction of alkyl substituted *gem*-dichlorocyclopropane with nitrosyl chloride and aluminum chloride afforded a mixture of 3-alkyl and 4-

alkyl 5-chloroisoxazoles **129** in high yields at -20-20 °C (**Scheme 47**).[75]



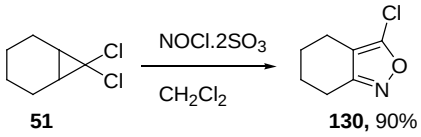
Scheme 47. NOCl-$AlCl_3$ promoted electrocyclic ring expansion of dihalocyclopropane

Later in 2013, modification of this nitrosation was reported by the same group and a regiospecific nitrosation was achieved with $NOCl.2SO_3$ in CH_2Cl_2.[76] A mechanism for the formation of the isoxazole was also proposed (**Scheme 48**).



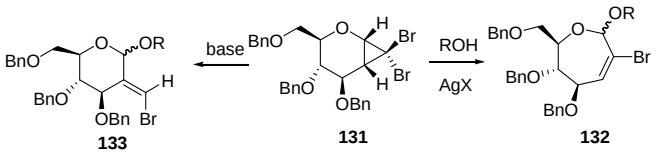
Scheme 48. Mechanism of NOCl-$AlCl_3$ promoted electrocyclic ring expansion of dihalocyclopropane

The modified method of nitrosation was used for the preparation of isoxazoles from dichlorocyclopropanes and polycyclic *gem*-dichlorocyclopropanes (**Scheme 49**).[77]



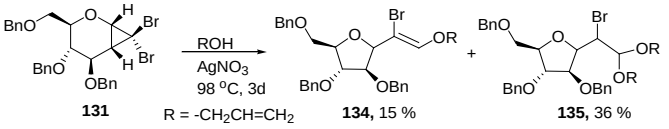
Scheme 49. Nitrosation of 7,7-Dichloro-bicyclo[4.1.0]heptanes with $NOCl.2SO_3$ in CH_2Cl_2

Ag(I) salt-promoted ring opening of *gem*-dihalocyclopropanes was applied in the synthesis of oxepines. Dihalocyclopropane fused carbohydrates provided an easy access to higher carbohydrate homologues, especially the septanoside family. *Gem*-dibromocyclopropane derivative of D-glucal **131** underwent Ag(I) induced thermal ring expansion into 2-bromooxepine**132**; but the same reaction under basic condition gave 2-*C* branched pyranoside **133** (**Scheme 50**).[78,79]



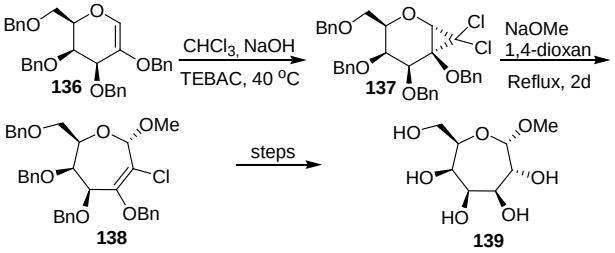
Scheme 50. Synthesis of oxepine *via* Ag(I)-promoted ring expansion

Harvey *et al.* showed that increasing the reaction time of this reaction led to the contraction of the ring resulting in some tetrahydrofuran derivatives **134** and **135**.[78] These results indicate that the C-furanoside is capable of acting as a precursor for C-nucleoside also (**Scheme 51**).



Scheme 51. Ag(I) assisted thermal ring expansion of cyclopropane derivative of carbohydrate in the presence of allyl alcohol

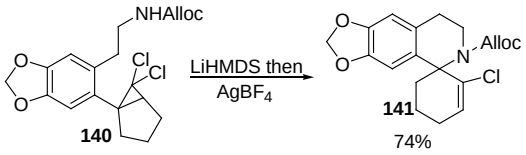
Dihalocarbene insertion of an oxyglycal followed by stereoselective ring expansion of the resulting dihalocyclopropane fused pyranoses **137** with a nucleophile (methoxide) as the key step in the synthesis of some unnatural septanosides was disclosed (**Scheme 52**).[80]



Scheme 52. Synthesis of septanoside using carbene insertion-ring expansion

The ring expansion chemistry is extended with other nucleophiles such as phenoxides, sugars and azide affording the corresponding septanoside derivatives in good yields with sugar nucleophiles showing high stereoselectivity.[81] Septanoside containing trisaccharides were also prepared by ring-expansion of cyclopropanated oxyglycals.[82] The ring-opening of dihalocyclopropanated oxyglycals yielded trisaccharides with 6-7-5 and 6-7-6 ring sizes.

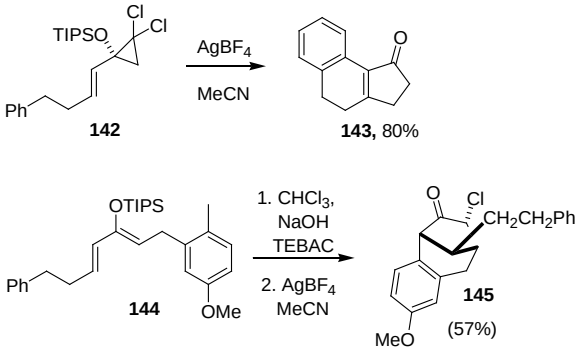
Banwell and co-workers achieved the first Ag(I) promoted electrocyclic ring opening of dihalocyclopropane **140** for the synthesis of erythrina alkaloid (**Scheme 53**).[13] Here, Ag(I)-promoted electrocyclic ring opening of the cyclopropane afforded a π-allyl cation which was trapped by the tethered nitrogen nucleophile **141** providing an excellent route towards the required erythrina alkaloid skeleton.



Scheme 53. Silver(I) assisted electrocyclic ring opening of *gem* dihalocyclopropane derivative

A similar Ag(I) assisted electrocyclic ring opening followed by Nazarov cyclization of dichlorocyclopropane derivative of 2-triisopropylsiloxydiene was reported by West *et al.* (**Scheme 54**).[14] Here Ag(I) mediated disrotatory ring opening affords the pentadienyl cation which on conrotatory Nazarov electrocyclization and arene trapping gave the benzohydrindinone. If the cyclopropane ring is tethered with

two pendent arene rings, the dichlorocyclopropane undergoes electrocyclic ring opening/interrupted Nazarov reaction generating an unexpected, unique, bridged bicyclic carbon framework **145** present in some alkaloids.



