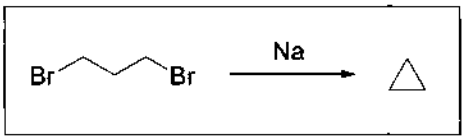
1.1 Freund Reaction

Frank Rong

1.1.1 Description



The Freund reaction refers to the formation of alicyclic hydrocarbons by the reaction of sodium on open chain dihalo compounds.[1]

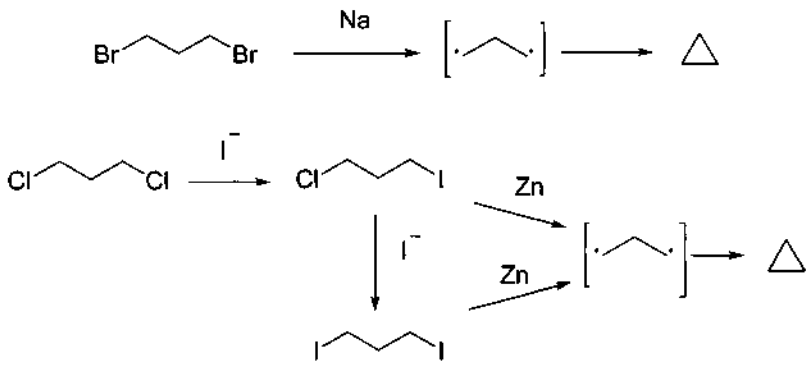
1.1.2 Historical Perspective

In 1882 Freund reported that treating trimethylene glycol with hydrobromic acid gave trimethylene dibromide, which was further treated with sodium in reflux temperature. As a result the sodium dissolved, the sodium bromide was precipited, and a gas from the reaction was collected. What is the gas? By treacting with bromine it went back to trimethylene dibromide. By treacting with hydriodic acid it gave iodopropane. Therefore, the gas was concluded to be cyclopropane for the first time.[1]

This reaction has been called the Freund reaction on occasion. However, reference to the original literature shows that although Freund was the first to make cyclopropane itself, he used an extension of the Wurtz reaction and therefore had no claim to the method of ring closure that employs zinc in the presence of protonic solvent. Gustavson published in 1887 a paper titled "Concerning a New Method of Preparation of Trimethylene."[2] Gustavson and Popper extended this method to the preparation of substituted cyclopropanes; using zinc dust-treated trimethylene dibromide gave cyclopropane.[2,3] In 1936 Hass reported addition of sodium iodide to the zinc dust and 1,3-dichloropropane reaction mixture, both the yield of cyclopropane and the conversion rate were changed singnificantly.[4]

1.1.3 Mechanism

The mechanism of Freund reaction is more likely as same as the Wurtz reaction, a free-radical mechanism. In the presence of iodide ions, the pathways might be a combination of substitution (S_N1 or S_N2) with a free-radical mechanism.[3]



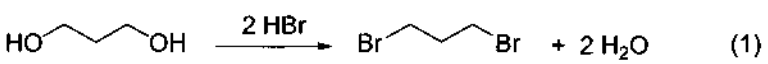
1.1.4 Variations and Improvements

Gustavson reported a new method in the preparation of cyclopropane.[2] Treating trimethylene dibromide (10 g) with zinc dust (12 g) suspended in aqueous alcohol at 50–60 °C gave cyclopropane. He tried different ratios of alcohol to water and found without water the reaction was very slow and at least 2% water was needed.

Hass has further modified the Gustavson reaction condition.[4] By using a large excess of zinc dust and by raising the temperature of the reaction mixture with high-boiling solvents, the rate of conversion was increased materially. When sodium iodide was added to a refluxing mixture of zinc dust, ethanol, and 1,3-dichloropropane, a marked acceleration of the reaction rate occurred. For example, using 1 mole of anhydrous sodium carbonate for each mole of 1,3-dichloropropane, a 100% excess of zinc dust, and 1/6 mole of sodium iodide in a solvent consisting of 75% ethanol and 25% water, a 95% yield of crude cyclopropane was obtained in 12 h in the same apparatus as before. A better yield and purer product were obtained if both sodium carbonate and acetamide were employed. The 1,3-dichloropropane was prepared by the chlorination of propane obtained from natural gas. This is called as Hass cyclopropane process.

1.1.5 Synthetic Utility

The cyclopropane was an important anesthetic in 1930s. Galasso said: "The safest anesthetic agent—the one which presents all the good qualities and none of the objectional side effects of the agents we have on hand—cyclopane."[5] This drug has been manufactured execusively by the following reaction sequence.

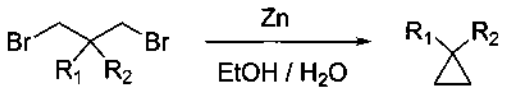


(1)

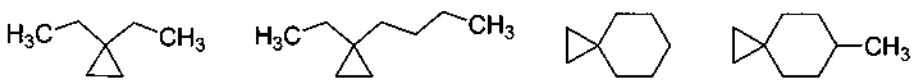
(2)

The 1,3-propanediol (trimethylene glycol) was obtained as a by-product of the soap industry, where it exists as a minor impurity in the glycerol. However, both 1,3-propanediol and hydrobromiic acid are relatively expensive compared to propane and chlorine.[4] Hass process made the production of cyclopropane more cost effective.

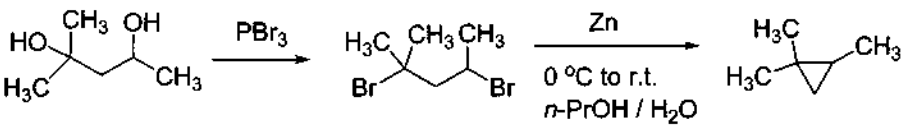
Shortridge and co-workers reported an extension of the Gustavson method for the synthesis of cyclopropane and its derivatives.[6] They successfully prepared spiranes containing a cyclopropane ring and provide an easy, straightforward way of producing this type of hydrocarbon in quantity and in a good state of purity. The corresponding dibromide **1** was cyclized by zinc in aqueous ethanol to give spirane **2** in excellent yield.



1 **2**



Yield: **3**: 92% **4**: 94% **5**: 91% **6**: 89%

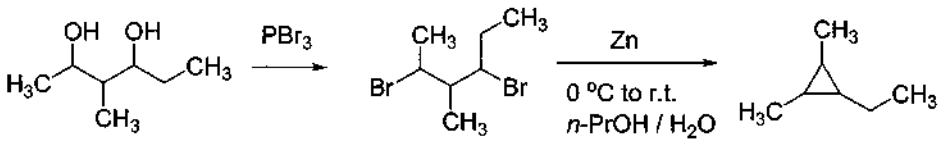


7 **8** **9**

The Freund reaction for the preparation of cyclopropane derivatives has in certain cases been unsatisfied due largely to the formation of olefins as the principal product. In general primary–primary 1,3-dibromides give high yields, primary–secondary dibromides give good yields. Secondary–secondary dibromides give fair yields, and all condensations involving a tertiary bromide give products containing an olefin as the principal or sole product. Bartleson and co-workers found that this problem can be solved at low terperature for the ring closure reaction.[7] The 1,1,2-trimethylcyclopropane **9** was prepared from 2-methyl-2,4-dibromopentane **8** by the Freund reaction at low temperature. The yield of crude product was

86% and the purity can reach 95% by fractional distillation in a high efficiency distilling column.

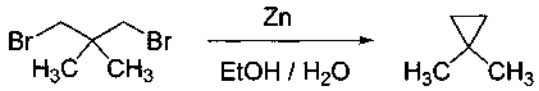
The 1,2-dimethyl-3-ethylcyclopropane **12** was similarly synthesized from 3-methyl-2,4-dibromohexane **11**.[7] A yield of 90% was obtained in the ring closure step. The secondary–tertiary and secondary–secondary 1,3-dibromides, **8** and **11**, were prepared in 90% yields by the reaction of phosphorus tribromide with the diols, **7** and **10**, at low temperature (–24 °C). The low temperature prevents the loss of hydrogen bromide from the reaction mixture.



10 **11** **12**

1.1.6 Experimental

Preparation of 1,1-dimethylcyclopropane (14)[6]



13 **14**

In a 2 L three-necked flask equipped with a dropping funnel, mercury-sealed stirrer and reflux condenser (connected to a trap surrounded by a dry ice–acetone bath) were placed 900 mL 95% ethanol, 90 mL distilled water and 628 g (9.6 mol) zinc dust; it was necessary to maintain vigorous stirring at all times to prevent caking of the zinc. The mixture was brought to gentle reflux, and 562 g (2.4 mol) of 1,3-dibromo-2,2-dimethyl-propane **13** was added dropwise at the temperature. Heating and stirring were continued for 24 h after the last of the dibromide had been added; the bulk of the hydrocarbon collected in the trap during this period. The remaining 1,1-dimethylcyclopropane (along with some alcohol) was then distilled from the reaction flask and was collected in the trap. The crude product **14** (162 g) was washed with ice water and dried. The product **12** was obtained in 96% yield (based on distilled dibromide) with these physical properties: b.p. 20.63 °C (760 mm) and n^{20}_{D} 1.3668.

Preparation of 1,1,2-trimethylcyclopropane (9)[7]

The reaction was carried out in a 1 L, three-necked flask fitted with a reflux condenser, thermometer, dropping funnel and mercury sealed stirrer. To the flask was added 100 mL water, 300 mL *n*-propyl alcohol and 196 g oxygen-free zinc dust prepared from commercial-grade zinc dust. The flask was placed in an ice-bath and 244 g (1 mol) of freshly distilled 2-methyl-2,4-dibromopentane was added dropwise with efficient stirring over a period of about 90 min. The icebath was then removed and the mixture was stirred at room temperature for about 32 h. After about 10 h an immiscible layer of hydrocarbon had formed. At the end of the reaction the hydrocarbon product was separated by distillation. The crude product **9** was collected over a temperature range of 49–51 °C and weighed 78.1 g, a yield of 86%. The refractive index of the crude product was $n^{20}{}_{D}$ 1.3847. The crude product was further purified by fractional distillation in a high-efficiency distilling column to give 95% pure product **9** with these physical properties: b.p. 52.1 °C (736 mm) and $n^{20}{}_{D}$ 1.3850.

1.1.7 References

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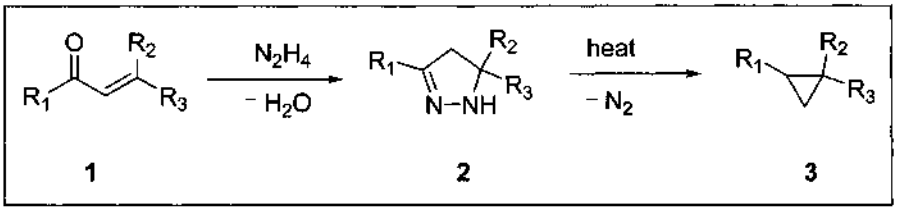
1.2 Kishner Cyclopropane Synthesis

Frank Rong

1.2.1 Description



1 2 3

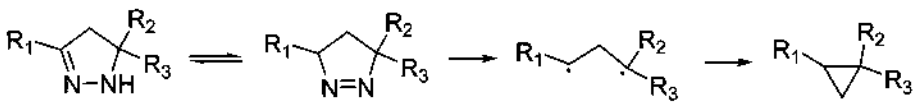
Kishner cyclopropane synthesis refers to the formation of cyclopropane derivatives **3** by decomposition of pyrazolines **2** formed by reacting α,β-unsaturated ketones or aldehydes with hydrazine.[1]

1.2.2 Historical Perspective

In 1912 Kishner and Zavadovskii reported the synthesis of phenylcyclopropane by heating decomposition of 5-phenyl-3-pyrazoline.[1] The Kishner cyclopropane synthesis has become wellknown due to its unique and the smallest cyclic core structure.[2]

1.2.3 Mechanism

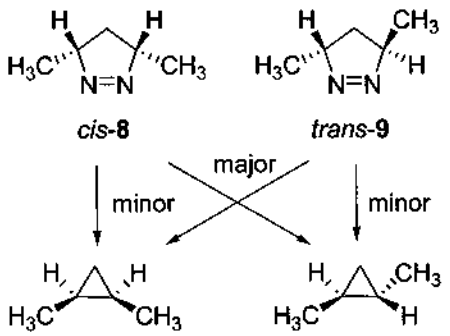
It is believable that the pyrazoline, **4** or **5**, undergoes thermolytic decomposition and gives the diradical **6** first. Then, the diradical formed a bond quickly to give the cyclopropane **7**.[2,3] This could be a reversible reaction between the diradical **6** and the cyclized product **7**.



