

Studies on the Simmons-Smith Reaction

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I. INTRODUCTION

I-1, General Scope of Organometallic Reagents and Reactions for the Cyclopropane Synthesis

Organic structures containing small ring have been received increasing attention in recent years. Cyclopropane derivatives¹⁾ in particular have been found not only widely in nature²⁾ as the substance with characteristic physiological activity, but also aroused much interest from the theoretical viewpoint in physical organic chemistry.³⁾

To date, several methods for preparation of cyclopropane derivatives have been developed, most of which, however, suffer from a lack of general applicability. From the standpoint of organic synthesis, the addition of divalent carbene to carbon-carbon unsaturation, especially when it is stereospecific, presents a highly general approach.

Syntheses utilizing this concepts have been realized in the classical reaction of aliphatic⁴⁾ and aromatic⁵⁾ diazo compounds with olefins, and in the addition of halocarbenes⁶⁾ to olefins. The reactions of diazoesters⁷⁾ with olefin, which lead to carboalkoxy-cyclopropanes, have been extensively investigated in the presence or absence of metallic copper or its salts.⁸⁾ Diazomethane adds to the olefinic double bond of α , β -unsaturated esters⁹⁾ and ketones giving pyrazolines¹⁰⁾ which lose nitrogen by heating to give rise to a mixture of cyclopropane derivatives along with β -methyl analogues of the parent compounds. The light-induced reaction of diazomethane with simple olefins results in the production of a large amount of difficultly separable, isomeric hydrocarbons along with the desired cyclopropanes.¹¹⁾ Dihalocarbenes¹²⁾ react stereospecifically with olefins to give 1,1-dihalocyclopropanes in higher yields which, however, must undergo further chemical transformation¹³⁾ for obtaining the nonhalogen cyclopropanes.

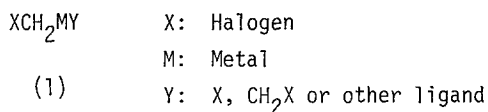
The direct addition of methylene to olefin has been accomplished with methylene radical produced from the photolysis of ketene. It has been shown that the methylene radical from this source, as well as those from the photolysis of diazomethane, has too high energy¹⁴⁾ to discriminate between the olefinic and carbon-hydrogen bonds.

Recently the ylid chemistry has been developed for the cyclopropane synthesis too. Although this is not the direct methylene transfer to the double bond, several research groups¹⁵⁾ have examined the reaction of the stabilized phospho-

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nium ylids with epoxides, α , β -unsaturated esters and ketones to give corresponding cyclopropanes, and claimed synthetic utility. Phosphinoxy carbanions¹⁶⁾ and other ylid compounds¹⁷⁾ involving nitrogen¹⁸⁾ and sulfur¹⁹⁾ atoms have been investigated widely. An example of the methylene addition to olefin has been reported by Bravo²⁰⁾ who has carried out the reaction of dimethyloxosulfonium methylene with α , β -unsaturated ketone to give the corresponding cyclopropylketone.

A stereospecific addition of unsubstituted methylene to carbon-carbon double bond has been developed and the satisfactory yields of cyclopropane products in a high purity have been obtained through the intervention of one of the organometallic reagents (1), as follows ;

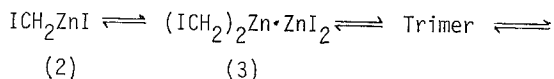


Forty years ago, Emschwiler observed the reaction of methyleneiodide with magnesium²¹⁾ and also with zinc-copper couple²²⁾ in ether solution. He assumed the product as iodomethylzinc iodide, ICH_2ZnI (2) in the latter case, although any attempts have not been done for further studies on the behavior of this very attractive reagent toward olefins.

In 1958, a novel and very useful synthetic method for cyclopropanes was achieved and developed by Simmons and Smith,²³⁾ which has been improved to a simpler procedure, that is, methyleneiodide was treated with zinc-copper couple²⁴⁾ in ether, by the same way as by Emschwiler, and the organozinc solution thus prepared was allowed to react with variously substituted olefins.

In general, the formalistic structures and equilibrium composition of any active organometallic reagents, including even the Grignard reagent²⁵⁾ in solution, have not yet been elucidated and only inferred either from the information supplied by the mode of reaction to optional substrates or from other physical properties of the reagents.

As to the elegant organozinc reagent, which is called the Simmons-Smith reagent in honor of the discoverers, the feature of the ingredients remains obscure, and the evidence for it is based merely on assumption from the stoichiometry, ebullioscopy and *ex post facto* explanation of the reaction results. This tolerably stable reagent may be described in an equilibrium of, so called, the Schlenk type²⁶⁾ which is generally encountered in normal organometallic reagents.

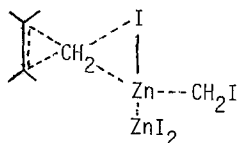


The Simmons-Smith reaction seems to have the essential feature that higher electron density at the carbon-carbon unsaturation enhances the rate of the cyclopropane formation²⁷⁾ due to the electrophilic nature of the reagent, thus resulting in better yields. Furthermore, it has been known that the reaction

occurs²⁸⁾ with high discrimination between unsaturations and with stereospecificity.²⁹⁾

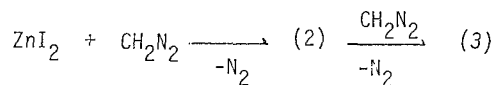
It also seems that basic solvent, such as tetrahydrofuran and triethylamine, reduces its reactivity toward olefin and results in the formation of by-products; methane, ethane, ethylene and polymethylene.

As to the reaction mechanism, Simmons and Smith have proposed a carbene-like "one-step methylene-transfer" (4), in which the electrophilic methylene in bis-iodomethylzinc·zinc iodide (3), may primarily attack olefinic double bond, followed by simultaneous cyclopropane formation with elimination of (2). Their claim of the dimeric species (3) as the operating species in the bimolecular process, however, has been based only on the competition studies,^{28-b)} and the proof has not been kinetically borne out as yet. Then the contribution of the monomeric (2) has not completely excluded and awaits further prosecution in future.