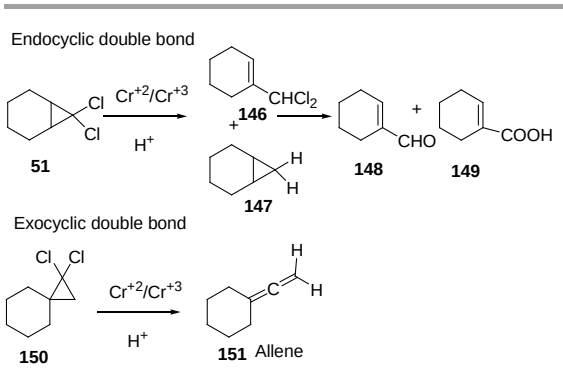
Scheme 54. Ag(I) assisted electrocyclic ring opening/Nazarov cyclisation of dihalocyclopropanes

5.3 Rearrangements

The strained *gem*-dihalocyclopropanes readily underwent rearrangement reactions. The first such rearrangement was reported in 1992.[83] The rearrangement reactions of *gem*-dihalocyclopropanes are important in organic synthesis because they provide an easy route towards steroids, terpenoids and naphthalene derivatives.

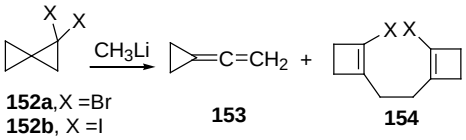
Rearrangements of dihalocyclopropane derivatives under the influence of Hiyama type reagents[84] were extensively studied.[85] The Hiyama reagent is *in situ* generated Cr+2/Cr+3H-, which facilitates rearrangement of dihalocyclopropanes leading to the formation of dihalomethyl moieties, which are potential precursors for α,β-unsaturated aldehydes and acids.

A detailed mechanistic study of the rearrangement of both exocyclic and endocyclic dihalocyclopropane to cyclohexene was also reported.[86,87] Here, the reaction proceeds *via* a biradical mechanism involving Cr intermediate and the mechanistic study was performed by isotopic labeling. Under acidic conditions in presence of Cr^{2+}/Cr^{3+}, dihalocyclopropanes generate dihalomethyl vinyl derivative; the existence of the latter was presumed since a mixture of α,β-unsaturated aldehyde and acid along with dehalogenated products were isolated from the reaction mixture (**Scheme 55**). In the case of dihalocyclopropanes capable of forming exocyclic double bond, allenes are formed; the method is used in the synthesis of various allenes **151**.



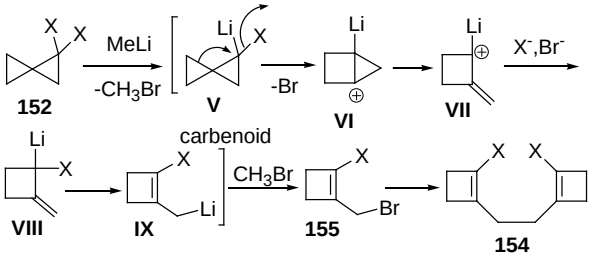
Scheme 55. Rearrangement of exocyclic and endocyclic dihalocyclopropane to cyclohexene and allene derivatives

Literature reports show that *gem*-dibromo- **152a** or diiodospiropentanes **152b** react with methyllithium in an unusual way.[88] The product of the rearrangement may be vinylidenecyclopropane **153** or biscyclobutenyl ethane **154** depending on temperature (**Scheme 56**).



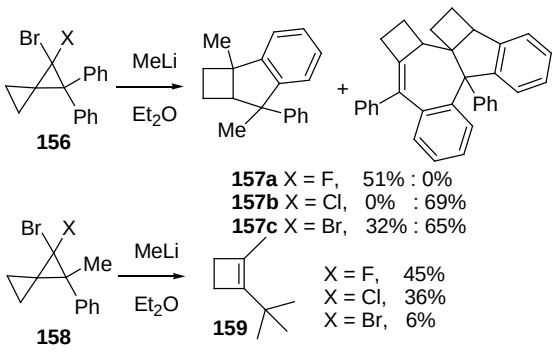
Scheme 56. Methyllithuim induced rearrangement of *gem*-dihalospiropentanes

It is suggested that a carbenoid mechanism prevails in the reaction (**Scheme 57**). The nature of the substituent on the spiropentanes and the reaction temperature affect the nature of the product.[34]



Scheme 57. Proposed mechanism of methyllithuim induced rearrangement of *gem*-dihalospiropentanes by Averina *et al.*

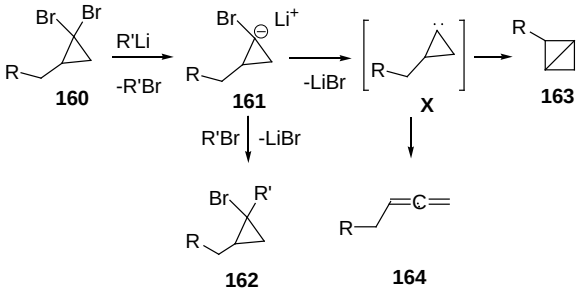
The methyllithium assisted rearrangement of dihalogenospiropentanes gave different products depending on halo substituent. Bromofluorospiropentane on treatment with MeLi gave a tricyclic system exclusively (**Scheme 58**).[24] At the same time the reaction between MeLi and bromochlorospiropentane gave exclusively the hexacyclic dimeric product. If the dibromo compound was subjected to the reaction, a mixture of tricyclic and dimerized products was obtained. The formation of the two products was attributable to the presence of two phenyl groups, which facilitated cyclization via ortho electrophilic substitution in the phenyl ring. If one of the phenyl groups is replaced by a methyl group, an entirely different product **159** was obtained. A possible mechanism for the formation of all the products is reported.