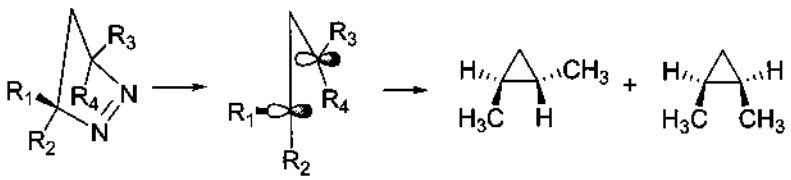
4 5 6 7

Stereochemical crossover in the pyrolysis of 3,5-disubstituted pyrazolines was proposed.[3,4] The observation of a stereochemical crossover phenomenon stimulated a consideration of the mechanism from a different viewpoint. The loss of molecular nitrogen in the pyrolysis of a *cis*-3,5-disubstituted pyrazoline, *cis*-**8**, might be expected to give a trimethylene

intermediate that could cyclized to a *cis*-disubstituted cyclopropane **10**, if internal rotations were slow, or to a mixture of *cis*- and *trans*-cyclopropanes, if internal rotations were fast. In the later case, the *cis*- and *trans*-pyrazoline, **8** and **9**, should give identical mixtures of cyclopropanes **10** and **11**. The experimental facts, however, are inconsistent with either of these models since the stereochemistry of the cyclopropane product in each case is predominantly (3:1) opposite to that of the pyrazoline. Obviously, a stereorandomized trimethylene cannot be the sole intermediate. In fact, the stereochemistry of deazetation of pyrazolines is still not completely understood.

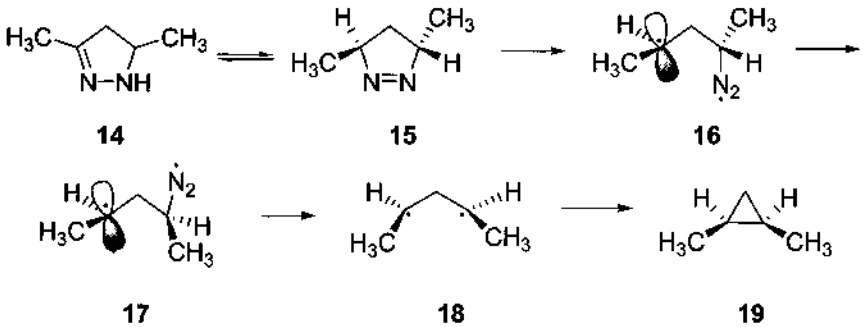


The research groups of McGreer[5,6] and Crawford[7–11] have done comprehensive investigation on the cyclic azo compounds thermal decomposition. Crawford's group investigated the stereochemistry problem in the thermal decomposition of *cis*- and *trans*-3,5-dimethylpyrazolines (**12** and **13**).[7] The major products of these decompositions are the stereoisomeric dimethylcyclopropane, and the major pathway is apparent single inversion of stereochemistry in each case. Crawford and Mishra rationalized these observations by assuming that the pyrazolines decompose in the envelope conformation leading directly to 0,0 intermediates. Predominant conrotatory closure then leads to overall single inversion of stereochemistry.[7]



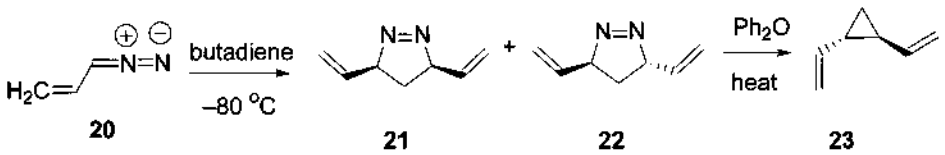
12) $R_1 = R_3 = CH_3$ and $R_2 = R_4 = H$ *trans*- 66.1% *cis*- 33.2%
13) $R_1 = R_4 = CH_3$ and $R_2 = R_3 = H$ *trans*- 25.4% *cis*- 72.6%

One of the most difficult mechanisms to rule out rigorously involves the possibility than only one C–N bond breaks initially, leading (in the case of *trans*-pyrazoline **14** or **15**) to diradical **16**. If the radical center at C-2 is now required to carry out a backside displacement of N_2 at C-4, a product of the correct stereochemistry is produced.[12] However, Crawford and his co-workers have carried out a number of elegant studied that provide support for a mechanism that involves simultaneous cleavage of both C–N bonds.[7–11]



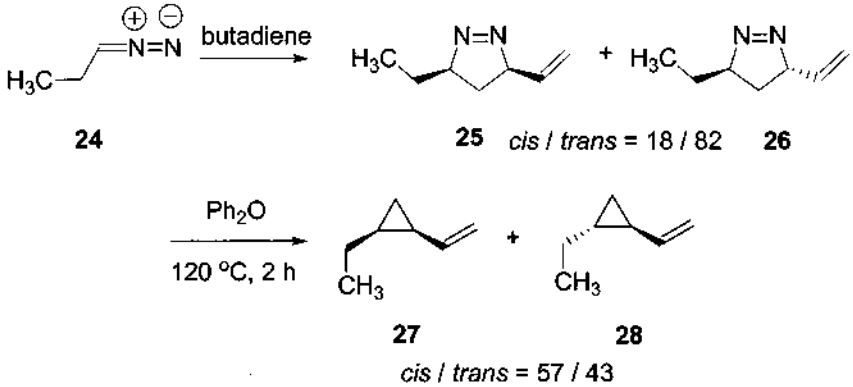
1.2.4 Variations and Improvements

A couple of different approaches in the synthesis of pyrazolines were shown. Crawford and Ohno synthesized a 40:60 mixture of *cis*- and *trans*-3,5-divinyl-1-pyrazoline, **21** and **22,** by adding a concentrated solution of vinyldiazomethane **20** in diethyl ether, purified by distillation, to a large excess of 1,3-butadiene maintained as a liquid in a pressure bottle at low temperature.[8] The intermolecular 1,3-cycloaddition of the diazoalkane proceeded more rapidly than the intramolecular cyclization to pyrazole. The kinetic of the thermolysis of these compounds in diphenyl ether at 35–65 °C producing divinylcyclopropane **23** were studied by measuring the rate of nitrogen evolution. They concluded that both carbon–nitrogen bonds are being broken in the rate determining step.[8]



The *cis*- and *trans*-3-ethyl-5-vinyl-1-pyrazoline, **25** and **26,** were similarly prepared by the cycloaddition of 1-diazopropane **24** to 1,3-butadiene.[8] The mixture of *cis*-**25** and *trans*-**26** (18% *cis*, 82% *trans*, by NMR) was heated at 120 °C for 2 h. The product proportions were

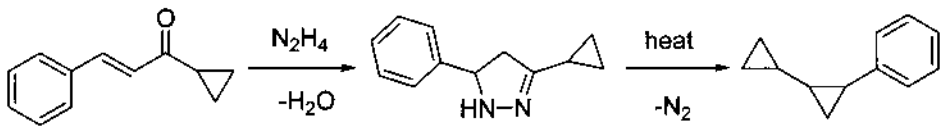
determined by GC to be 57% *cis*- and 43% *trans*-ethyl-2-vinylcyclopro-pane, **27** and **28**, respectively.



24 **25** **26** **27** **28**

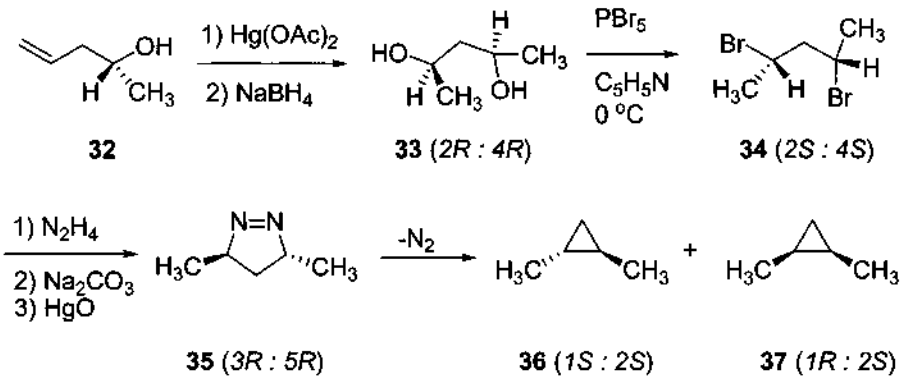
1.2.5 Synthetic Utility

A great attention has been paid on the cyclopropane derivatives after Kishner reported his discovery due to the similarities between olefins and cyclopropane with respect to both their chemical and physical properties.[2,3] Cyclopropane resembles ethylene in some respects, and both systems can enter into conjugation with other unsaturated groups such as a carbonyl group, a phenyl group, or a pyridyl group. Smith and Rogier synthesized the 2-phenylbicyclopropyl by the Kishner method.[13] The styryl cyclopropyl ketone **29** was converted to pyrazoline **30**, which was decomposed at 220 °C to give the 2-phenylbicyclopropyl **31** in 74% yield. The physical and chemical properties of this compound were also studied. The results indicated that this compound does not exhibit any of the conjugative effect shown by phenylcyclopeopane.



29 **30** **31**

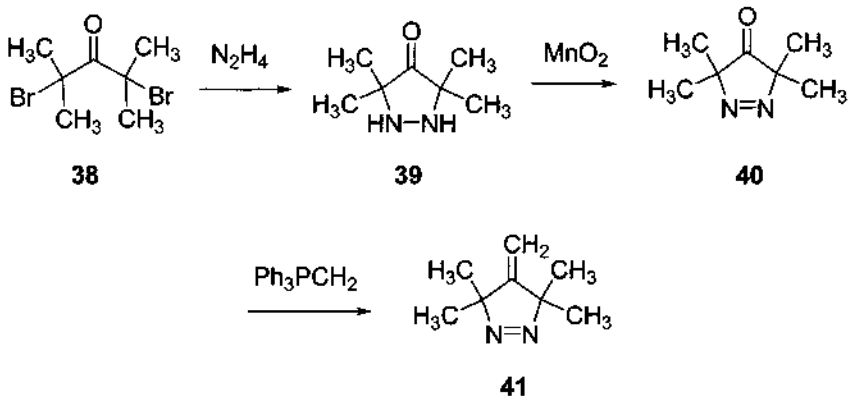
Mishra and Crawford reported the synthesis of (*3R,5R*)-(+)-*trans*-3,5-dimethyl-1-pyrazoline **35** by different approach starting from alcohol **32**.[7] The pyrazoline **35** undergoes thermolysis, producing 25.6% of *trans*-1,2-dimethyl-cyclopropane **36**, processing 23% optical purity, and having the *S:S* configuration.



32 **33** (*2R : 4R*) **34** (*2S : 4S*)

35 (*3R : 5R*) **36** (*1S : 2S*) **37** (*1R : 2S*)

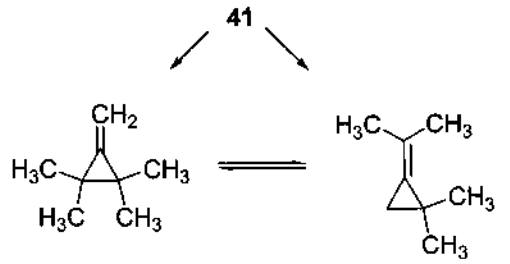
Crawford and Tokunaga synthesized 3,3,5,5-tetramethyl-4-methylene-1-pyrazoline **41** by a different approach.[10] The tetramethyl-4-pyrazolidone **39** was prepared by the reaction of hydrazine with α,α′-dibromodiisopropylketone **38**. Then oxidizing **39** by MnO_2 gives intermediate **40**, which was converted to **41** by following Mock's procedure.[14]



38 **39** **40**

41

They also studied the thermolysis of the compound **41**.[10] They found the thermolysis of **41** proceeds at 1/63 the rate of 4-methylene-1-pyrazoline. The **41** is undergoing thermolysis by a mechanism different from that for 4-methylene-1-pyrazoline. The 2,2,3,3-tetramethylmethylenecyclopropane **42** produced rapidly isomerizes under the reaction conditions to 2,2-dimethylisopropylidenecyclopropane **43**. The four opposed methyl groups of **42** have created sufficient ground state destabilization as to cause its isomerization to be 147 times faster than the conversion of 2,2-dimethylmethylenecyclopropane **44** to isopropylidenecyclopropane **45**.

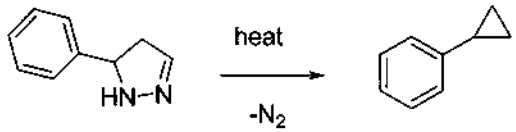


42 43

44 45

1.2.6 Experimental

Preparation of phenylcyclopropane 47.[15]



46 47

A mixture of 118 g 5-phenyl-3-pyrazoline **46**, prepared by published procedure; 30 g pulverized potassium hydroxide; and 2.5 g platinized asbestos was heated in a 1 L, three-necked flask equipped with a stirrer and a Claisen distillation head. The temperature was raised slowly and the heat was shut off at the first sign of reaction. When the exothermic reaction ceased the temperature was again raised and the product was distilled. Both the distillate and the residue were steam distilled and the steam distillate was taken up in ether and dried first with sodium sulfate and then with sodium and redistilled. The product **47** was collected at 60–63 °C (11 mm Hg) and was finally redistilled giving a colorless oil, 11.5 g (12%), b.p. 173.5 °C (740 mm Hg), and n^{20}_{D} 1.5320.

Preparation of 2-phenylbicyclopropyl (31)[13]

Preparation of 3-cyclopropyl-5-phenyl-2-pyrazoline (30): Styryl cyclopropyl ketone **29** (42 g, 0.245 mol) was added to a solution of aqueous hydrazine (25 mL, 0.42 mol) in ethanol (95%, 70 mL); the mixture became

warm and acquired a green color. It was allowed to stand for 45 min., then warmed on the steambath for 1 h, after which excess hydrazine and solvent were removed under reduced pressure. Distillation of the residue gave **30** as a light green liquid (37.8 g, 86%), which boiled at 164 °C (1 mm Hg).