(4)

The transition state (4) has been given a support by Wittig and his co-workers.³⁰⁾ They have carried out the reaction of diazomethane with zinc iodide and also with the salts of other metals. The active solution prepared has shown to bear substantially the same activity as that of the Simmons-Smith reagent. The existence of (3) in ether solution has been inferred from the proportionality of diazomethane to zinc iodide, (2:1 in mol ratio), and from the analogy to bis-chloromethylzinc etherate which has been characterized as a strong tetrameric associate^{30-b,c)} by the ebullioscopic determination.



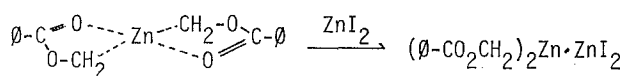
The latter argument may be based on the difference of the molecular association between the organometallic compounds containing chlorine and iodine atoms, which is generally accepted, for example, in the case of the Grignard reagent, phenylmagnesium chloride, bromide and iodide.³¹⁾

The organometallic species described formula-ly as XCH_2MY (1) may well be expected to differ noteworthy in the activity and the over-all reaction mechanism owing to substituents, X, M and Y with wide variation. Wittig has found that the stability and the tendency of decomposition of the organometallic complex prepared by the reaction of diazomethane with various metal halides are parallel to the normal potential of the corresponding metals, that is, the more negative potential of the metal, the more unstable the complex is, and thus, the more easily the methylene leaves.

They^{30-c)} reported the cyclopropane formation from olefins by means of bis-

Normal Potential	-2.4	-1.7	-1.5	-0.5	-0.76	-0.4	-0.34	+0.72	+0.86
	Mg	Be	Al	Ga	Zn	Cd	In	Tl	Hg
	Polymethylene								
	Ethylene								
	M(CH ₂ X) _n								

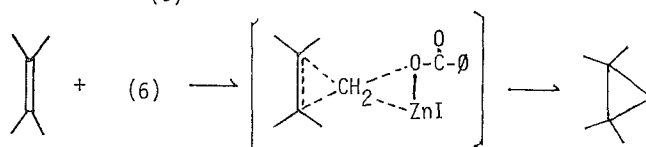
benzoxymethylzinc (5), which was obtained in a crystalline state, only in the presence of zinc iodide. Benzoxymethylzinc iodide (6) which has the same constitution as (1) seems to give up methylene in the one-step methylene-transfer mechanism (7) as described below ;



(5)

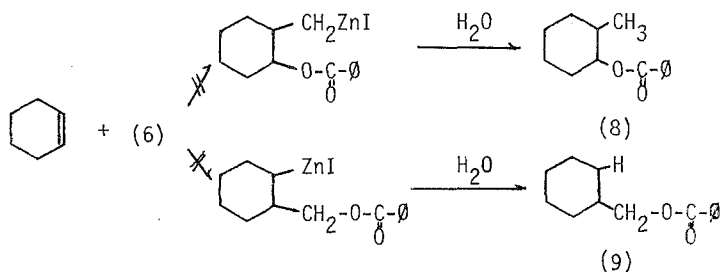


(6)



(7)

This assumption has been supported by the evidence that neither (8) nor (9) which may be expected from the four-center two-step mechanism,³²⁾ has been detected at all by the g. l. p. c. analysis.

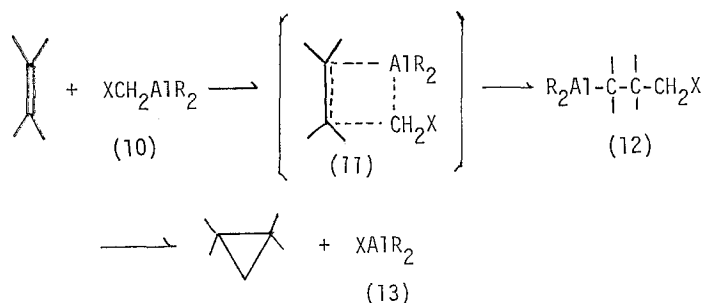


(9)

Hoberg²³⁾ has carried out the reaction of dialkylaluminum halide (13) with diazomethane in ether solution to give halomethylaluminumdialkyl (10) and has isolated iodomethyl aluminumdiethyl in a crystalline state.

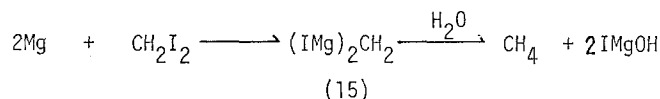
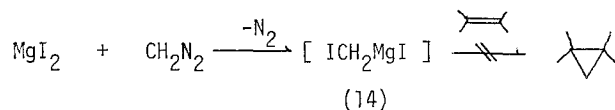
Organoaluminum compounds of this sort have also been shown to be effective at cyclopropane synthesis from olefins. As to the reaction mechanism of (10), he has proposed a four-center two-step process (11), in which (10) adds to olefin

at first and subsequently cyclopropane is formed in an S_N2 type cyclization with elimination of (13).



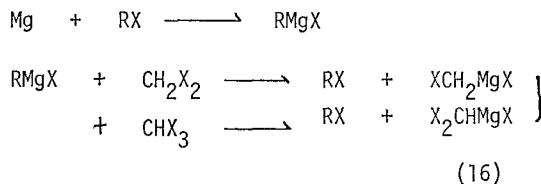
This mechanism in the reaction of the aluminum compound has been applied as such to the Simmons-Smith reaction by analogy to the organozinc reagent. According to the Hoberg postulation, therefore, the reagent would be expected to behave as a nucleophile through a rather "ionic" process, whereas in the Simmons and Smith mechanism (4), it would be more "carbene like" and in fact is of electrophilic nature.