Scheme 58. Reaction of methyllithium with 2,2-disubstituted *gem*-bromohalo spiropentanes

5.4 Doering-Moore-Skattebol reaction

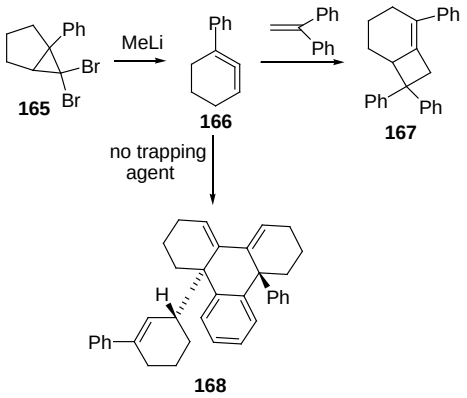
The Doering-Moore-Skattebol (DMS) reaction provides a very expedient method for the synthesis of substituted allenes. In DMS reaction the dihalocyclopropane reacts with alkyl lithium by lithium-halogen exchange (**Scheme 59**).[89,90,91] After lithium-halogen exchange, the cyclopropylidene formed by the α-elimination of bromide ion rearranged to allene. The activation energy for this reaction is found to be generally low.



Scheme 59. Mechanism of Doering-Moore-Skattebol reaction (Reprinted with permission from Eccles, W *et al. J. Org. Chem.*, **2008**, *73*, 5732)

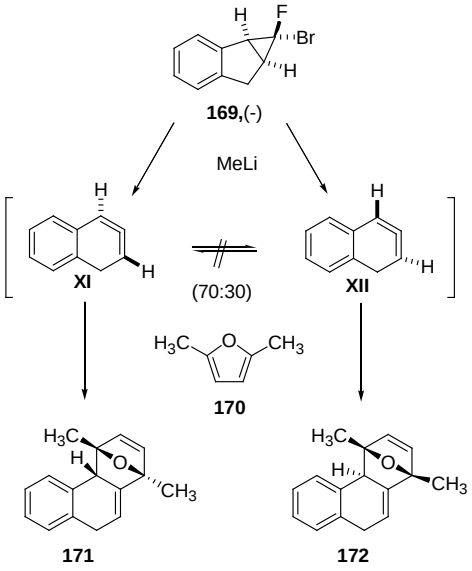
There is competition between the two pathways. The route leading to DMS reaction is favored by less strain, but has no electronic effects.

The DMS reaction provided a nice way for the generation of 1-phenyl-1,2-cyclohexadiene (**Scheme 60**).[35,92] In the absence of a trapping agent, 1-phenyl-1,2-cyclohexadiene was converted to a dimer or trimer depending on the mode of generation of the diene.



Scheme 60. Generation and subsequent reactions of 1-phenyl-1,2-cyclohexadiene

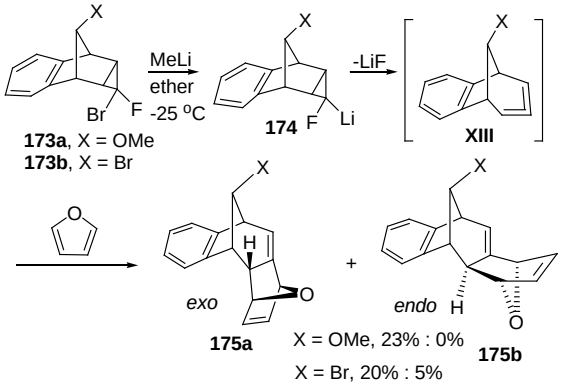
The bromofluorocyclopropane derivative of indene having *endo* fluorine substitution **169** acts as a very good substrate for isonaphthalene synthesis by Doering-Moore-Skattebol reaction (**Scheme 61**).[28] The allene formation in DMS reaction was proved by trapping the former with activated olefins such as furan.



Scheme 61. Formation of isonaphthalene and trapping with furan (Reprinted with permission from Christl, M *et al. Eur. J. Org. Chem.*, **2006**, 5045)

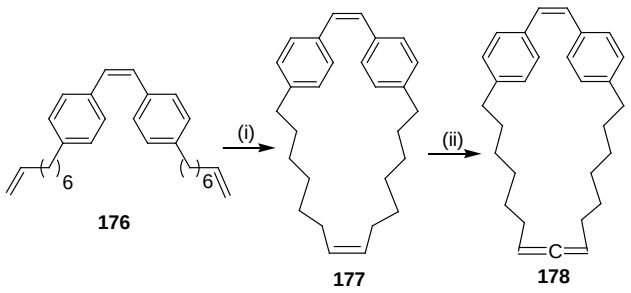
A comparative study on the Doering-Moore-Skattebol reaction of dibromocyclopropane derivative of spiro-fused 1,3-dioxane and cyclohexane derivative was carried out.[93] Results showed that the dioxane derivative was resistant to rearrangement and consequently neither allene nor any other expected rearranged product could be isolated.

The DMS product of mixed dihalocyclopropane derivative of bromo- or methoxy-substituted benzonorbornadiene was reported.[30] The allene formed was trapped with furan; the methoxy derivative gave only the *exo* product where as the bromo derivative gave the *exo* and *endo* products in the ratio 4:1 (**Scheme 62**).



Scheme 62. DMS reaction of dihalocyclopropane derivative of benzonorbornadiene and subsequent trapping of the allene

Allenic cyclophanes have important applications as chiral ligands and as host molecules. A combination of Ru-catalyzed ring closing metathesis (RCM) with DMS reaction on the dibromocyclopropane generated by Seyferth reagent ($PhHgCBr_3$) offered an excellent route for the preparation of allenic cyclophanes (**Scheme 63**).[94] This method offers an improved procedure for allene ring closing metathesis.