Preparation of 2-phenylbicyclopyl (31): Powdered potassium hydroxide (7.2 g) and platinized asbestos (3.2 g) were placed in a 100 mL round-bottomed flask arranged for distillation, and immersed in a metal bath. The bath was heated to 220 °C (thermometer in the bath), and the pyrazoline **30** (38.8 g, 0.2 mol) was slowly added. After the rapid evolution of nitrogen cased, the product **31** was distilled from the reaction mixture; it distilled at 92–96 °C (0.8 mm Hg), and weighed 22.5 g (74%). The products from several runs were combined and fractionated through a column (15 × 1.5 cm) packed with glass helices. A center cut was taken for analysis. This boiled at 57 °C (0.12 mm), and had $n^{20}{}_{D}$ 1.5352, $d^{20}{}_{4}$ 0.9587, and molar refraction 51.40.

1.2.7 References

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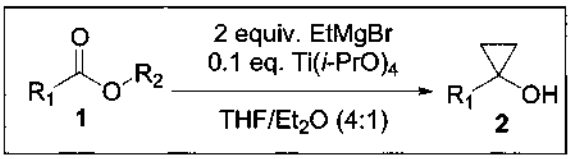
1.3 Kulinkovich Cyclopropanol Synthesis

Jie Jack Li

1.3.1 Description



Kulinkovich cyclopropanol synthesis, also known as Kulinkovich reaction or Kulinkovich cyclopropanation, is titanium-catalyzed transformation of esters **1** to its corresponding cyclopropanols **2**.[1–9] The EtMgBr/Ti(*i*-OPr)$_4$ mixture resulting in bis-ethoxytitanacyclopropane is known as the Kulinkovich reagent, which is considered a synthetic equivalent of a two-carbon-1,2-dianion synthon ($^{\ominus}CH_2CH_2^{\ominus}$).

1.3.2 Historical Perspective

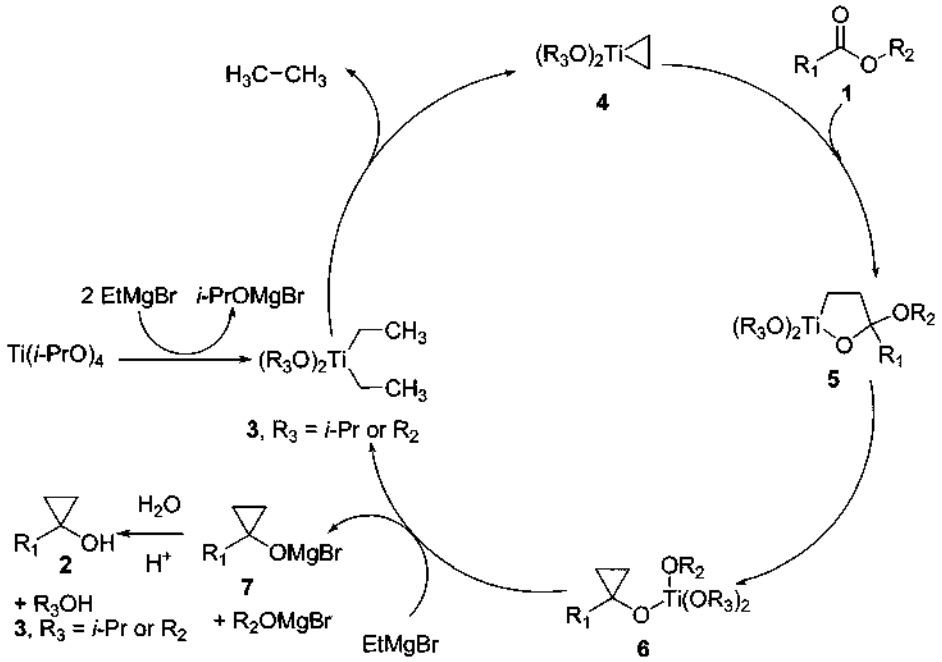
Professor Oleg Grigor'evich Kulinkovich,[10] a student of I. G. Tischenko of the Tischenko reaction fame, discovered the titled reaction in 1989 at Belorussian State University.[11–14] The unprecedented transformation has received great attention and utility, as testified by the references cited herein.

1.3.3 Mechanism

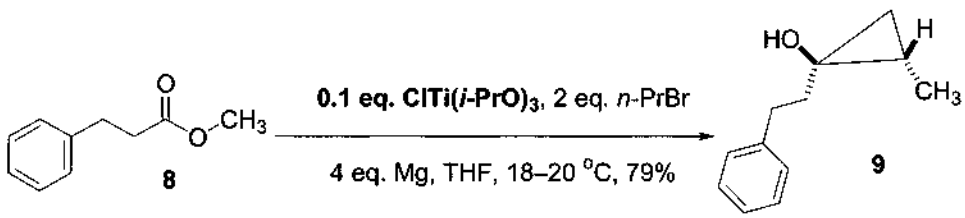
Kulinkovich himself proposed that the dialkoxytitanacyclopropanes as the key intermediate in the Kulinkovich cyclopropanation.[12] Extensive theoretical study on mechanism was published in 2001.[15] Eisch also provided detailed exploration of the mechanism for the Kulinkovich reaction in 2003.[16] In 2007, Kulinkovich proposed a modified "ate" complex mechanism for titanium-mediated cyclopropanation of carboxylic esters with Grignard reagents.[17]

Summing up the state-of-the-art understanding, the mechanism may be described as the following: When Ti(O*i*-Pr)$_4$ was mixed with the ethyl Grignard reagent, they react to provide diethyl titanium intermediate **3**, which immediately undergoes β-elimination with formation of the titanacyclopropane **4** and with release of ethane gas. Next, a nucleophilic attack at the ester carbonyl furnishes the titanoxacyclopentane **5**. Rearrangement to the homoenolate with concomitant activation of the carbonyl group allows for an intramolecular attack of the titanium–carbon

bond to give the titanium cyclopropane alkoxide **6**. Metal exchange reaction with excess of Grignard reagent liberates the product as the magnesium alkoxide **7** and regenerates the catalytically active species **3**.



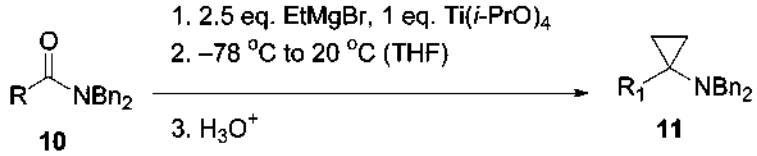
1.3.4 Variations and Improvements



Initially, the ethyl Grignard reagent was successfully employed in the prototypical Kulinkovich reaction. In 1994, Corey demonstrated that when chlorotitanium(IV) triisopropoxide was better suited for higher substituted Grignard reagents, such as *n*-butylmagnesium bromide, can be used.[18] As exemplified by transformation **8** to **9**, the reaction was completely diastereoselective to give the *cis*-1,2-dialkylated cyclopropanol **9**. Furthermore, Corey also carried out the preliminary studies of an enantioselective version of the cyclopropanol synthesis with promising

results. Employing a chiral TADDOL-based titanium reagent, 85:12 to 89:11 enantio-selectivity was achieved.

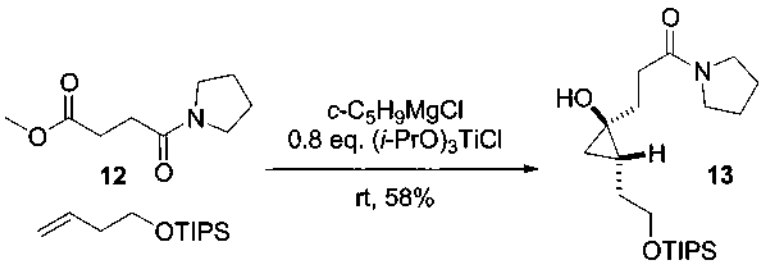
The other significant variation of the prototypical Kulinkovich reaction is the so-called Kulinkovich–de Meijere reaction, where de Meijere extended the substrates from esters to amides.[19,20] Other carboxylic acid derivatives including (cyclic) carbonate, imides, and nitriles also react with the key Kulinkovich intermediate. Szymoniak[21] developed an efficient new synthesis of cyclopropanes via hydrozirconation of allylic ethers (e.g., using $Cp_2Zr(H)Cl$) followed by addition of a Lewis acid (e.g., $BF_3{\bullet}OEt_2$). Casey et al. further investigated the stereochemistry of this interesting cyclopropanation reaction using deuterated allylic ethers.[22]



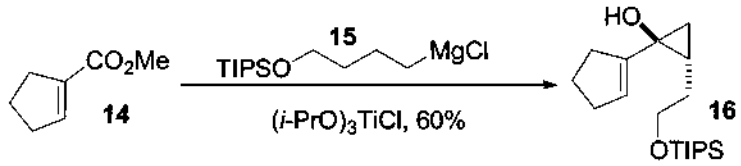
1.3.5 Synthetic Utility

1.3.5.1 General Utility

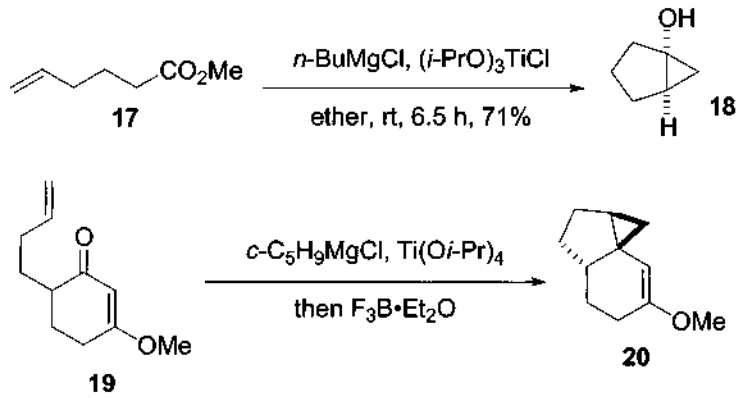
In general, esters, acid chlorides, and anhydrides are most reactive toward the Kulinkovich reagent. Carbonates and thioesters are of moderate reactivity, whereas carbonamides are least reactive. Case in point was made by chemoselective Kulinkovich reaction of succinic ester–amide **12**.[23] Cha observed that only the ester portion underwent the Kulinkovich reaction to afford cyclopropanol **13**. Szymoniak[24] demonstarted that nitriles are more reactive than ester and amides.



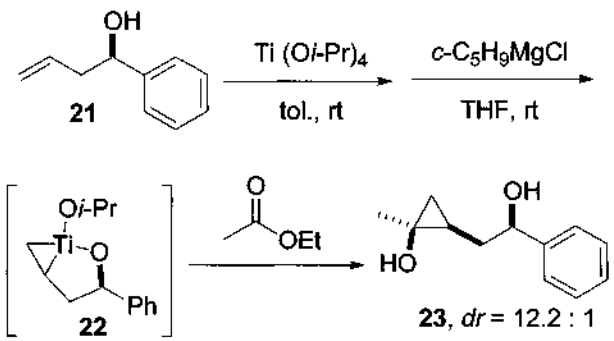
Cha's group was among the earlier researchers to investigate and extend the utility of the Kulinkovich reaction. Employing 4-alkoxybutyyl Grignard reagents such as **15** (several other Grignard reagents such as 2-phenethylmagnesium bromide did not work) and chlorotitanium(IV) triiso-propoxide converted cyclopropanol **16** as a single diastereomer.[25]



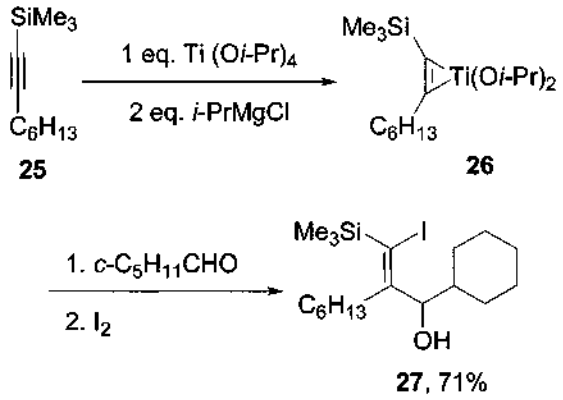
An important contribution from Sato[26] and Cha[27] was their successful extension of the Kulinkovich reaction to the intramolecular version. For instance, reductive coupling of carboxylic ester **17** with a terminal olefin provided bicyclo[3.1.0]hexan-1-ol (**18**) in 71% yield.[27] Cha also extended the low-valent titanium-mediated cyclopropanation to vinylogous esters as substrates. An interesting application is an intramolecular version of the methodology that transformed vinylogous ester **19** with a pendent terminal olefin to tricycle **20**.[28]

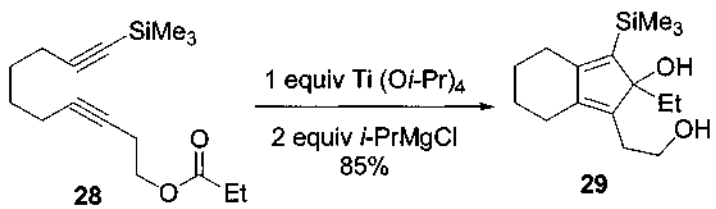


Cha also explored substrate directed asymmetric synthesis using the Kulinkovich reaction. Sequential treatment of homoallylic alcohol **21** with $Ti(O\textit{i}\text{-}Pr)_4$ and *c*-C_5H_9MgCl furnished the putative intermediate **22**, which upon exposure to ethyl acetate produced *trans*-1,2dialkylcyclopropanol **23** in 12.2 : 1 *dr*.[29]