The organometallic reagents which transfer methylene ligand to olefin are also known where the metal is lithium, magnesium, cadmium, mercury and indium. Of these compounds, preparation of iodomethylmagnesium iodide (14) has been tried by the method of Wittig.³⁰⁾ The organomagnesium solution prepared from magnesium iodide with diazomethane, when allowed to react with olefins, however, gave rise to only ethylene and polymethylene without formation of any cyclopropane derivatives and on hydrolysis of the solution, methyl iodide formed in a 12% yield at most. Magnesium also has been allowed to react with methylene iodide. The reagent prepared, however, is methylene bis-iodomagnesium (15)³³⁾ and not iodomethylmagnesium iodide (14) which has been identified by hydrolysis of the organomagnesium solution through the following sequence;

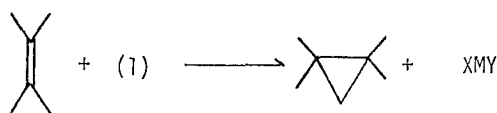


On the other hand, an interesting and potentially useful development in the organomagnesium chemistry is the discovery by Normant and Villieras³⁴⁾ that α -haloalkyl Grignard reagents (16) can be prepared and utilized for the formation of terminal methylene group at a low temperature. Iodomethylmagnesium iodide (14) by their procedure at -70°C , however, was not effective as well for methylene transfer to olefins.³⁵⁾

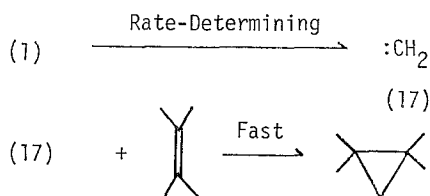
The other methylene transfer reagents are chloromethylsodium,³⁶⁾ bis-iodomethylcadmium,^{30,37)} iodomethylmercuric iodide,³⁸⁾ bis-bromoethylmercury,³⁸⁾ and tri-



iodomethylindium.³⁰⁾ As to the reaction mechanism and kinetics, little has been done to date, but a useful body of indirect evidence has suggested that methylene transfer reaction of the type shown below may be considered to proceed through several different pathways.



In conclusion, the reactions of all the reagents of the type-(1) may be classified in the following three categories of mechanism; (1) a carbene (17) mechanism, in which the rate-determining decomposition of the organometallic reagent to the active intermediate is followed by a rapid addition of this intermediate to olefin to form the cyclopropane derivative; (2) a bimolecular, one-step methylene-transfer (4), in which the electrophilic methylene reacts directly with olefin through a three-center transition state, as suggested by Simmons and Smith;²⁸⁾ and (3) a bimolecular two-step process (11) for example, as proposed by Hoberg³²⁾ for the nucleophilic reaction of chloromethyldiethylaluminum (10). The scheme for (1) is given below;

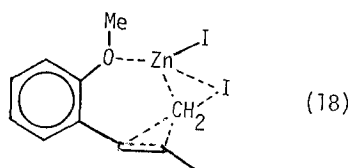


The alteration of the three paths seems to depend upon the normal potential of the metal involved in the complex.

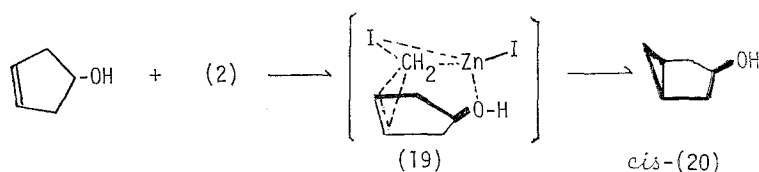
It is known that the active organometallic compounds interact with heteroatoms bearing lone pair such as oxygen³⁹⁾ and nitrogen.²⁵⁾ The oxygen functions such as alcohol⁴⁰⁾ and ether⁴¹⁾ have been found to contribute much to acceleration of the cyclopropane formation with stereospecificity by the electrostatic attraction or coordination of the lone pair with the Simmons-Smith reagent.

Simmons and co-workers have pointed out in their first publication^{23-a)} that 1-(*o*-methoxyphenyl)-propene with the reagent gave a higher yield of the corresponding cyclopropane than did the unsubstituted, *m*- and *p*-substituted isomers. They have inferred the coordination of zinc atom in the reagent with oxygen of the substrate which stabilizes the transition state (18) in the case of the ortho-isomer.

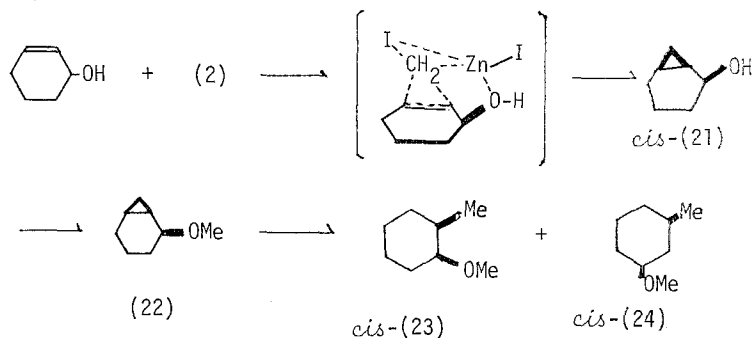
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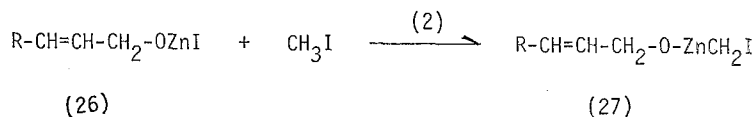
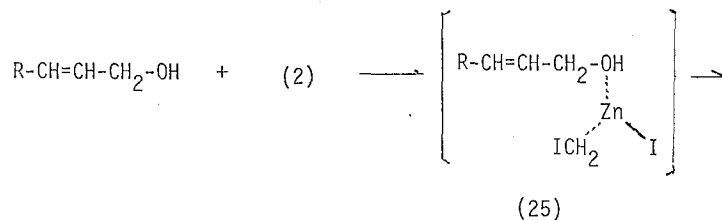
The hydroxyl function in olefinic alcohol influences not only the rate of cyclopropane formation but also the steric course of the reaction. Namely, Winstein and Sonnenberg⁴²⁾ carried out the Simmons-Smith reaction which gave rise to exclusively *cis*-bicyclo-[3, 1, 0]-hexan-2-ol (20) from 3-cyclopentene-1-ol, and they have proposed a cyclic transition state (19) as follows;



This intra-cyclic (19) has been confirmed definitely by Dauben and Berezin.⁴³⁾ Cyclohexen-2-ol has been treated with the reagent and the methylether (22) which was prepared by the conventional method from (21), was hydrogenated under a high pressure to supply completely *cis*-(23) and -(24).