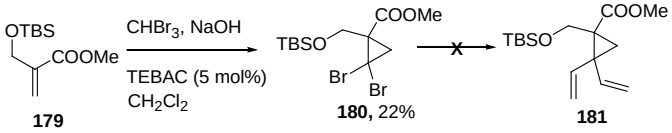
(i) $Cl_2(Cy_3P)_2Ru$=CHPh, 93%, *Z*:*E* 3:2

(ii) $PhHgCBr_3$, MeLi, 21%

Scheme 63. Sequential RCM-DMS reaction for the generation of allenic cyclophanes

5.5 Substitution reactions

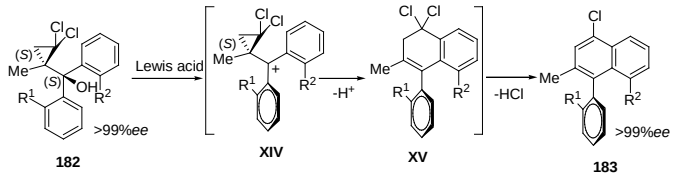
Direct substitution of halogen from *gem*-dihalocyclopropanes is limited. The *gem*-dibromocyclopropane prepared from acrylate derivative under phase transfer catalysis failed to undergo vinylation under Stille, Kumada and Sonogashira conditions (**Scheme 64**).[95]



Scheme 64. Attempted substitution of *gem*-dibromocyclopropane with vinyl organometallic compounds

5.6 Bezannulation

The biaryl motif is present in many bioactive compounds and chiral auxiliaries. The first chirality transfer from sp^3 chirality to axial chirality was reported by Tanabe and co-workers.[96] This chirality exchange was made possible by the benzannulation of aryl(aryl')-2,2-dichlorocyclopropylmethanol (AACM) into α-aryl naphthalenes **183** (**Scheme 65**). A cyclic transition state was proposed for the chirality transfer.



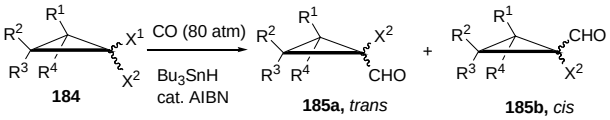
R^1 = Cl, Me, MeO; R^2 = H, Cl, Me

Scheme 65. Single step chirality transfer from sp3 centre to axial: benzannulation of chiral aryl(aryl')2,2-dichlorocyclopropylmethanols (Reprinted with permission from Tanabe, Y *et al. J. Am. Chem. Soc.*, **2004**, *126*, 5358)

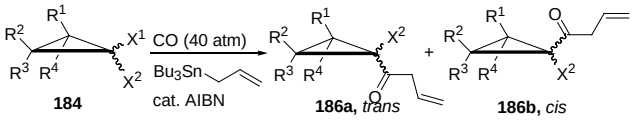
The unsymmetrical α-aryl naphthalenes provide an easy access to biologically active lignan lactones which show antiviral, antifungal, antitumor, anti PAF and anti HIV properties.[97] The Lewis acid catalyzed benzannulation protocol was used for the synthesis of lignan type lactones such as justicidin B and retrojusticidin.

5.7 Radical carbonylation

A number of efficient methods have been developed for carbon chain elongation of dihalocyclopropanes. Radical carbonylation is one among the most successful routes for chain lengthening of dihalocyclopropanes. The synthesis of cyclopropylcarbonyl and hydroxymethylcyclopropyl derivatives has special importance due to the occurrence of these skeletons in many natural products and their application in heterocyclic synthesis. Most of these routes were applicable only to dibromocyclopropanes, but in 2007 Nishii and co-workers reported a highly stereoselective radical type carbonylation of inherently less reactive *gem*-dichlorocyclopropanes.[98] The carbonylation was achieved by using CO and Bu_3SnH or $Bu_3Sn(CH_2CH{=}CH_2)$ with good *trans* selectivity for 2,3-*cis* disubstituted 1,1-dihalocyclopropanes (**Scheme 66**). Here, less reactive dichloro and bromochlorocyclopropanes afforded good yields and high stereoselectivity.



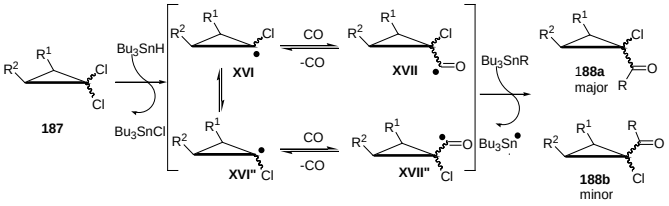
R^1 = Ph, R^2 = H, R^3 = H, R^4 = H, X^1 = Cl, X^2 = Cl, 51%, *trans:cis* 75:25
R^1-R^2 = -$(CH_2)_4$-, R^3 = H, R^4 = H, X^1 = Cl, X^2 = Cl, 55%, *trans:cis* >99:1
R^1-R^2 = -$(CH_2)_4$-, R^3 = H, R^4 = H, X^1 = Br, X^2 = Cl, 73%, *trans:cis* >99:1
R^1-R^2 = -$(CH_2)_6$-, R^3 = H, R^4 = H, X^1 = Cl, X^2 = Cl, 47%, *trans:cis* 95:5
R^1-R^2 = -$(CH_2)_6$-, R^3 = H, R^4 = H, X^1 = Br, X^2 = Cl, 67%, *trans:cis* 95:5



R^1 = Ph, R^2 = H, R^3 = H, R^4 = H, X^1 = Cl, X^2 = Cl, 51%, *trans:cis* >99:1
R^1 = Hex, R^2 = H, R^3 = H, R^4 = H, X^1 = Cl, X^2 = Cl, 47%, *trans:cis* >99:1
R^1-R^2 = -$(CH_2)_4$-, R^3 = H, R^4 = H, X^1 = Cl, X^2 = Cl, 54%, *trans:cis* >99:1
R^1-R^2 = -$(CH_2)_4$-, R^3 = H, R^4 = H, X^1 = Br, X^2 = Cl, 64%, *trans:cis* >99:1
R^1-R^2 = -$(CH_2)_6$-, R^3 = H, R^4 = H, X^1 = Cl, X^2 = Cl, 48%, *trans:cis* >99:1
R^1-R^2 = -$(CH_2)_6$-, R^3 = H, R^4 = H, X^1 = Br, X^2 = Cl, 54%, *trans:cis* >99:1

Scheme 66. Stereoselective carbonylation of dihalocyclopropane using CO and $Bu_3SnH/Bu_3Sn(CH_2CH{=}CH_2)$

A mechanism is also proposed for the transformation (**Scheme 67**).