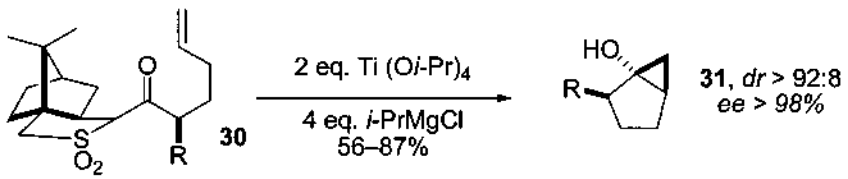


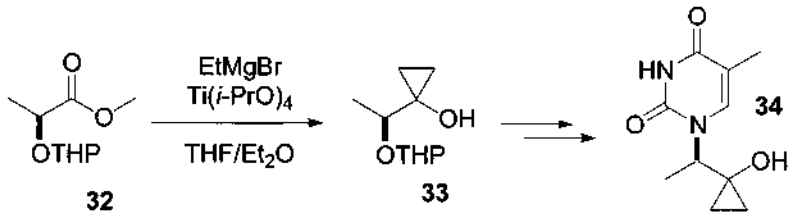
Sato and colleagues discovered a new titanium complex, (η^2-propene)Ti(O*i*-Pr)$_2$ (**24**), generated in situ, by treatment of Ti(O*i*-Pr)$_4$ with 2 equiv of *i*-PrMgX.[3] Compond **24** was proven to a versatile reagent in synthetic reactions involving alkynes. At the onset of the investigation, the Sato group soon discovered that use of *i*-PrMgX as the Grignard reagent was very important for generating a titanium compound that afforded alkyne–titanium complexes by the reaction with alkynes.[30] When silyl alkyne **25** was treated with **24**, the putative complex **26** was formed. Exposure of **26** to cyclopentyl aldehyde was followed by iodine to afford adduct **27** in 71% yield. An intramolecular version of the aforementioned transformation has been developed. Therefore, intramolecular coupling of diyne **28** provided [5,6]-bicyclic cyclopentadienol **29**.[31]



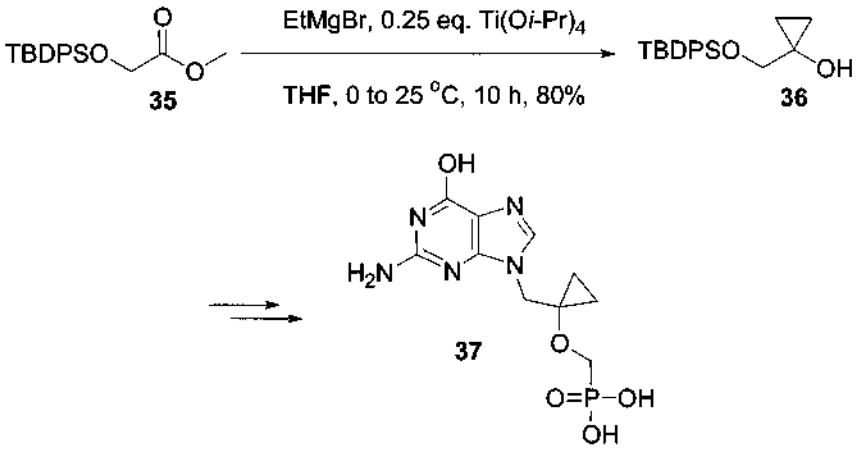


In addition, Sato et al. developed an interesting enantioselective synthesis of bicyclic cyclopropanols **31** from *N*-acylcamphorsultam (the Oppolzer's chiral auxiliary) derivatives **30**.[32]



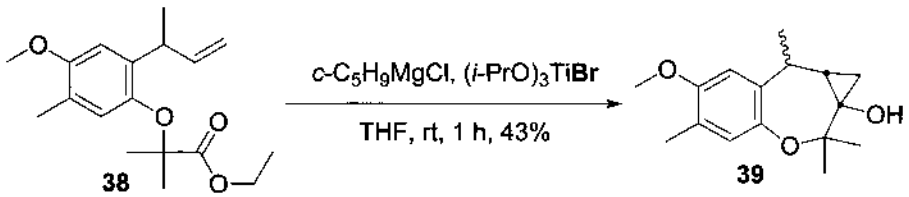


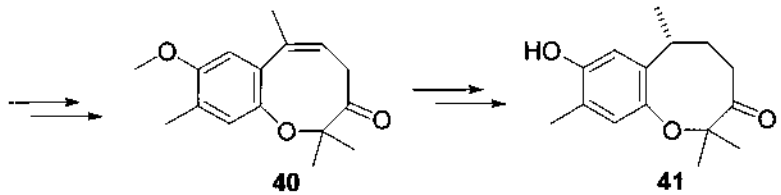
In the realm of medicinal chemistry, cyclopropanol provides a unique rigidity for the side chain. For instance, cyclopropanol **33**, from ester **32**, was incorporated into nucleoside **34**, an analogue of acyclovir.[33] Similarly, ester **35** was converted to cyclopropanol **36**, which was assembled onto guanine **37**, an anti-HBV agent.[34]



1.3.5.2 Applications in the total synthesis of natural products

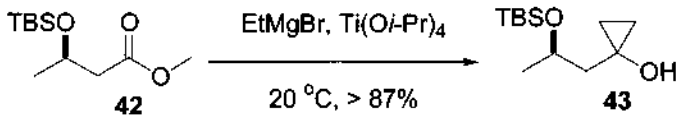
Ollivier and co-workers used the Kulinkovich reaction in their total synthesis of heliannuols K and L.[35,36] Thus, conversion of ester **38** with pendent olefin to cyclopropanol **39** was achieved using **bromo**titanium(IV) triisopropoxide and cyclohexyl Grignard reagent. Cyclopropanol **39** then underwent oxidation using $FeCl_3$ and dechlorination to yield benzoxocinone **40**, an intermediate for both heliannuols K (**41**) and L.



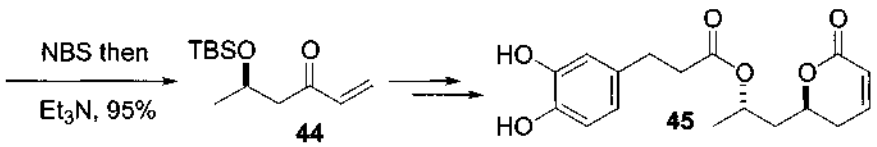


40 41

Singh's group converted ester **42** to its corresponding cyclopropanol **43**, which was treated with NBS and then Et_3N to deliver enone **44** via the intermediacy of β-bromoketone.[37] Enone **44** was transformed to tarchonanthuslactone **45**.

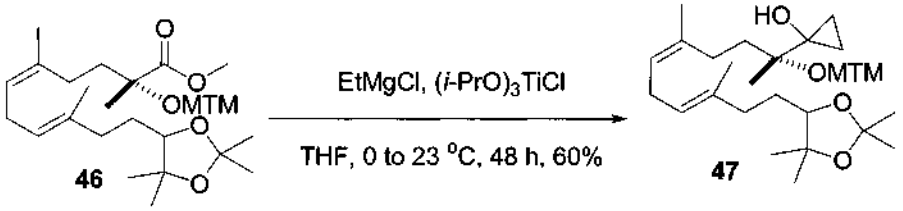


42 43

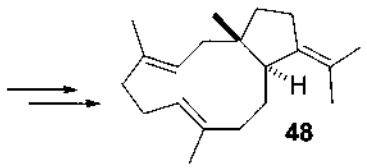


44 45

Corey employed the Kulinkovich reaction in the total synthesis of β-arianeosene (**48**).[38] Ester **46** was converted to cyclopropanol **47**, which served as the substrate to make cyclobutanone by treating **47** with $Al(Me)_3$.



46 47



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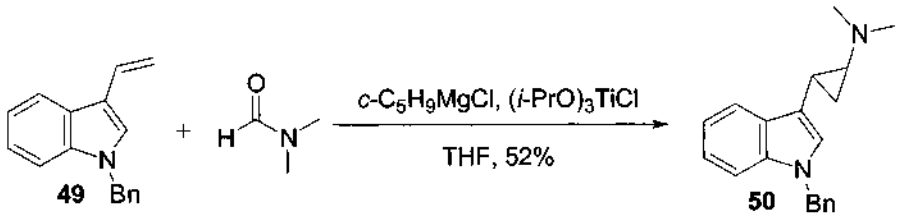
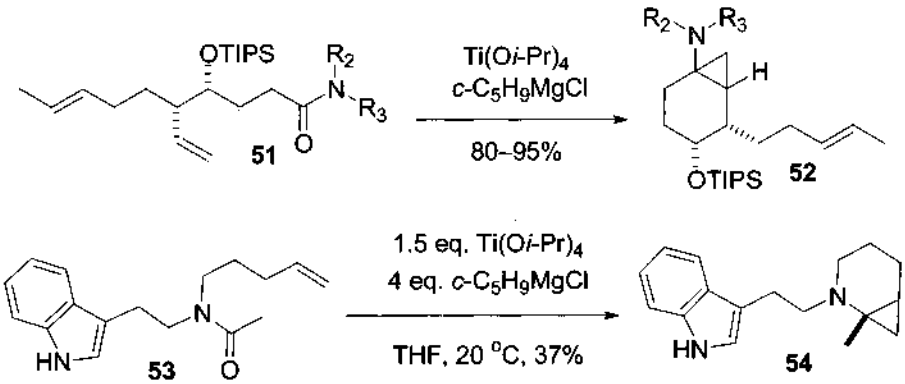
1.3.5.3 Utility of the Kulinkovich–de Meijere reaction



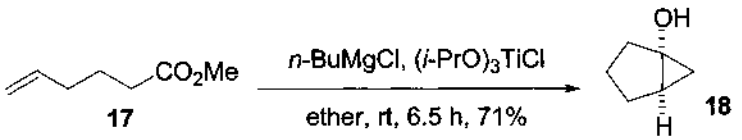
Joullié took advantage of the Kulinkovich–de Meijere reaction and synthesized a series of constrained *N,N*-dialkyl neurotransmitter analogues.[39] For instance, indolylcyclopropylamine **50** was assembled from indole-olefin **49** and DMF in 52% yield.

While intermolecular Kulinkovich–de Meijere reaction assembles cyclopropylamine, many have taken advantage of a pendent olefin at the substrates to synthesize bicycles. Cha converted olefinyl amide **51** to bicyclic amine **52** in excellent yields.[40] Six and co-workers prepared eight bicyclic aminocyclopropanes including **54** (from substrate **53**) with yields ranging from 26 to 87%.[41,42]



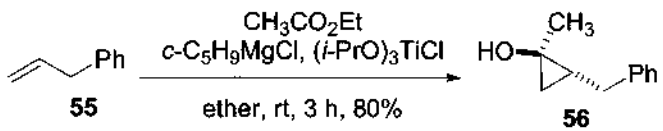
1.3.6 Experimental

1.3.6.1 Intramolecular Kulinkovich cyclopropanation reaction of carboxylic ester with olefin: bicyclo[3.1.0]hexan-1-ol (2)[43]



To a 500-mL, round-bottomed flask, equipped with a magnetic stirring bar and rubber septum, is added at room temperature a mixture of 2.0 g (15.6 mmol) of methyl 5-hexenoate (**17**, 11.2 mL, 11.2 mmol) of a 1 M solution of chlorotitanium triisopropoxide in hexane, and 54 mL anhydrous ether under a nitrogen atmosphere. A 1 M solution of *n*-butylmagnesium chloride in ether (52 mL, 52 mmol) is added over a period of 6.5 hr via a syringe pump at room temperature. After the addition is complete, the resulting black reaction mixture is stirred for an additional 20 min. The mixture is cooled to 0 °C with an ice bath, diluted with 50 mL ether and then quenched by slow addition of water (14 mL). The resulting mixture is stirred for an additional 3 h at room temperature. The organic phase is separated and the aqueous phase is extracted with ether (3 × 100 mL). The combined organic extracts are washed with brine (2 × 50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator. Purification of the crude product by column chromatography on 40 g silica gel using a gradient of 5% to 10% ether/pentane as the eluent provides 1.09 g (71%) of bicyclo[3.1.0]hexan-1-ol (**18**) as a colorless oil.