Dauben and his co-workers have not mentioned, however, whether the reagent (2) coordinates merely electrostatically with the hydroxyl function in the transi-



corresponding reaction system.

Hida also interpreted this duality in terms of the interaction between the reagent- and substrate-orbitals⁵⁴⁾ by means of quantum mechanical treatment.

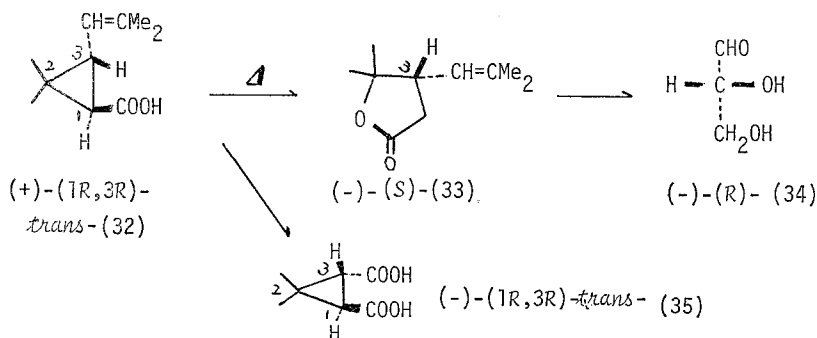
A miscellaneous and also interesting example is the formation of a cyclopropylamine by the reaction of an enamine⁵⁵⁾ with the reagent, which, however, is accompanied by the formation of a viscous precipitate of ate-onium complex⁵⁶⁾ in conventional ether medium.

More recently, an improved route of the Simmons-Smith synthesis has been developed by Furukawa and his co-workers,⁵⁷⁾ in which zinc-copper couple was replaced by diethylzinc etherate⁵⁸⁾ and diethylcadmium etherate⁵⁹⁾ in a specified reaction condition. They have claimed the remarkable improvement in yield of cyclopropane products from olefins. This modification⁶⁰⁾ is featured in particular by its excellent performance even with cation-sensitive olefins, such as vinyl ethers, in which with the conventional reagent the competitive polymerization of olefins caused by the Lewis acid catalysis of zinc iodide in the medium outweighed the formation of the desired cyclopropanes. In spite of their claim of much-improved yields of cyclopropane products, however, explosion hazards on handling diethylzinc greatly reduce the usefulness and applicability of this modification in practice.

I-2, The Absolute Configuration of Chiral Cyclopropanes

It is one of the important problems in stereochemistry to determine the absolute configuration of chiral molecules. The knowledge of it enables us to discuss the reaction mechanism and to deduce the transition state topology more accurately. It is then natural that the symmetry or chirality element of cyclopropane compounds has attracted much attention of organic chemists as did the methods of synthesis.

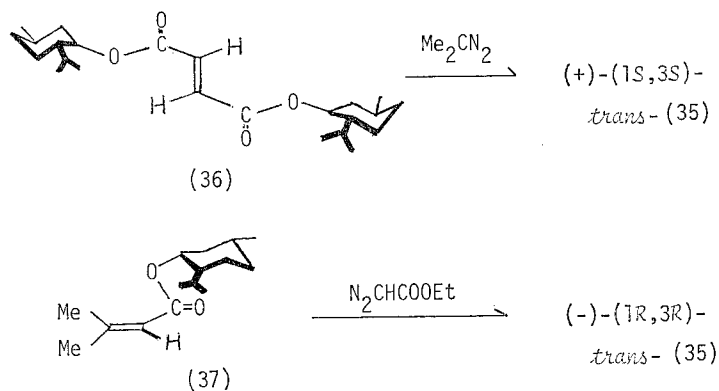
The stereochemistry of chiral cyclopropane systems has not been determined until 1963 when Crembie and his co-worker⁶¹⁾ transformed (+)-*trans*-chrysanthemic acid (32) of natural origin into (-)-pyrocin (33) with cleavage of the cyclopropane ring by thermolysis. This compound was related eventually to (-)-(*R*)-glyceraldehyde (34), which possesses the well-defined configuration at the C-3 asymmetric carbon of (32) and (1*R*, 3*R*)-configuration was assigned to (+)-(32). In the consequence, the (1*R*, 3*R*)-configuration was deduced to (-)-*trans*-caronic acid (35), which was obtained by the degradation of (+)-(32).



This finding promoted the Japanese workers⁶²⁾ to exploit a novel asymmetric synthesis⁶³⁾ as a useful means of absolute assignment of configuration to chiral cyclopropane systems which are in most cases very difficult to be transformed or correlated with or without ring cleavage to some other compounds of the known chirality.

Sugita and Inouye⁶²⁾ have for the first time achieved a partial asymmetric synthesis of cyclopropanes by the addition of diazo-compounds to chiral olefinic esters which resulted in an optically active cyclopropane esters. Thus the reaction of (-)-dimenthyl fumarate (36) with dimethyldiazomethane afforded (+)-*trans*-(35) in preponderance over the (-)-enantiomer, whereas in the reaction of (-)-menthyl β , β -dimethylacrylate (37) with ethyl diazoacetate, (-)-*trans*-(35) predominated in the product.