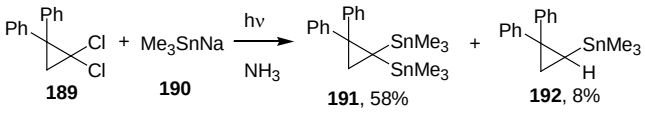


Scheme 67. Proposed mechanism of carbonylation of dihalocyclopropane using CO and Bu_3SnH(R) (Reprinted with permission from Nishii, Y *et al. Org. Lett.*, **2007**, *9*, 563)

5.8 Organometallic Chemistry

Preparation of cyclopropane ring containing organometallic substituent has been a subject of intense interest for many decades. Many reviews are available in this area.[99,100] The synthesis of 1,1-bis(trimethylstannyl)cyclopropanes from the

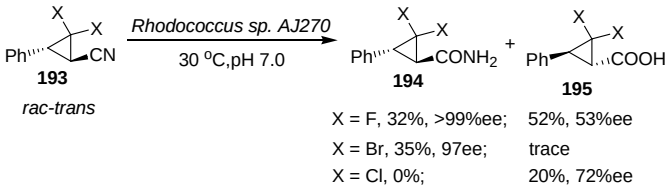
corresponding dichlorocyclopropanes by reaction with Me_3SnNa has been reported (**Scheme 68**).[101] The reaction proceeds *via* unimolecular radical nucleophilic substitution ($S_{RN}1$) mechanism and takes place in presence of liquid ammonia under light irradiation. A mechanism is also proposed for this reaction.



Scheme 68. Synthesis of 1,1-bis(trimethylstannyl)cyclopropane from *gem*-dichlorocyclopropane

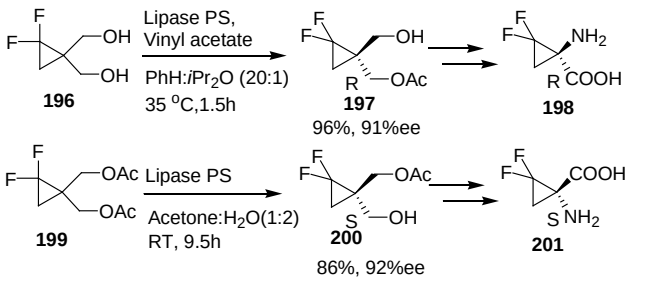
5.9 Biotransformations

Gem-dihalocyclopropanecarbonitriles underwent enantioselective transformation in presence of *Rhodococcus sp. AJ270* at 30 °C under neutral pH (**Scheme 69**).[102] Here the nature of halogen played an important role in determining the reaction rate and enantioselectivity. The difluoro and dibromo cyclopropane derivatives afforded the amide with moderate yield and high *ee* while the dichloro derivative gave the acid with moderate yield and moderate *ee*.



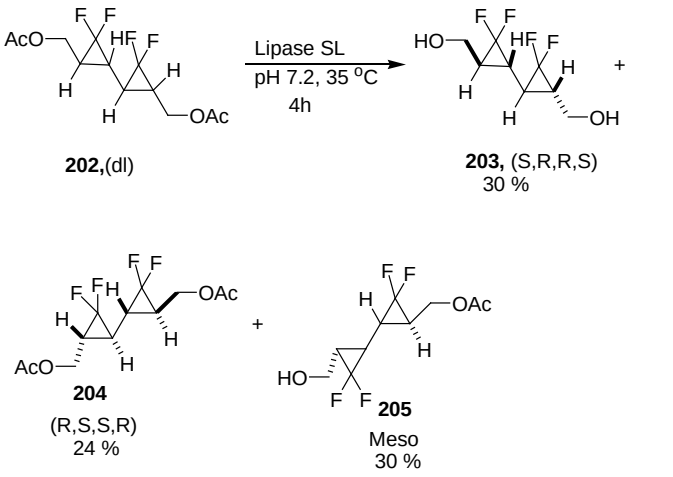
Scheme 69. Biotransformation of racemic *gem*-dihalocyclopropylnitrile

A chemo-enzymatic synthesis of 1-amino-2,2-difluorocyclopropane-1-dicarboxylic acid was reported in which lipase catalyzed desymmetrization of prochiral alcohol/ester was utilized for the enantioselective synthesis of (*R*) and (*S*) isomers of 1-amino-2,2-difluorocyclopropane carboxylic acids with high enantiomeric purity (**Scheme 70**).[103] The desymmetrization of prochiral diol was achieved using lipase PS in benzene-iPr_2O while that of the diacetate was achieved using lipase PS in acetone affording 91% and 92% *ee* respectively.



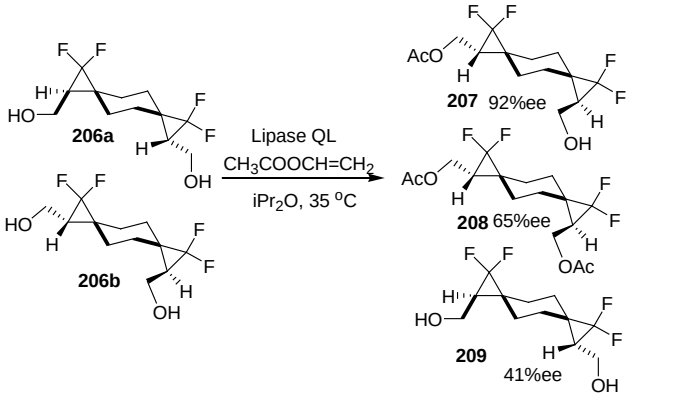
Scheme 70. Lipase catalyzed desymmetrization of *gem*-difluorocyclopropane derivatives

Itoh *et al.* also reported a chemo-enzymatic strategy for the geneneration of *trans,trans*-bis-*gem*-difluorocyclopropane **204** (**Scheme 71**).[104]



Scheme 71. Synthesis of *trans,trans*-bis-*gem*-difluorocyclopropane by chemo-enzymatic method

A mixture of *meso* and racemic bis(*gem*-difluorocyclopropylmethanol) tethered by a phenyl spacer was resolved by vinylation in presence of Lipase SL-25.[42] Resolution of racemic 1,1,7,7-tetrafluoro-2,8-bis(hydroxymethyl)dispiro[2.2.2.2]decane was achieved using Lipase QL catalyzed enantioselective transesterification (**Scheme 72**).[43]

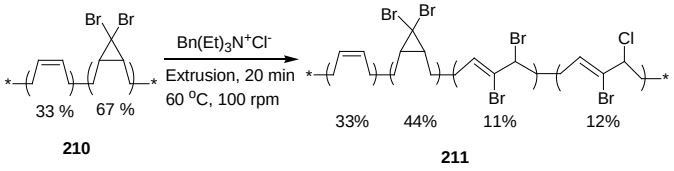


Scheme 72. Resolution of racemic 1,1,7,7-tetrafluoro-2,8-bis(hydroxymethyl) dispiro[2.2.2.2]decane using Lipase QL

5.10 Applications in Polymer chemistry

The importance of mechanophores (mechanically activatable functional groups) in polymeric systems has long been studied.[19] These materials along with polymer backbone are capable of acting as stress responsive materials and provide fine molecular stress distribution.[20] The incorporation of dichlorocyclopropane in a monomer results in the increase in the degree of polymerization and consequently large enhancement in the physical properties of the polymer was observed. This include increase in number average molecular mass, polydispersity, glass transition temperature and decrease in viscosity, melt flowability and flow temperature.