1.3.6.2 Intermolecular Kulinkovich cyclopropanation reaction of carboxylic ester with olefin: *trans*-2-benzyl-1-methylcyclopropan-1-ol (56)[43]



To a 500 mL, round-bottomed flask, equipped with a magnetic stirring bar and rubber septum, is added a mixture of 2.5 g (21 mmol) allylbenzene (**55**, 2 mL, 20 mmol) ethyl acetate, 20 mL of a 1 M solution of chlorotitanium triisopropoxide in hexane, and 160 mL anhydrous tetrahydrofuran (THF). After the mixture has been cooled to 0 °C with an ice bath under a nitrogen atmosphere, a 1 M solution of cyclopentylmagnesium chloride in ether (80 mL, 80 mmol) is added over a period of 2.5 h via a syringe pump. After the addition is complete, the resulting black reaction mixture is stirred for 30 min at 0 °C, then is quenched by the cautious addition of water (15 mL). The resulting mixture is stirred for an additional 1 h at room temperature and filtered through a pad of Celite, which is rinsed thoroughly with ether (4 × 50 mL). The combined filtrate and rinsings are poured into a separatory funnel containing 50 mL water and shaken thoroughly. The organic phase is separated, washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator. Purification of the crude product (obtained as a pale yellow oil)

by column chromatography on 80 g silica gel using 1:20 ethyl acetate:hexane as the eluent provides 2.6 g (80%) *trans*-2-benzyl-1-methylcyclopropan-1-ol (**56**) as a colorless oil.

1.3.7 References

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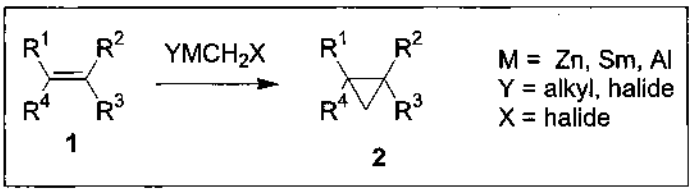
1.4 Simmons–Smith Cyclopropanation

Matthew J. Fuchter

1.4.1 Description

The stereospecific addition of a metal carbenoid (mainly zinc based) to a double bond is known as the Simmons–Smith cyclopropanation.[1–6] It is one of the most powerful methods of converting olefins to cyclopropanes.

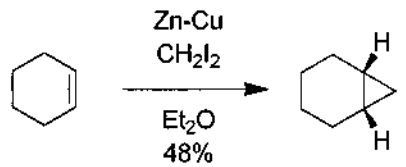


The classical conditions use the zinc-copper couple (Zn–Cu) and diiodomethane to prepare the active carbenoid species, although there are alternative conditions (see 1.4.5.1), the most important being the Furukawa modification, which uses diiodomethane in the presence of diethylzinc. Samarium and aluminium carbenoids are also effective as cyclopropanating reagents (see 1.4.5.2). The reaction can be performed in a range of solvents, however, increased rates are observed in noncoordinating solvents such as dichloromethane. A wide range of alkenes can be used, including simple olefins, α,β-unsaturated systems, and electron-rich alkenes such as enol ethers. In general, the reaction conditions are highly tolerant of most functional groups. The reaction takes place stereospecifically whereby the stereochemistry of the double bond is preserved in the product. If a substituted methylene group is added to the double bond, in the majority of cases a *syn* product is observed. Many polar functional groups (OH, OAc, OMe, NHR) have a directing effect on the cyclopropanation either enabling regioselective reactions for substrates containing multiple double bonds, or stereoselectivity for chiral substrates. Asymmetric Simmons–Smith cyclopropanations are possible by either using stoichiometric chiral auxiliaries, or by the use of chiral catalysts (see 1.4.4.3.3).

1.4.2 Historical Perspective

In 1958, Howard Simmons and Ronald Smith reported a general method for preparing cyclopropane compounds from olefin substrates.[7,8] For example, cyclohexene (**3**) was converted to cyclopropane **4** in moderate yield. The development of this method was built on earlier work by Emschwiller in

1929, who reported the preparation of diiodomethane and its reaction with the zinc-copper couple to form iodomethyl zinc iodide.[9] In fact, even Emschwiller's studies were preceded by extensive work from numerous other chemists, with the reaction of diiodomethane and a variety of metals attracting attention ever since the 1860s. In the field of cyclopropane synthesis, the procedure developed by Simmons and Smith was particularly notable for its broad generality. At the time, the only other viable options were the classical addition of diazo compounds to olefins,[10] or the production and use of dihalocarbenes.[11]



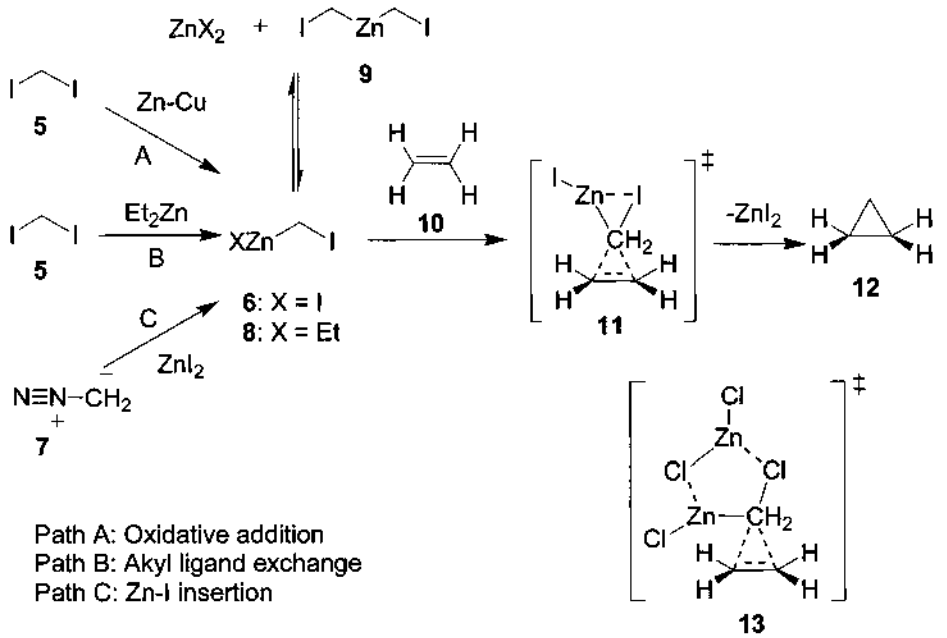
3 **4**

The only downside of this method was the irreproducibility of generating the active reagent from the zinc-couple and diiodomethane. Furukawa and co-workers provided one solution in 1966 when they showed that a mixture of diethyl zinc and diiodomethane gives very reproducible results in generating the active reagent (see 1.4.5.1 for this and other methods).[12] It has subsequently been shown that other carbenoid species, including samarium[13] and aluminium,[14] are also effective reagents in the cyclopropanation reaction, and in some cases demonstrate interesting chemoselectivity. Nowadays, the Simmons–Smith reaction has developed into one of the most powerful methods of cyclopropane formation available to synthetic chemists. Indeed, in their 2001 review, Charette and Beauchemin documented all the examples of the Simmons–Smith reaction to appear in the literature between 1973 and 1999, and this totaled more than 1500 olefin substrates. Since the 1990s, the major developments in the Simmons–Smith reaction have focused on asymmetric methods to stereoselectively prepare chiral cyclopropanes. One of the most widely used methods in this regard originates from a report by Charette and co-workers in 1994 on the use of chiral dioxaborolane auxiliaries (see 1.4.4.3.2).[15]

1.4.3 Mechanism

Simmons–Smith cyclopropanation proceeds via the addition of a zinc carbenoid (**6**/**8**) to an olefin. There are three classes of reactions, however, that can generate the reactive zinc species, each with it is own mechanistic pathway.[5] The oxidative addition of an activated form of zinc metal into a C–X bond is by far the most widely used method for the formation of **6**

(Pathway A). Indeed, it was this method that Simmons and Smith first used in their seminal study,[7,8] with many methods of zinc activation available (see 1.4.5.1). Furukawa's modification of the reaction uses diethyl zinc, and proceeds via alkyl ligand exchange to give **8** (Pathway B). Finally, Wittig reported the insertion of diazomethane (**7**) into zinc iodide to give **6**,[16] although this method is not widely used.



Zinc carbenoids **6** and **8** are in Schlenk equilibria with dialkyl zinc **9** and ZnX_2, although the position of the equilibrium depends on the counter ligand X. Spectroscopic studies have shown that in the case of iodomethyl zinc iodide (**6**), the equilibrium lies strongly in favour of the active species **6**.[17,18] For ethyl-substituted carbenoid **8**, however, Et_2Zn and dialkyl zinc **9** are far more prevalent, and an additional self-destructive pathway is apparent, giving rise to PrZnI.[17] Since this destructive reaction can be competitive with cyclopropanation, in certain cases it may be advantageous to add additional diiodomethane (to convert PrZnI to the active species).

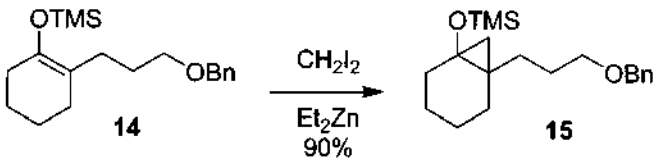
After generation of the active species, the reaction proceeds via concerted addition of the methylene group to the olefin substrate with retention of configuration. This process was postulated to proceed via a three-centre "butterfly-type" transition state **11** on the basis of experimental observations, and numerous theoretical calculations are in agreement with this postulate.[5] However this transition state may not be the favoured reaction pathway under all relevant experimental conditions. For example,

theoretical studies on the cyclopropanation of ethylene with chloromethylzinc chloride, in the presence of zinc chloride indicated the five-centered complex **13** to be the kinetically favoured transition state.[19]

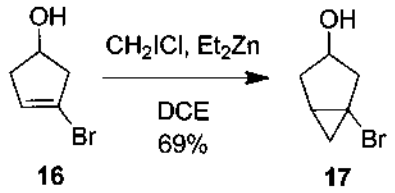
1.4.4 Synthetic Utility

1.4.4.1 Substrate Scope

The Simmons–Smith reaction is a broadly applicable procedure and has a wide-ranging functional group tolerance. In general, higher reactivity is observed with electron-rich alkenes, due to their increased nucleophilicity. Enol ethers are just one example of substrates whose cyclopropanation under the reaction conditions is generally facile.[5] Silyl enol ethers are the most widely used in this regard since they are readily available from enolization of the corresponding ketone. For example, substrate **14** was converted to **15** in excellent yield using Furukawa's conditions (see 1.4.5.1).[20]

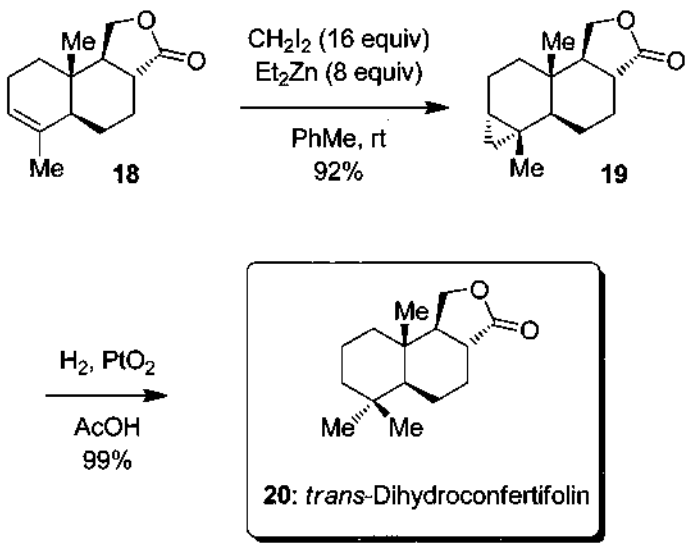


The cyclopropanation of vinyl halides is also effective, with fluoro-, bromo- and iodo-substituted olefins all being suitable substrates. For example, vinyl bromide **16** underwent the reaction in good yield, using Denmark's modification of the reaction (see 1.4.5.1).[21]



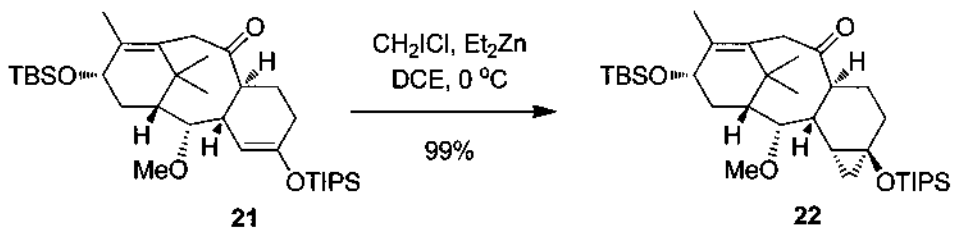
While the classical Simmons–Smith regent (Zn/Cu) is often used, Furukawa's conditions (Et_2Zn/CH_2I_2, see 1.4.5.1) are the preferred choice for less reactive olefin substrates. This is since generation of the active carbenoid under Furukawa's conditions can be performed in noncomplexing solvents, which in turn, leads to a reagent with a higher electrophilicity.[5] Taber and co-worker's synthesis of *trans*-dihydroconfertifolin (**20**) employed such conditions in their endgame strategy, cyclopropanating substrate **18** in

excellent yield.[22] The resulting cyclopropane was subjected to catalytic hydrogenolysis to give *trans*-dihydroconfertifoin (**20**).