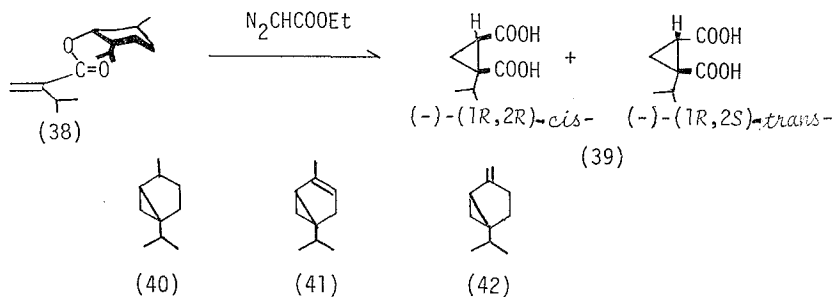
The stereochemical outcome in these reactions of this type enabled them to conclude that in the reasonable transoidal coplaner conformations of (36) and (37), the *re-re* face in the former and the *re-si* face in the latter are sterically less hindered and permit easier access of diazo-compounds than their opposite faces respectively. This means that the Cram-Prelog model applies to the stereochemistry in the addition reaction of diazo-compounds to α , β -unsaturated esters and provides one with the means of determining absolute configurations of cyclopropane systems in general.



As a successful application of this method for assigning absolute stereochemistry to natural cyclopropane compounds in terpenes, the following example can be cited. According to the same scheme of asymmetric synthesis as described above *i.e.* by the addition reaction of ethyl diazoacetate to (-)-menthyl α -isopropylacrylate (38), (-)-*(1R, 2R)*-*cis*- and (-)-*(1R, 2S)*-*trans*-configurations were assigned to the optically active umbellularic acid isomers (39), which were isolated from the reaction products.

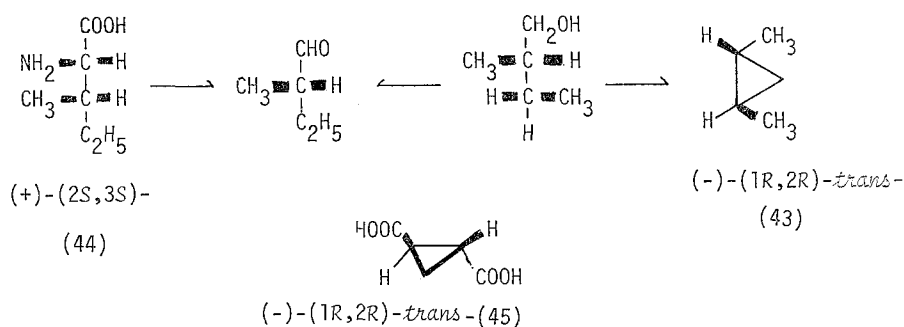
Up to that time, nothing has been known about the absolute configurations of the thujane terpenoids,⁶⁴⁾ involving cyclopropane ring in the carbon skeleton. This establishment of the absolute configurations, in particular, of the *cis*-umbellularic acid, enabled one to assign the topology of all the thujane monoterpenes and their numerous derivatives such as umbellulone (40), thujane (41), sabinenes

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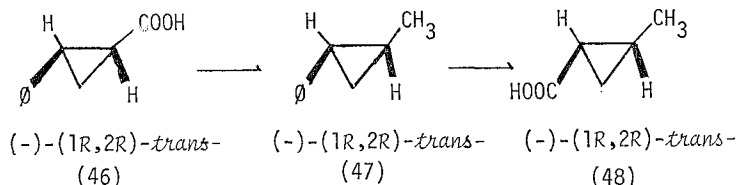


(42) and so on which are described in details from p. 1 through 60, by Simonsen in "The Terpenes" vol. II.⁶⁵ In this way the then sole pending problem in stereochemistry of monoterpenes was elegantly resolved.

The absolute configuration of $(-)-(1R, 2R)\text{-trans-1, 2-dimethylcyclopropane}$, (43), has been related to $(+)\text{-}(2S, 3S)\text{-2-amino-3-pentanoic acid}$ (44) by Doering and his co-worker⁶⁶ in the following scheme ;

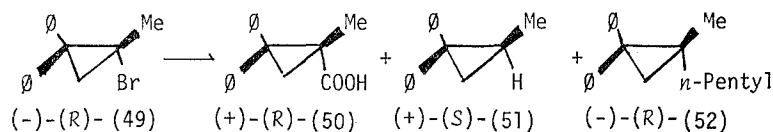


By utilizing this correlation, Inouye and Sugita⁶⁷ have established the stereochemistry of $(-)-(1R, 2R)\text{-trans-cyclopropane-1, 2-dicarboxylic acid}$ (45). They⁶⁸ assigned also $(-)-(1R, 2R)\text{-trans-2-phenylcyclopropanecarboxylic acid}$ (46) and succeedingly, $(-)-(1R, 2R)\text{-trans-}$ (47) and $(-)-(1R, 2R)\text{-trans-}$ (48) in the scheme below ;

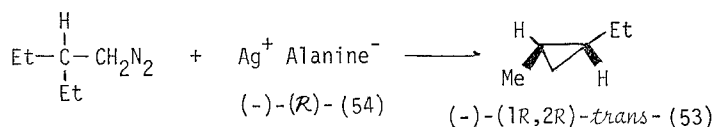


The topology has been allotted by Walborsky and his co-workers⁶⁹ in the series of chiral diphenylcyclopropane compounds. In the halogen-metal exchange reaction⁷⁰ applied to $(-)-(R)\text{-1-bromo-2, 2-diphenyl-1-methylcyclopropane}$ (49), the original configuration at the reaction site was kept unchanged without inversion or racemization and in the subsequent carbonation process, giving rise to $(+)\text{-}(R)\text{-2, 2-diphenyl-1-methylcyclopropanecarboxylic acid}$ (50), $(+)\text{-}(S)\text{-2, 2-diphenyl-1-methylcyclopropane}$ (51) and $(-)-(R)\text{-2, 2-diphenyl-1-methyl-1-n-pentylcyclopropane}$