Polymers incorporated with *gem*-dihalocyclopropanes were activated in the solid state as a function of compressive stress.[105] Single molecule force spectroscopic data were obtained for textural studies of mechanophore embedded polybutadiene. The results showed that high mechanical force is concentrated over the length of only a few monomers. The *gem*-dihalocyclopropane embedded polybutadiene has superior properties over bare polybutadiene.[106] The mechanophore properties and consequent reactivity of *gem*-dihalocyclopropanated-polybutadiene (gDHC-PB) co-polymers in solid state were investigated by the same group.[107] *Gem*-dihalocyclopropanes when placed along with suitable polymer backbone act as excellent mechanophores. Mechanical stimulation was attained by extrusion in a twin-screw micro-compounder. The extrusion of dihalocyclopropanated polymers were carried out in the presence of benzyltriethylammoniumchloride, which not only opened the cyclopropane rings but also led to subsequent bond formation in solid state (**Scheme 73**). The molecular weight of the gDHC-PB gets reduced on extrusion and consequently the polymer viscosity gets lowered. This stress induced bond formation might be a feasible method for preparation of stress-responsive polymers such as self healing materials.

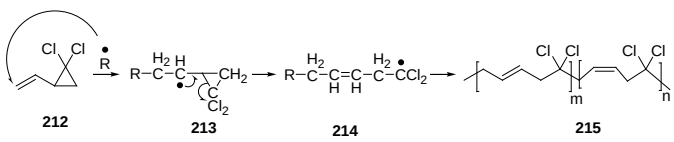


Scheme 73. Stress-induced covalent bond-formation of *gem*-dibromocyclopropanated-polybutadiene (gDBC-PB) co-polymer.

Craig *et al.* also carried out a detailed analysis of mechanically activated domain of *gem*-dihalocyclopropanated-polybutadiene.[106] The compression and tensile loading experiments showed that high mechanical force is concentrated over the length of only a small number of monomers.

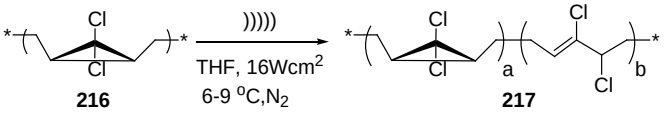
Craig and co-workers described the synthesis and sonochemical activation of ABA triblock copolymers of desirable molecular weight with a mechanophore rich region.[108] These block copolymers showed long term stability and act as stress-responsive materials.

Vinyl *gem*-dichlorocyclopropanes **212** underwent radical polymerization in the presence of radical type initiators to afford stereoblock copolymers with mostly the *trans* structure (**Scheme 74**).[109]



Scheme 74. Radical polymerization of vinyl *gem*-dichlorocyclopropanes

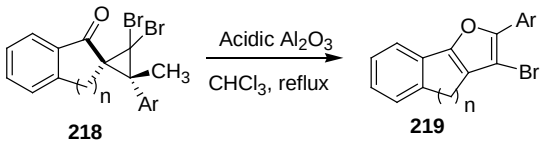
Pulsed ultrasound mediated mechanochemical ring opening of *gem*-dihalocyclopropanated-polybutadiene **216** was reported.[110] The pulsed ultrasound sonication acts as a reagent-less route for the preparation of highly organized polymers (**Scheme 75**).



Scheme 75. Sonication of *gem*-dichlorocyclopropanated-polybutadiene leading to ring opening

5.11 Applications in the synthesis of heterocycles

Nitrogen- and oxygen- containing heterocycles are important moieties in many naturally occurring and synthetically obtained biologically active compounds. Transformation of aryl substituted dihalocyclopropanes into nitrogen- and oxygen-containing heterocycles was reviewed by Mochalov *et al*.[111] Cyclopropane derivatives have been used as key scaffolds in the synthesis of many complex heterocycles. Ring expansion of vinyl cyclopropyl ketones to bromofurans *via* Clock-Wilson rearrangement was reported (**Scheme 76**).[112]



n = 1, Ar = electron rich/electron deficient; Yield 76-89%
n = 2, Ar = electron rich; Yield 70-87%
n = 3, Ar = electron rich/electron deficient; Yield 81-90%

Scheme 76. Clock-Wilson rearrangement of dibromocyclopropanes to fused furans

π-allyl carbocations are generated from *gem*-dihalocyclopropanes by silver salt or heat assisted electrocyclic ring opening reaction. The fate of the allyl cation depends on the reaction conditions and these allyl cations are utilized in the synthesis of a number of natural products. The trapping of π-allyl cations are carried out by different means and the methodology is used for the synthesis of a large number of alkaloids such as (-)-erythramine and tazettine.[113]

The technique of thermally induced electrocyclic ring opening of dihalocyclopropanes was used by Banwell and co-workers in the first total synthesis of Hamayne, an alkaloid belonging to the subset of Crinine alkaloids (**Figure 1**).[13]

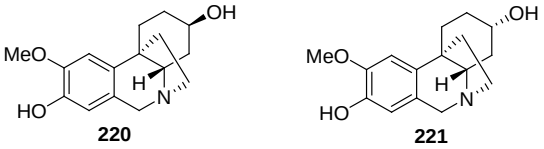
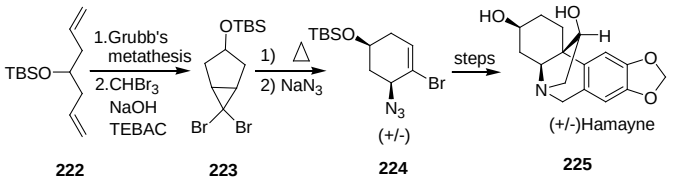