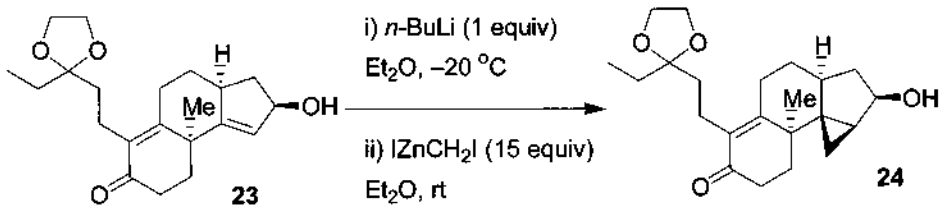
1.4.4.2 Regioselectivity and Stereoselectivity

When more than one double bond is available to react within a substrate, a combination of both steric and electronic effects control the regioselectivity of cyclopropanation.[5] In light of the electrophilic nature of the reagent, highly regioselective Simmons–Smith reactions are observed when one double bond is significantly more nucleophilic than another. For example, the high reactivity of enol ethers can be used to obtain excellent regioselectivity. Winkler et al. capitalized on such high regioselectivity in their conversion of substrate **21**, into cyclopropane **22**, a key derivative in the synthesis of taxol analogs.[23]

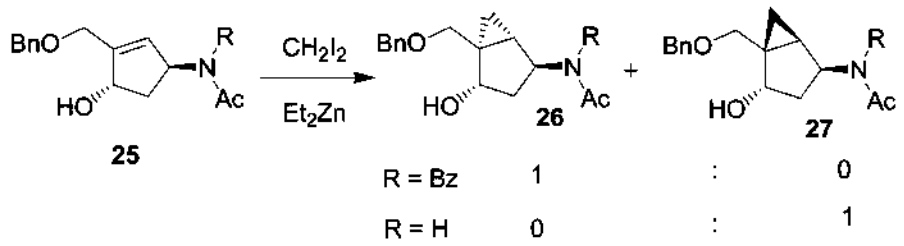


Polar functionality remote from the double bond can also be used to direct both the regioselectivity and stereoselectivity of the Simmons–Smith reaction. Much work has been performed on the directing effect of basic

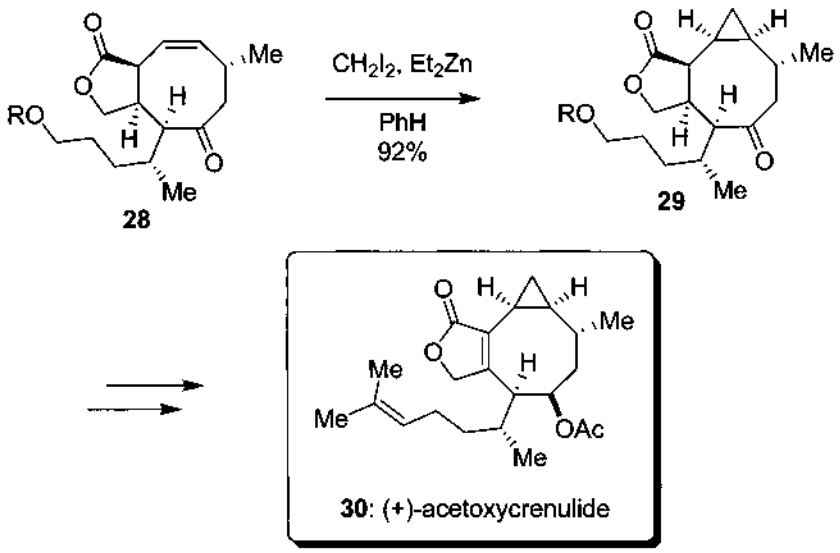
functional groups in the allylic position of cyclic alkenes.[5] Indeed, it was recognized early on that proximal hydroxyl groups can direct the cyclopropanation reaction.[24] In general, cyclopropanation of five-, six-, and seven-membered ring 1-cycloalken-3-ols proceed with high levels of *syn* selectivity.[6] Such diastereoselectivity has been used to good effect, even with more complex substrates, such as the use of derivative **23** by Corey and co-workers.[25] It is interesting that a switch in selectivity is observed with the analogous eight- and nine-membered ring systems. In these cases, high *anti* selectivity is often observed, a fact that can be readily rationalized by the conformation of the ground state molecule.[6]



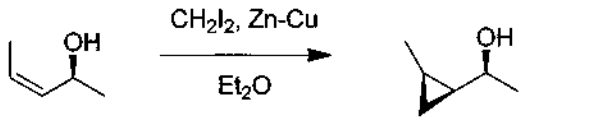
While the hydroxyl group has been most extensively used to direct the Simmons–Smith reaction, other basic groups such as ethers, esters and acetamides are also able to direct the zinc reagent in certain cases.[5] For example, in the case of substrate **25**, the unsubstituted acetamide (R = H) is a better directing group than the hydroxyl group, giving cyclopropane **27** as the sole stereoisomer. Once benzoylated however (**25**, R = Bz), the selectivity is reversed, resulting in the selective formation of compound **26**.[26]



In the absence of a directing group, the cyclopropanation of cyclic olefins is generally under steric control. The stereochemical preference can be predicted from the ground state conformation of the molecule and often high levels of stereocontrol are observed. For example, Paquette and co-workers used a Simmons–Smith reaction in their total synthesis of the secondary marine metabolite (+)-acetoxycrenulide (**30**), whereby high β-face selectivity was observed.[27]



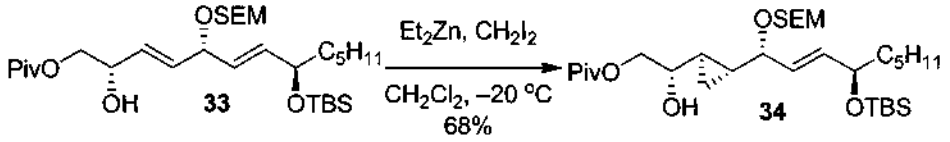
The stereoselective Simmons–Smith reaction of a chiral acyclic allylic alcohol was first reported by Pereyre and co-workers in 1978.[28] They observed very high *syn* selectivities (> 200:1) when (*Z*)-disubstituted olefins such as **31** were treated under classical Simmons–Smith conditions. The analogous reaction of (*E*)-olefins however was reported to only give modest selectivity (< 2:1). In depth studies by Charette and co-workers however has revealed that the nature zinc carbenoid used in these reactions is key to obtaining high selectivities.[29,6] While in the case of simple (*E*)-disubstituted olefins, the classical Simmons–Smith conditions (Zn–Cu, CH_2I_2, Et_2O) gives only modest selectivity, the use of Furukawa's reagent (Et_2Zn, CH_2I_2) in excess produces a much higher degree of selectivity, especially when dichloromethane is used as the solvent.[29,6] Indeed, these trends are generally maintained for more complex acyclic systems, although it should be stated that stereoelectronic effects also play an important role.[6]

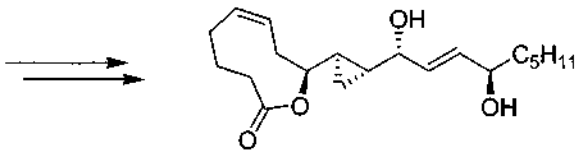


31 **32** *syn*:*anti* >99:1

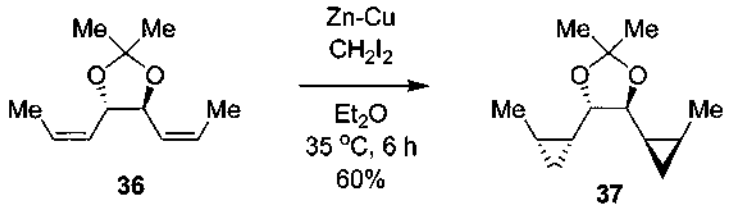
Impressive regioselectivity and stereoselectivity has been reported for a number of complex acyclic systems, including the synthesis of halicholactone (**35**) by Takemoto and co-workers. In their total synthesis, substrate **33** was converted into the desired product **34** in good yield and total

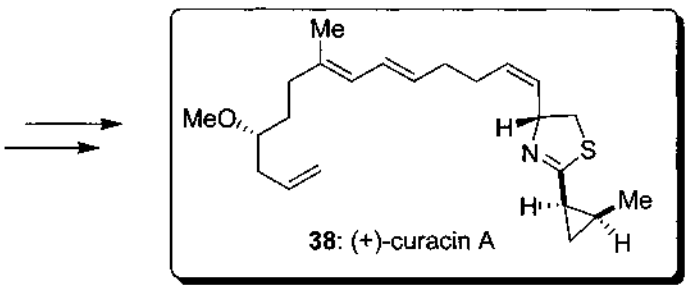
selectivity.[30,31] It is interesting that a hydroxyl group was required to direct the reaction (an acetal being ineffective), and the protecting groups used were crucial to its success.





35: halicholactone



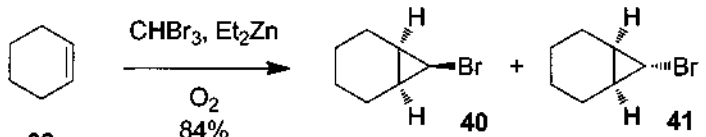


As is the case with cyclic substrates, other basic functional groups are able to effectively direct the reaction in certain cases. An impressive example was reported by Iwasaki and co-workers in their synthesis of the antimitotic agent (+)-curacin A (**38**), whereby an acetal oxygen was used to direct the reaction.[32] In a two-directional approach, substrate **36** was converted into product **37** as a single diastereoisomer in good yield. This compound was subsequently deprotected and subjected to oxidative cleavage to give the desired 2-methylcyclopropane carboxylic acid, which was required to form the thiazoline portion of curacin A. Indeed, such a stereoselective two-directional cyclopropanation of tartrate derived substrates had been

previously reported by Barrett and co-workers and used in their total synthesis of FR-900848.[33,34]

The stereocontrol in acyclic chiral olefins in which the basic directing group is not the stereogenic centre is generally quite poor.[6] One exception to this rule however, was reported by Panek et al., who demonstrated that a stereogenic bulky silicon group in the allylic position of acyclic substrates can induce good diastereoselectivities.[35]

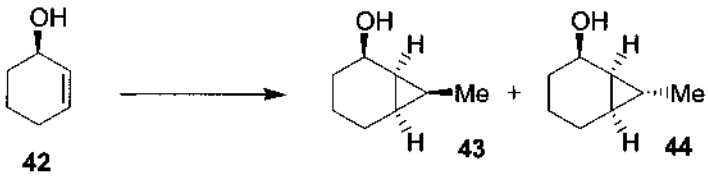
In terms of the synthesis of substituted cyclopropane derivatives using either halo- or alkyl-substituted reagents, *endo*:*exo* selectivity of the product is often poor.[5] For example, cyclohexene (**39**) was converted into an approximately 2:1 ratio of **40** and **41** on exposure to bromoform and diethylzinc.[14]



39 **40** **41**

1.9 : 1

The use of directing groups is effective at controlling the relative stereochemistry of the cyclopropane and the directing functionality, however once again, *endo*:*exo* selectivity is usually modest. For example, relatively poor selectivity was observed in the conversion of substrate **42** into derivative **44**, although the samarium-derived reagent (see 1.4.5.2) provided slightly better results.[36]

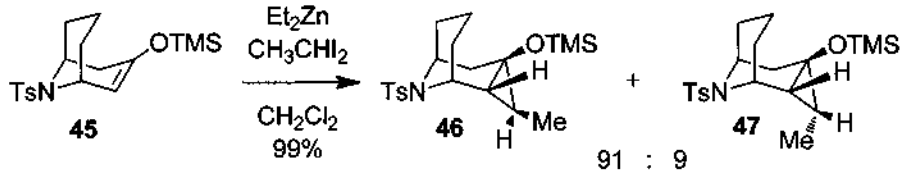


42 **43** **44**

Sm, $MeCHI_2$ (> 99%)	17	:	83
Et_2Zn, $MeCHI_2$ (64%)	37	:	63
Zn-Cu, $MeCHI_2$ (84%)	28	:	72

As is usually the case, however, specific results are dependent on the substrate in question, and the selectivity observed a case of both steric and electronic factors. For example, in their enantioselective synthesis of (–)-pinidine, Momose et al. reported a highly diastereoselective reaction employing the reagent derived from 1,1-diiodoethane and diethyl zinc.[37] Substrate **45** was selectively converted to stereoisomer **46** in excellent yield.

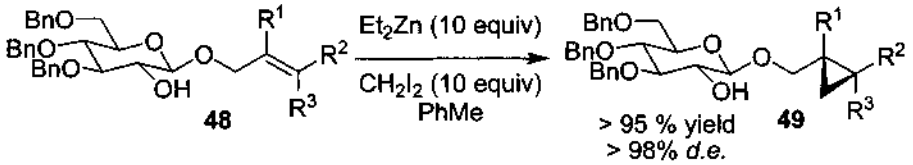
It is important to note, however, that the nitrogen-protecting group was crucial to the success of this reaction.