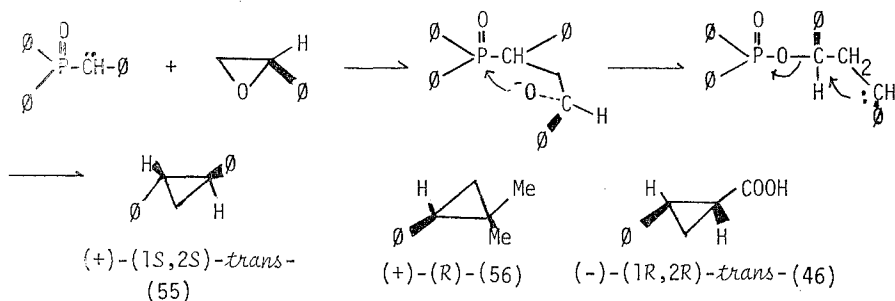
pane (52), in which the absolute configuration of (52) had been determined previously by other independent process.⁷¹⁾



Kirmse and his collaborators⁷²⁾ have recently assigned the absolute configuration of *trans*-1-ethyl-2-methylcyclopropane (53) based on the experimental observations that the decomposition of 2-ethyl-butyl diazomethane in the presence of silver-(-)-(R)-alaninate (54) gave (-)-(1R,2R)-*trans*-(53) whereas that with (+)-(S)-salt-(54) gave the enantiomeric product, (+)-(1S,2S)-*trans*-(53). They reported the evidence to support the above deduction by the experiments using silver nitrate-(-)-(S)-ethyl lactate or -(+)-(R)-butyl tartarate complexes as chiral catalyst.



Tömösközi has deduced (+)-(1S,2S)-*trans*-1,2-diphenylcyclopropane (55) by the chemical correlation of (+)-(S)-styrene oxide by means of aryl-activated P=O carbanions⁷³⁾ and also (+)-(R)-1,1-dimethyl-2-phenylcyclopropane (56) and (-)-(1R,2R)-*trans*-(46)⁷⁴⁾ by the same procedure.



A few physicochemical methods have been introduced and employed practically for the determination and/or prediction of the absolute configurations of chiral organic molecules. Physical correlation of an empirical nature is exemplified by quasi-racemate formation by Fredga.⁷⁵⁾

The Octant rule⁷⁶⁾ is another example of elegant achievements developed by Djerassi⁷⁷⁾ and his co-workers in the physicochemical measurements for stereochemical studies. The chirality of organic molecules was nicely correlated with the sign of the Cotton effect of optical rotatory dispersion and circular dichroism. They have also proposed the "Reversed octant rule" for the wide variety of chiral epoxides and cyclopropyl ketones^{78,79)} although this rule seems to remain in ambiguity as yet.

Sawada⁸⁰⁾ has applied the Octant rule to the derivatives of dicarboxylic acids

including a small carbon rings of C_3-C_6 . The optically active dicarboxylic acids have been converted into the corresponding N-substituted thionamides.⁸¹⁾ The chirality of the parent acids has been related good to the sign of the Cotton effect of the derivatives at their $n-\pi^*$ transition ranges by the optical rotatory dispersion measurement.

II. THE PRESENT RESERCH

II-1 The Reaction of the Simmons-Smith Reagent with (-)-Menthyl α , β - and β , γ -Unsaturated Carboxylates

Little has been known about the formation, equilibrium, reaction species and reaction mechanism of active organometallic compounds in solution, which may offer invaluable application for practical synthesis in organic chemistry. The Simmons-Smith reagent also is not an exception and it seems of interest to undertake the study of this reaction in expectation of successful synthesis and asymmetric induction of cyclopropane systems as a possible means of mechanistic solution.

As to the mechanism of the Simmons-Smith reaction, Hoberg⁸²⁾ has postulated the cyclopropane formation as proceeding *via* (11), addition of active (2) or (3) to olefin and subsequent elimination of zinc iodide.

As an alternative, the three-center reaction (4), involving one-step methylene-transfer mechanism⁸³⁾ has also been suggested. According to the former mechanism, therefore, the reagent would be expected to behave as a nucleophile in a rather ionic process, whereas in the later, it would be more "carbene like" and therefore of electrophilic nature.

With the molar ratio of olefinic ester : methyleneiodide : zinc-copper couple of 1 : 2 : 4 in absolute ether and a reflux period of 10-60 hr, all the substrates afforded stereospecifically the corresponding cyclopropane compounds, which were isolated pure from the reaction mixture by the usual work-up, that is, ozonolysis to remove unreacted ester and subsequent hydrolysis in alkaline solution.

As is seen from the data in Table 1, all the (-)-menthyl esters except the cinnamate, when treated with the Simmons-Smith reagent, afforded dextrorotatory cyclopropanecarboxylic acids of the configuration of (S), (1S, 2S) and (1R, 2S) of the same optical series. This is, however, in contrast to what should be expected by the direct addition of methylene ligand of the reagent to the transoidal and most stable co-planar conformation of the conjugated ester systems, *e.g.* (36), (37) and (38).

It may be considered that the addition did take place in an ionic and two-step fashion (11), as Hoberg postulated. This seems, however, unlikely since the electrophilicity of the reaction was evidently shown in favor of the mechanism proposed by Simmons and Smith denying the apparent nucleophilic nature to be demanded by the Hoberg postulation. The yields of cyclopropane products were far much higher in runs 6 and 14 where the unsaturation was removed from the electron-withdrawing group than in α , β -conjugated series.

It has been known that the steric course is altered dramatically by the pres-

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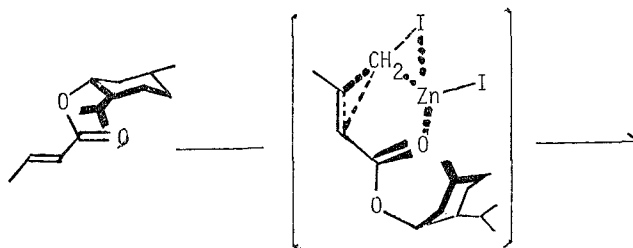
Table 1.