Figure 1. The Crinine alkaloids

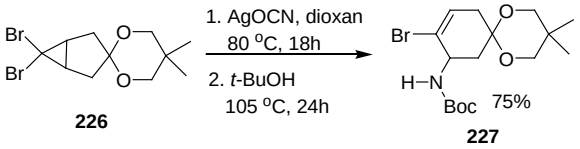
The key step in the first total synthesis of the crinine alkaloid Hamayne **225** involves electrocyclic ring expansion of

gem-dibromobicyclo[3.1.0]hexane derivative obtained from an *in situ* generated cyclopentene by cyclopropanation under Makosza condition using bromoform, alkali and triethylbenzylammonium chloride (**Scheme 77**).[13,114]



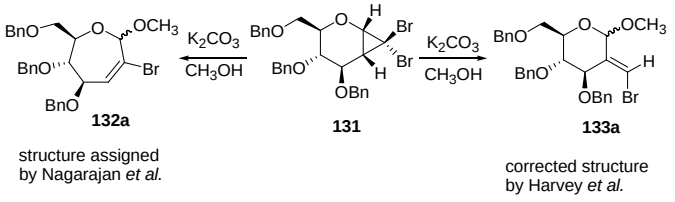
Scheme 77. Synthesis of Hamayne by electrocyclic ring expansion of *gem*-dibromocyclopropyl derivative

Banwell *et al.* also extended the protocol for the generation of C3a-arylhexahydroindole moiety *via* Ag(I) promoted electrocyclic ring opening reaction of *gem*-dibromocyclopropane derivatives.[115] The C3a-arylhexahydroindole is a versatile precursor for various amaryllidaceae alkaloids including Tazettine. The key steps in the synthesis toward Tazettine precursor involved a Ag(I) promoted electrocyclic ring opening of ketal protected *gem*-dibromo bicyclo[3.1.0]hexanone **226** generating a π-allyl cation which was intercepted with cyanate anion producing allyl isocyanate which was then quenched with *tert*-BuOH affording N-Boc protected cyclohexene amine **227** (**Scheme 78**).



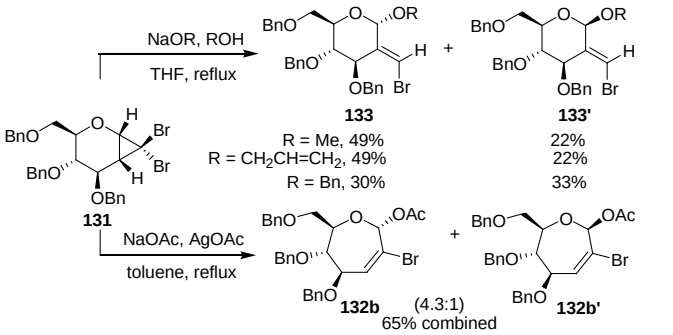
Scheme 78. Key steps in the synthetic route toward Tazettine precursor

Nagarajan *et al*. assigned an oxepine structure for the product obtained when D-glucal derived *gem*-dibromocyclopropane **132a** was refluxed with anhydrous K_2CO_3 in methanol (**Scheme 79**). Recently Harvey *et al.,* by extensive NOE experiments and chemical transformations proved the correct structure of the ring opened product of D-glucal derived *gem*-dibromocyclopropane as 2C-branched pyranoside **133a**.[78]



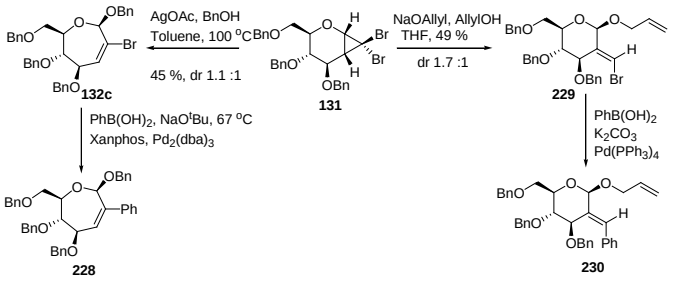
Scheme 79. Synthesis of 2C branched pyranoside from *gem* dibromocyclopropane fused carbohydrate

Faster reaction and better yields were obtained when methanolic sodium methoxide was used (**Scheme 80**). The protocol was then extended to allyl and benzyl glycosides. When the reaction was carried out in presence of AgOAc and NaOAc in refluxing toluene, anomeric bromooxepines were obtained in 65% yield and 4.3:1 ratio.



Scheme 80. Synthesis of 2-bromooxepines *via* Ag(I) supported electrocyclic ring opening

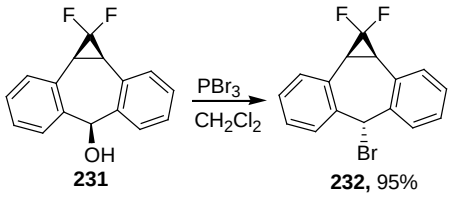
Harvey *et al.* converted the 2-C(bromo methylene)-pyranose and 2-bromooxepine prepared by ring opening reactions of *gem*-dibromocyclopropane derivatives into aryl substituted pyranose and oxepine derivatives (**Scheme 81**).[116]



Scheme 81. Synthesis and Suzuki reactions of 2-C-(bromo methylene)-pyranose and 2-bromooxepines

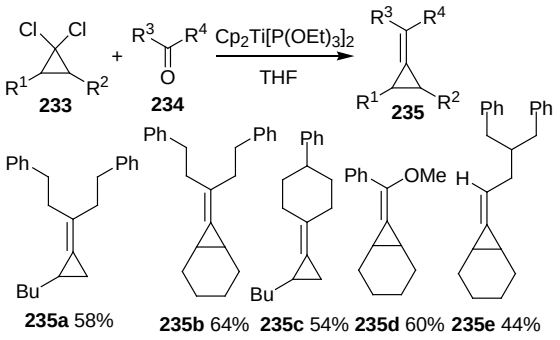
5.12 Miscellaneous reactions and applications

Nucleophilic displacement reaction of 1,1-difluorocyclopropyldibenzosuberanyl derivatives was observed by Barnett and co-workers in 2004 (**Scheme 82**).[117] The reaction proceeds through a homotropylium ion intermediate and the solvent plays an important role in the stereochemistry of the product.