1.4.4.3 Asymmetric Simmons–Smith Reactions

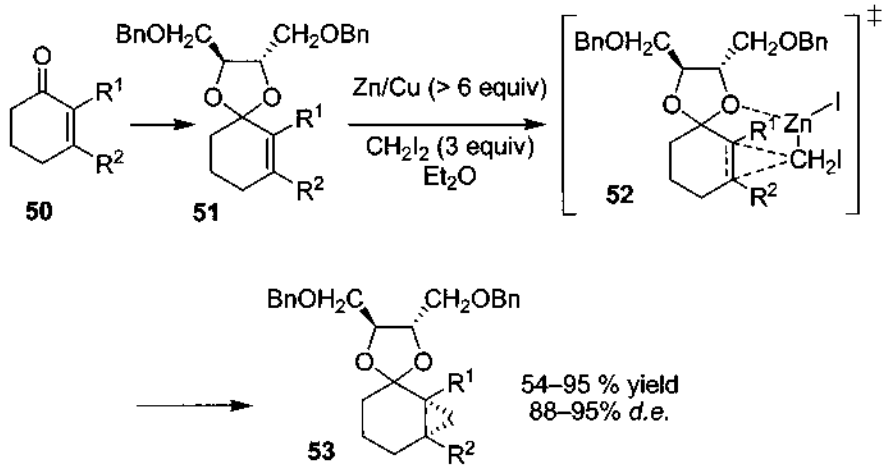
1.4.4.3.1 Chiral Auxiliaries

The use of a chiral auxiliary is one strategy of preparing enantiomerically pure cyclopropyl derivatives after cleavage of the auxiliary. There are several classes of auxiliary that have been used for different substrates, and these can be divided into chiral allylic ethers, acetals, α,β-unsaturated carbonyl derivatives, enamines, and enol ethers.[6] In the case of chiral allylic ethers, carbohydrate derivatives have proved particularly effective, inducing excellent levels of diastereoselectivity in the reaction. For example, substrates of the general class **48**, were cyclopropanated asymmetrically in excellent yield and very high levels of diastereoselectivity.[38] It is believed that the chiral auxiliary acts as a bidentate ligand for the zinc reagent, and indeed, structurally simplified auxiliaries are almost as effective.[39]



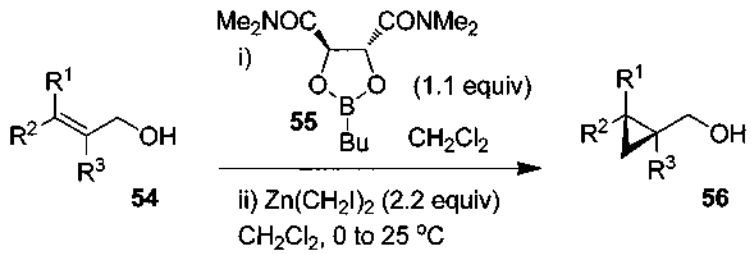
A number of chiral acetal derivatives have also proved effective in asymmetric cyclopropanation reactions, with auxiliaries based on tartaric acid proving to be particularly useful.[6] In the case of cyclic α,β-unsaturated compounds, di-*O*-benylthreitol derivatives (see **51**) undergo efficient and diastereoselective Simmons–Smith reactions to give the cyclopropanated products **53**.[40]

The configuration of the products can be rationalized by model **52**, whereby coordination of the zinc reagent occurs to the least sterically hindered dioxolane oxygen atom proximal to the olefin.



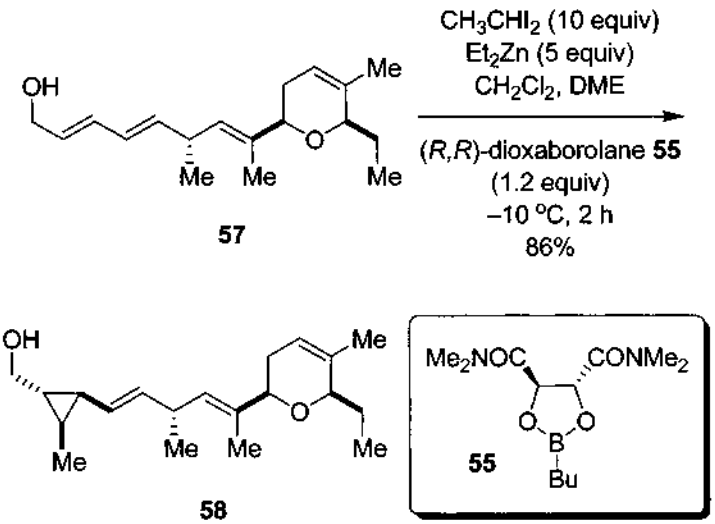
1.4.4.3.2 Stoichiometric Chiral Ligands

As early as 1968, the addition of chiral ligands to the reaction was performed in an attempt to induce asymmetry.[41] Despite several early attempts, however,[6] only modest enantioselectivities were obtained. Fujisawa and co-workers reported the first moderate levels of asymmetric induction by adding stoichiometric amounts of diethyl tartrate to the Furukawa's Simmons–Smith conditions.[42] In 1994, however, a major breakthrough was reported by Charette and co-workers, who demonstrated that bifunctional non-racemic chiral ligands induced good levels of enantioselectivity in the reaction.[15] These ligands contained both acidic and basic sites that allowed simultaneous chelation of the acidic halomethylzinc reagent and the basic zinc alkoxide. In particular, dioxaborolane **55**, prepared from *N,N,N',N'*-tetramethyltartaric acid diamide and butyl boronic acid, was a particularly useful chiral controller. This stoichiometric ligand shows good substrate scope, and the products (**56**) are usually isolated in good yield and high enantiomeric purities.[6]



Charette's procedure is so efficient that it has been used in numerous syntheses of complex molecules. For example, en route to (+)-ambruticin,

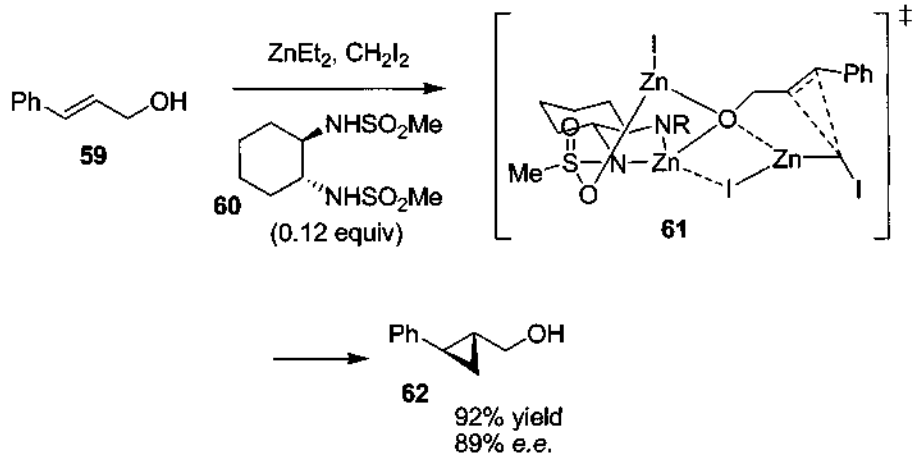
Jacobsen and co-workers used the Charette ligand to mediate asymmetry in the cyclopropanation of substrate **57**.[43] This reaction is particularly notable since a substituted cyclopropane is installed with high diastereoselectivity.



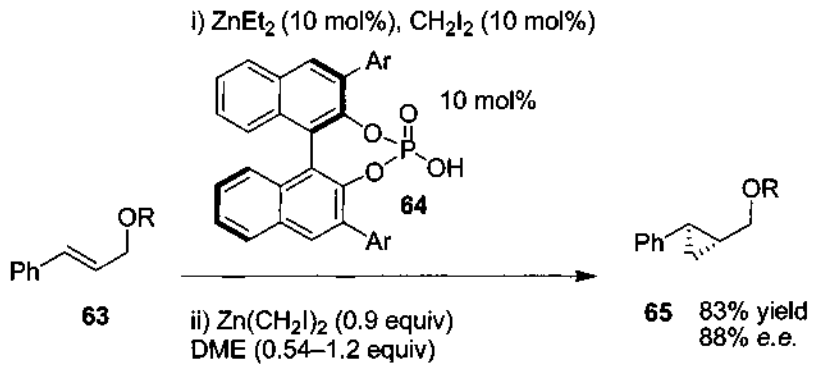
Although other stoichiometric mediators of the Simmons–Smith reaction have been reported, such as biaryl alcohols[44] and dipeptides,[45] none have to date shown such broad applicability as the Charette ligand.

1.4.4.3.3 Sub-Stoichiometric Chiral Ligands

Several examples have been reported of asymmetric Simmons–Smith reactions whereby the chiral, nonracemic ligand is added in sub-stoichiometric quantities. Kobayashi and co-workers were the first to report such a system, and showed that catalytic quantities of disulfonamide ligand **60** could result in isolation of the product (for example **62**) in good enantioselectivity.[46] This method has broad applicability and results in consistently high enantioselectivities for a wide range of substrates.[6] Denmark and co-workers subsequently reported an in-depth study of this reaction and highlighted that the rate and selectivity of the catalytic cyclopropanation greatly depends on the order of addition of the reagents.[18] Preformation of the ethylzinc alkoxide and bis(iodomethyl)zinc was crucial and the reaction was shown to be autocatalytic due to the generation of zinc iodide. These and other observations led to the proposed transition state assembly **61**, in which three zinc atoms are involved in the methylene delivery process.



Charette and co-workers reported a chiral Lewis acid-catalysed Simmons–Smith reaction, using a titanium TADDOL complex, although in general this system shows limited substrate scope compared to the Kobayashi system.[47]



More recently, however, the group have developed chiral zinc phosphate reagents as mediators of the asymmetric Simmons–Smith reaction. A chiral, nonracemic zinc reagent derived from phosphoric acid **64** was shown to be effective for the enantioselective cyclopropanation of substrates **63** when used in stoichiometric quantities. After significant optimization, it was shown that modified conditions could allow the use of just 10 mol % of **64**, resulting in the production of the product **65** with good levels of enantiomeric excess.[48] Charette and co-workers have extended this work, developing alternative ligands such as a TADDOL derived phosphoric acid.[49]

1.4.5 Variations and Improvements

1.4.5.1 Methods of generating active species

There are three classes of reaction that can generate the reactive haloalkylzinc species: (1) Oxidative addition of zinc metal into a carbon-halogen bond, (2) alkyl group exchange between and organozinc reagent and a dihaloalkane, and (3) the insertion of a diazoalkane into a zinc iodide bond.

Class 1, oxidative addition

The oxidative addition of activated zinc metal into a carbon-halogen bond is still one of the most widely used methods for the cyclopropanation of simple olefins. Indeed, it is this method that Simmons and Smith used in their seminal publications, whereby they favoured the use of a zinc-copper couple.[7,8] While their procedure involved heating a mixture of zinc dust and cupric oxide under a hydrogen atmosphere, this has been replaced by more convenient methods, including treatment of zinc powder with a cupric sulphate solution, treatment of zinc dust with a hot solution of cupric acetate in acetic acid, and mixing zinc dust with cuprous chloride under nitrogen.[5] While these procedures have remained the mainstay of Simmons–Smith reactions over the past 25 years, related activation procedures exist, including the use of the zinc-silver couple.[50] Despite the wide use of these procedures, irreproducible results are occasionally observed as a result of inconsistencies in forming the active zinc reagent. The other major disadvantage is that an ethereal solvent must be used for the activation process. Under such conditions the electrophilicity of the active zinc reagent is reduced, thus lowering its reactivity. Also, the majority of stereoselective Simmons–Smith reactions (see 1.4.4.3) require noncomplexing solvents to maximize stereoselectivity and so this method is not applicable.[5]

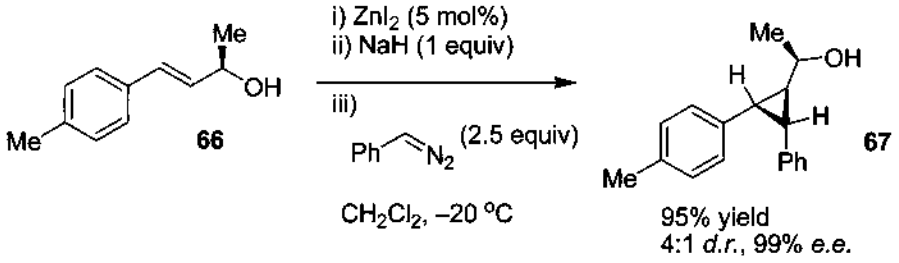
Class 2, alkyl group exchange

Many of the downsides highlighted above were overcome by Furukawa and co-workers, who showed that a mixture of diethyl zinc and diiodomethane gives very reproducible results in generating the active reagent via alkyl group exchange.[12] This procedure can be performed in non-coordinating solvent and thus is highly useful in stereoselective Simmons–Smith reactions (see 1.4.4.3). Subsequent work by Denmark and co-workers showed that in certain cases (especially for deactivated olefin substrates) it is advantageous to use bis(chloromethyl zinc as the active species, which is prepared from $ZnEt_2$ and CH_2ICl.[51] Another underused method for preparing $IZnCH_2I$ involves the treatment of EtZnI with CH_2I_2.[52] This method is particularly

useful on large scale because it avoids the use of pyrophoric Et_2Zn. More recently, several other highly effective reagents have been reported for use in Simmons–Smith reagents, prepared via alkyl group exchange. Iodomethylzinc trifluoroacetate, prepared by mixing tifluoroacetic acid, diethyl zinc and diiodomethane is a very effective cyclopropanating reagent.[53] Likewise, substituted iodomethylzinc aryloxides (for example 2,4,6-$Cl_3C_6H_2OZnCH_2I$) are very useful in the cyclopropanation of unfunctionalized olefins.[54]