Run	(-)-Menthyl ester (M)	Cyclopropane	Reagent	yield, %	$[\alpha]_D^{20}$ (neat) deg	Optical yield, %	Absolute confign
1			Zn/Cu	21	+1.73	2.8 ^a	
2			Zn	20	+4.3	7.0	
3		(48)	Zn, AlCl ₃	35	+2.40	3.8	1S,2S ^a
4			Zn/Cu, Et ₃ N	12	+4.45	7.1	
5			Cd/Cu, BF ₃	25	+0.80	1.3	
6			Zn/Cu	54.5	+1.77	...	1R,2S ^b
7			Zn/Cu	16.5	+6.6 (MeOH)	...	S ^b
8			Zn/Cu	14	+12.8	6.4 ^c	1S,2S ^d
9			Zn/Cu	33	-29.3	9.3 ^d	
10			Zn	20	-21.8	7.0	
11		(46)	Zn/Cu, AlCl ₃	12.5	-7.8	2.5	1R,2R ^e
12			Zn/Cu, CuCl	11	-13.5	4.3	
13			Cd/Cu, BF ₃	7	-15.1	5.0	
14		(60)	Zn/Cu	35	+4.1	1.4	1R,2S

a; Based on the maximum rotation, +61, ref.68; b; ref. 82; c; Based on the maximum rotation +200, ref. 81; d; maximum rotation, +311, ref.67; e; ref. 74,

ence of catalytic amount of cuprous ion⁸³) in the conjugate-addition of the Grignard reagent to α, β -unsaturated esters. This possibility can be safely excluded by the experimental fact that even in the absence of copper (runs 2 and 10), the reactions gave rise to the cyclopropane acids of the same sign of rotation as those in the presence of copper and cuprous chloride (run 12).

In general the organometallic reagent coordinates with the lone pair on oxygen function. It then seems more likely that the present operation involves the simultaneous coordination of zinc atom of the reagent with the ester carbonyl oxygen. This would necessitate a twisted cisoidal conformation of the substrate in order to attain a bicyclo-[3, 1, 0]-transition state (57), and therefore should naturally lead to the formation of (+)-(S), (+)-(1S, 2S) and (+)-(1R, 2S)-cyclopropane products in predominance over the respective enantiomers.

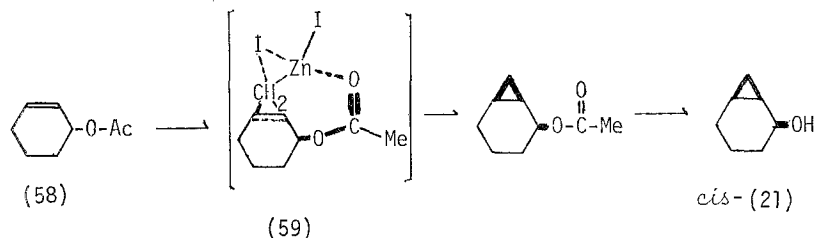


(57)

Sims⁵⁰) and Wittig³⁰) have suggested the complex formation of the ester carb-

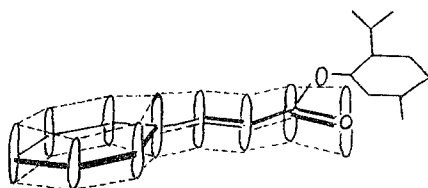
Studies on the Simmons-Smith Reaction

onyl function with the reagent. In the present work, the addition of the Simmons-Smith reagent to 2-cyclohexenyl acetate (58) gave exclusively *cis*-(21) which was the same geometrical isomer as that resulted from 2-cyclohexenol, thereby supporting the probable coordination (59) of zinc atom in the reagent with ester carbonyl oxygen.



As a test for the validity of the postulated bicyclic intermediate formation (57), (-)-menthyl *trans*-3-pentenoate (run 6) was subjected to the same procedure. In this system, the double bond is removed by one methylene from the carbomethoxy group. This isolation would favor the electrophilic addition of the reagent to the double bond and would also accommodate the reagent in a less strained bicyclo-[4, 1, 0]-cisoidal transition state conformation. Consistent well with this prediction, the corresponding cyclopropane product was obtained in a higher yield with the same sign of rotation.

Now in the exceptional cases of (-)-menthyl cinnamate (runs 9-13), the Cram-Prelog model was obeyed. In simpler olefinic systems, a phenyl group is often more effective than an alkyl function in releasing electron⁸⁴⁾ to the reaction site, so that the ester carbonyl oxygen of the cinnamate is expected to be more basic to coordinate with zinc atom of the reagent. On the other hand, the effective and strong overlap resonance of this fully conjugated system (64) would inhibit the deviation from the co-planarity of the system, especially from the transoidal co-planarity, to attain the twisted cisoidal transition state. Consequently the cinnamate would maintain the transoidal co-planar conformation predominantly even though the reagent may or not coordinate with the ester carbonyl function. Subsequently the methylene ligand should attack to the carbon-carbon unsaturation from, so called, the less hindered side, *re-re* face, of the substrate and should naturally give rise to the (-)-(1*R*, 2*R*)-(46) predominantly.



(64)

In connection with the anomaly in the cinnamate system and the postulate of twisted cisoidal coordination intermediate (57) in others, the reaction of (-)-menthyl *trans*-4-phenyl-3-butenate (run 14) is of particular interest. Here the full

conjugation in the cinnamate system was intercepted by the introduction of one methylene between the double bond and carboxylate, and there would be no more reluctance of this system to undergo deviation from the co-planarity. A similar situation to run 6 may now prevail in the present system; a twisted cisoidal conformation of bicyclo-[4, 1, 0]-pattern could be readily accommodated in a less strained transition state complex. Thus the transition state geometry was reflected in the opposite sign of rotation and the (1*R*, 2*S*)-configuration of the product **60**.

The addition of catalytic amount of Lewis acids and base, such as aluminum chloride, boron trifluoride, cuprous chloride and triethylamine (run 3-5 and 11-13), neither resulted any influence on the yield nor altered the steric course of the reaction. The role of these acids in this reaction may be considered as merely facilitating the formation of the reagent²³⁾ and enhance the electrophilicity of it as demonstrated by the cadmium counterparts.

Zinc may be replaced by cadmium in the Simmons-Smith reaction (runs 5 and 13). The formation of a cadmium complex from methylene iodide and cadmium-copper couple was effected readily by the presence of boron trifluoride and the reaction of this reagent with olefins differed little in yield and steric course from that with zinc reagent.