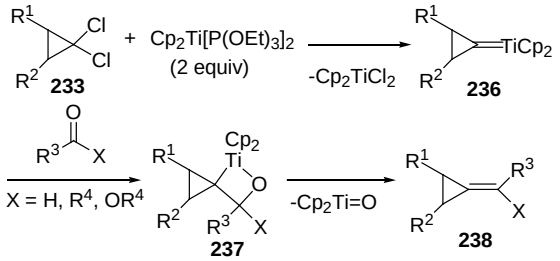
Scheme 82. Nucleophilic displacement reaction of 1,1-difluorocyclopropyldibenzosuberanyl derivative

An efficient method for cyclopropylidenation of carbonyl compounds **234** (aldehydes, ketones and esters) using dichlorocyclopropane and titanocene complex in a way similar to the Wittig olefination was introduced (**Scheme 83**).[118] A Titanocene(II) reagent $Cp_2Ti[P(OEt)_3]_2$ was used for this purpose and the methodology offered a facile route for cyclopropanation of highly enolizable carbonyl compounds.



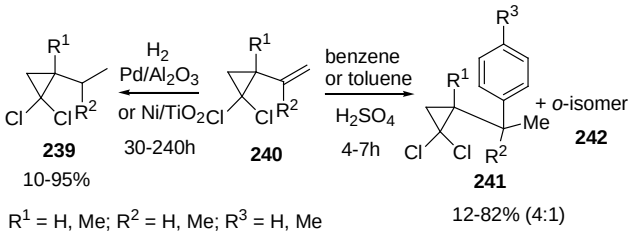
Scheme 83. Cyclopropylidenation of carbonyl compounds using titanocene(II) reagent

The mechanism of the reaction involves the formation of titanium cyclopropylidene complex which is generated by reductive titanation of bicyclooctane (**Scheme 84**). Reaction of carbene complex with carbonyl compounds affords oxatitana cyclobutanes, which give alkylidene cyclopropanes through the expulsion of titanocene oxide.



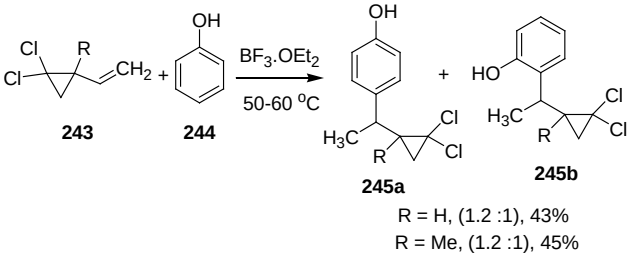
Scheme 84. Mechanism of cyclopropylidenation of carbonyl compounds using titanocene(II) reagent

The relative reactivity of alkenyl *gem*-dihalocyclopropanes in hydrogenation and alkylation was investigated (**Scheme 85**).[119] The results showed that the rate of hydrogenation was high for vinyl *gem*-dichlorocyclopropane compared to isopropenyl derivative; but for alkylation the rate was reversed due to the extra stability of tertiary carbocation.



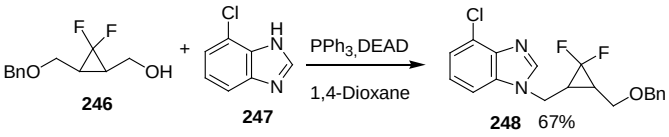
Scheme 85. Hydrogenation and alkylation of vinyl and isopropenyl *gem*-dichlorocyclopropanes

Alkylation of phenol was reported with alkenyl *gem*-dichlorocyclopropane derivatives in presence of BF_3-etherate affording moderate yields of *o*- and *p*-isomers in 1:1.2 ratio (**Scheme 86**).[120]



Scheme 86. Synthesis of *o*- and *p*-[1-(2,2-dichlorocyclopropyl)ethyl]phenol from phenol using BF_3-etherate

Reports are available on the synthesis of difluorocyclopropyl nucleoside derivatives **248** by treating difluorocyclopropyl methanol with nucleosides such as adenine, purine, thymine and uracil under Mitsunobu reaction conditions (**Scheme 87**).[121]



Scheme 87. Synthesis of difluorocyclopropyl nucleoside analogue by Mitsunobu reaction

The purine derivatives of difluorocyclopropanes **251** are also reported by the reaction of difluorocyclopropyl bromide with purine in presence of a base (**Scheme 88**).[47]

Scheme 88. Synthesis of purine derivative of difluorocyclopropyl nucleoside

Ferroelectric liquid crystalline compounds have wide applications in display appliances.[122] The physical properties of these compounds depend on the chemical structure of their chiral moieties. Some of the difluorocyclopropane derivatives show liquid crystalline properties.[41]

6. Biological activities of *gem*-dihalocyclopropanes

Gem-dihalocyclopropanes exhibit wide range of biological activity especially the fluorine analogue.[47] Ninomiya *et al*. reported that the *gem*-difluorocyclopropane derivative of 9-anthracenecarboxylic acid displayed DNA cleavage property upon photoirradiation.[123] A large number of nucleoside analogues have been synthesized as potential chemotherapeutic agents, especially as antiviral agents and incorporation of fluorine substituent in these compounds has shown benefits such as advanced action, greater bio-availability and retarded drug metabolism for several compounds studied.[47]

Recently Kailani *et al.* synthesized and studied the antimicrobial activities of dicarbamates prepared from various

arylisocyanates and (1*R*,3*S*)-2,2-dichloro-3-hydroxymethylcyclopropylmethanol.[18] The results showed that some of the dicarbamate derivatives of dichlorocyclopropyl methanols exhibit antibacterial and antimicrobial activities better than that shown by ampicillin and trichlocarban.

Conclusions

This review discusses the different methods of synthesis of *gem*-dihalocyclopropanes, their reactions and applications. A number of highly efficient and useful methods for the preparation of *gem*-dihalocyclopropanes are discussed. Among the many routes for the synthesis of *gem*-dihalocyclopropanes, the phase transfer catalyzed ones are the most popular ones. The transformations of *gem*-dihalocyclopropanes into useful compounds of varied applications as well as the synthesis of biologically active natural products are also included.

Acknowledgements

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