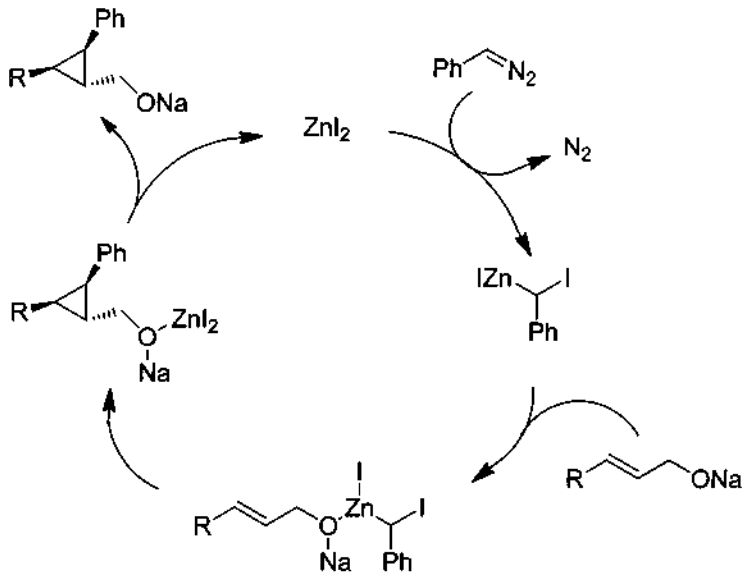
Class 3, insertion of a diazoalkane into a zinc iodide bond

Despite the fact that diazoalkane derived reagents were some of the first examined by Wittig and co-workers for the Simmons–Smith reaction,[10] and the huge growth of diazo compound usage in other cyclopropanating methods, this reagent preparation procedure has only appeared sporadically in the literature for Simmons–Smith reactions. A very recent publication by Charette and co-workers may draw more attention to this method however.[55] In an attempt to enantioselectively prepare aryl-substituted cyclopropanes, they showed that exposure of allylic alcohol substrates to a reagent formed from EtZnI, phenyldiazomethane, and their chiral ligand (**55**, see 1.4.4.3.2) resulted in the formation of the product in good yield and excellent diastereoselectivity and enantioselectivity.[55] Of particular note, however, was the fact that consideration of the mechanism led the team to consider the possibility of a Simmons–Smith reaction catalytic in zinc. Indeed, they found that exposure of nonracemic chiral substrate **66** to just 5 mol % of zinc iodide along with stoichiometric NaH and excess phenyldiazomethane, resulted in the formation of product **67** in excellent yield, good diastereoselectivity and excellent enantioselectivity. This is the first example of an asymmetric cyclopropanation catalytic in a zinc salt.

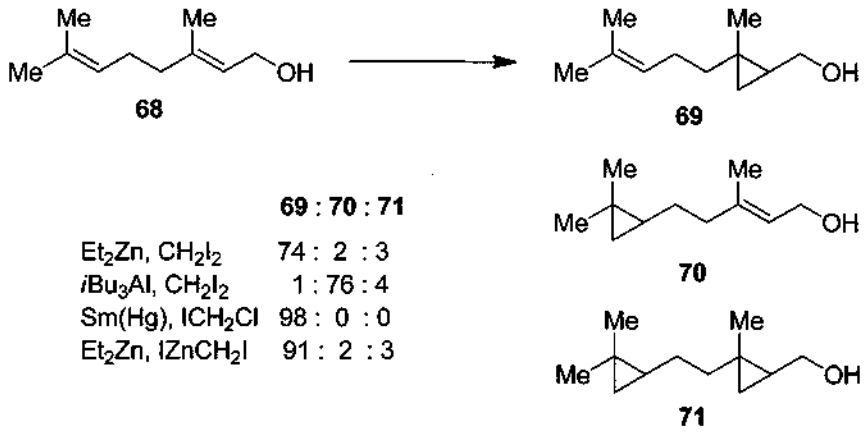


Mechanistically the reaction is hypothesized to proceed via reaction of zinc iodide with phenyldiazomethane to form a zinc carbenoid, which in turn reacts with the sodium alkoxide formed in situ (from the alcohol and

NaH) to produce the cyclopropanated product, regenerating the zinc iodide salt.[55]



1.4.5.2 Other Metal Carbenoids: Samarium and Aluminium

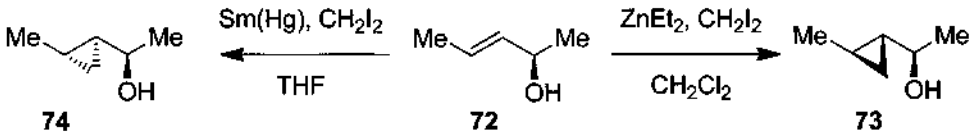


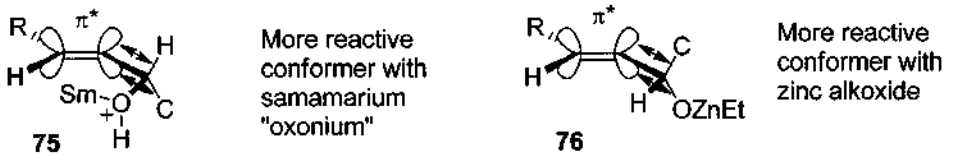
	69 : 70 : 71
Et_2Zn, CH_2I_2	74 : 2 : 3
iBu_3Al, CH_2I_2	1 : 76 : 4
Sm(Hg), ICH_2Cl	98 : 0 : 0
Et_2Zn, $IZnCH_2I$	91 : 2 : 3

In addition to zinc-based carbenoids, other potential active agents of the general structure "MCH_2X" have been proposed. For example in 1985, Yamamoto and co-workers described the preparation and use of aluminium based carbenoids (R_2AlCH_2I).[14] Subsequently, in 1987 Molander and co-workers reported the use of a samarium/mercury amalgam and CH_2I_2 to generate samarium carbenoids.[13] While these species are less well characterized than their zinc counterparts and their use has not been so

widely adopted, they do show some interesting chemoselectivity. This is clearly demonstrated in the cyclopropanation of geraniol (**68**). The allylic alcohol functionality is selectively cyclopropanated (see **69**) in the presence of the isolated olefin for the zinc and samarium derived reagents, whereas it is the terminal double bond that selectively reacts (see **70**) in the presence of the aluminium carbenoid.[6] It is interesting that if the alcohol is protected as a benzyl ether, all three reagents cyclopropanate the allylic position.

Other interesting selectivities are observed in the stereoselective cyclopropanation of acyclic chiral nonracemic allylic alcohols. For example, cyclopropanation of substrate **72** gave the *syn* isomer **73** as the major product in the case of the zinc carbenoid and the *anti* isomer **74** in the case of the samarium reagent.[6]

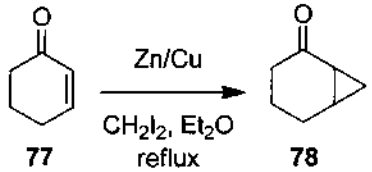




As stated in section 1.4.4.2, a variety of factors, including substrate ratios, solvent, and stereoelectronic effects, play important roles in the selectivity of these reactions, however, in general, the stereochemical outcome can be qualitatively predicted by assuming an oxygen group-assisted delivery of the methylene group from a conformation that minimizes A(1,3) strain.[6] The fact that the samarium reagent gives the *anti* isomer as the major product for substrate **72** suggests a different conformer is involved in the cyclopropanation reaction. One possibility is that deprotonation of the alcohol does not occur with the less basic samarium reagent, and the most reactive conformer is, therefore, the one in which the C–O(H)Sm is orthogonal to the π system (see **75**) to maximize the nucleophilicity of the alkene.[6] Delivery of the methylene group from the face away from the alkyl group would then lead to the *anti* isomer. This is in contrast to the proposed favoured conformer of the zinc alkoxide (see **76**).

1.4.6 Experimental

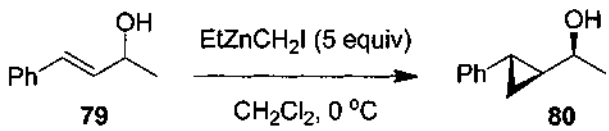
1.4.6.1 Standard conditions



Bicyclo[4.1.0]heptan-2-one (78)[56]

Cupric acetate monohydrate (0.16 g, 0.8 mmol) was dissolved in hot glacial acetic acid (5 mL). Zinc powder (2.8 g, 42.8 mmol) was added to this stirred solution, and after 30–60 s the green colouration disappeared and metallic red copper was deposited on the zinc. The supernatant liquid was decanted and replaced by fresh acetic acid (5 mL). The suspension was stirred, and then the supernatant liquid was once again decanted and replaced by Et_2O (10 mL). The couple was washed in the same fashion with Et_2O (3 × 10 mL). Finally, the couple was covered with Et_2O (20 mL). A few drops of CH_2I_2 was added, and an exothermic reaction occurred. A mixture of cyclohexen-2-one (**77**, 0.96 g, 0.01 mol) and CH_2I_2 (7.5 g, 28 mmol) was then added dropwise, inducing a gentle reflux for 30 min. to 1 h. The mixture was then heated to reflux for 36 hours, during which time a white precipitate appeared. After cooling, H_2O (2 mL) was added dropwise, and the mixture was separated by centrifugation. The ether phase was decanted and washed with 10% aqueous HCl and then three times with H_2O. The solution was dried over Na_2SO_4, filtered, and the solvent removed in vacuo. This gave bicyclo[4.1.0]heptan-2-one (**78**, 1.0 g, 90%) as a colorless liquid.

1.4.6.2 Furukawa modification

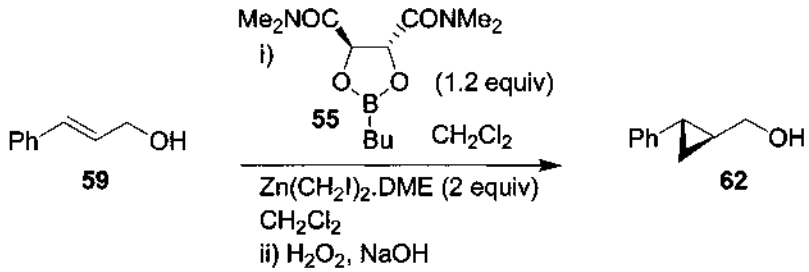


(*αR,1R,2R*)-α-Methyl-2-phenylcyclopropanemethanol (80)[29]

To a solution of alcohol **79** (296 mg, 2.0 mmol) in anhydrous CH_2Cl_2 (20 mL) at –10 °C was added dropwise diethylzinc (1.0 mL, 10 mmol) followed by CH_2I_2 (810 μL, 10 mmol). The mixture was then allowed to warm to

room temperature over 3 h. Saturated aqueous NH_4Cl (10 mL) was added, and the mixture diluted with Et_2O (80 mL) and 10% aqueous HCl (10 mL). The organic layer was successively washed with saturated aqueous Na_2SO_3 (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$, and filtered; the solvent was removed in vacuo. Silica gel chromatography (EtOAc:hexane, 15:85) gave the *syn* product **80** (280 mg, 86%) as the major isomer. The less polar anti isomer (40 mg, 12%) was also isolated.

1.4.6.3 Asymmetric Simmons–Smith Using the Charette Auxiliary



(+)-(*1S,2S*)-2-Phenylcyclopropanemethanol (62)[57]

To a solution of dry DME (1.60 mL, 14.0 mmol) in anhydrous CH_2Cl_2 (45 mL) cooled at –10 °C (internal temperature) was added diethylzinc (1.50 mL, 14.9 mmol). Then to this mixture was added CH_2I_2 (2.40 mL, 29.8 mmol) over 15–20 min while maintaining an internal temperature between –8 and –12 °C. After the addition, the resulting clear solution was stirred for an additional 10 min at –10 °C. A solution of dioxaborolane **55** (2.41 g, 8.94 mmol) in anhydrous CH_2Cl_2 (10 mL) was then added via cannula over 5 min, followed by immediate addition of cinnamyl alcohol (**59**, 1.00 g, 7.45 mmol) in anhydrous CH_2Cl_2 (10 mL) via cannula over a further 5 min, maintaining the internal temperature below –5 °C. The mixture was then allowed to warm to room temperature and stirred for 8 hours at this temperature. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and 10% aqueous HCl solution (10 mL). The mixture was diluted with Et_2O (60 mL), and the phases were separated. The reaction flask was further washed with Et_2O (15 mL) and 10% aqueous HCl solution, and these washings were combined with the extracts. The aqueous layer was further extracted with Et_2O (20 mL). A solution of 2 N aqueous NaOH (60 mL) and 30% aqueous H_2O_2 (10 mL) was added in one portion to the combined organic extracts. The biphasic mixture was stirred vigorously for 5 min. The two layers were the separated, and the organic layer was washed successively with 10% aqueous HCl solution (50 mL), saturated aqueous Na_2SO_3 (50 mL), saturated aqueous $NaHCO_3$ (50

mL), and brine (50 mL). The organic layer was dried over anhydrous $MgSO_4$, and filtered; the solvent removed in vacuo. Further drying of the product in vacuo was performed overnight to remove residual *n*-butanol from the oxidative workup. The product **62** was purified by Kugelrohr distillation (90 °C, 0.8 mm Hg) to after alcohol **62** (1.05 g, 95%, 94% *ee*. as determined by GC analysis of a chiral nonracemic trifluoroacetate ester derivative) as a colorless oil.

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