A viscous precipitate formed upon addition of triethylamine to the preformed solution of the reagent may be responsible for a poorer yield (run 4).

The dextrorotatory *trans*-(**60**) was assigned to (1*R*, 2*S*)-configuration by the unequivocal chemical transformation into (+)-*trans*-2-phenylcyclopropanecarboxy-

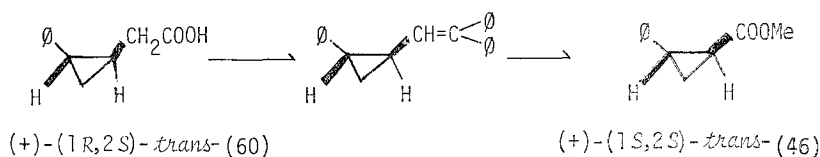


Table 2.

Physical Properties of Starting Menthyl Esters			
Menthyl ester	Bp (mm) or mp, °C	n_D^{20}	$[\alpha]_D^{20}$ (EtOH), deg
Crotonate ^a	114-118(5), 22.5	1.4662	-86.4 ^a
<i>trans</i> -3-Butenoate ^a	88-89(0.2)	1.4611	-72
Senecioate ^b	104-106(0.2), 35-36		-80.4
Fumarate ^c	194-195(0.1)	1.4824	-74
Cinnamate	140-141(0.1)	1.5422	-71.2
<i>trans</i> -4-Phenyl ^d 3-butenate	145-147(0.06)	1.5195	-68.3(MeOH)

a; H. Rupe, *Ann.*, **369**, 311 (1909), b; ref. 62, c; A. McKenzie and H. Wren, *J. Chem. Soc.*, **91**, 1215 (1907), d; The structure was substantiated by uv analyses ($\lambda_{\text{max}}^{250\text{m}\mu}$, ϵ 16,800), ozonolysis to give benzoic and malonic acids, and correct elemental analysis (*Anal.* Calcd for $\text{C}_{20}\text{H}_{28}\text{O}_2$: C, 79.95; H, 9.39. Found: C, 80.68; H, 9.08). Cf. R. P. Linstead and L. T. D. Williams, *J. Chem. Soc.*, 2741 (1926).

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Table 3.

Analytical Data of Derivatives of Cyclopropane Products

Product	Bp, °C(mm)	n_D^{20}	Derivative	Mp, °C	Molecular formula	Calcd, %		Found, %	
						C	H	C	H
(48)	98-100(18) ^a	1.4374	-Phenylphenacyl ester	108	C ₁₉ H ₁₈ O ₃	77.53	6.16	77.76	6.42
(63)	109-112(18)	1.4339	same above	58.5	C ₂₀ H ₂₀ O ₃	77.90	6.54	78.10	6.64
(62)	96-96.5(17) ^b	1.4390	same above	102	C ₂₀ H ₂₀ O ₃	77.90	6.54	77.42	6.54
(45)	96-99(16) ^c	1.4420	Acid	176	C ₅ H ₆ O ₄	46.16	4.65	45.21	4.62
(60)	117-118(0.1)	1.5329	Acid	41	C ₁₁ H ₁₂ O ₂	74.97	6.85	74.68	7.01
(46)	126-127(9.5) ^a	1.5284	Acid	89-90	C ₁₀ H ₁₀ O ₂	74.05	6.22	73.92	6.19

a; D.E. Applequist, *et.al.*, *J. Amer. Chem. Soc.*, **82**, 2372 (1960). b; E.R.Nelson, *et.al.* [*ibid.*, **79**, 3467 (1957)], recorded bp 95-98(12) and n_D^{20} 1.4405. c; M.Jacobson, *et.al.* *Science*, **147**, 748 (1965), recorded bp. 103-104(24) and n_D^{20} 1.4418.

lic acid (46), of the known (1*S*, 2*S*)-configuration. An identical conclusion may be reached by the Brewster calculation⁸²⁾ of the conformational asymmetry, $[\phi]_D$ calcd.+140°, found+476°.

Experimentals for II-1:

Partial asymmetric synthesis in the present Simmons-Smith reaction is illustrated by a typical run for the (-)-menthyl crotonate to give *trans*-2-methylcyclopropanecarboxylic acid (48), and the identical procedure was followed for others with small variation of additives.

trans-2-Methylcyclopropanecarboxylic acid (48):

A solution of methylene iodide (27 g., 0.1 mole) and zinc-copper couple (13g., 0.2 atom, in dust) in 150 ml of ether was stirred for 0.5 hr and then (-)-menthyl crotonate (11g., 0.05 mole) was added to the solution. After reflux for 60 hr, the reaction mixture was poured into ammonium chloride solution. The organic layer was washed several times with water, aqueous thiosulfate and dried over anhydrous magnesium sulfate. Ether was removed and the residue was distilled to give a fraction boiling at 110-30°/17 mm, which was treated with ozone in carbon tetrachloride solution. The ozonide was decomposed with dilute sodium hydroxide solution and the organic layer was dried over anhydrous magnesium sulfate. After removal of the solvent, the residual oil was hydrolyzed with sodium hydroxide in boiling water-ethylene glycol (2:1) solution for 36 hr. The alkaline solution was thoroughly extracted with ether to remove menthol. The water layer was acidified with hydrochloric acid and then extracted with ether. The combined extract was washed with aqueous sodium chloride and dried over anhydrous sodium sulfate. Distillation of the solvent-free product gave (48), b.p. 98-100°/18 mm, n_D^{20} 1.4374, yield 1.2 g., (21 %), $[\alpha]_D^{20}$ +1.73° (neat), optical yield 2.8 % (See Table 1, 2 and 3).

Chemical Correlation of (+)-*trans*-(60) to (+)-(1*S*, 2*S*)-*trans*-(46):

The dextrorotatory (60) (0.9 g., $[\alpha]_D^{20}$ +4.1°) was converted with diazomethane into the corresponding methyl ester (b.p. 150-2°/17 mm, n_D^{20} 1.5164). An excess of phenylmagnesium bromide (4 mole equiv.) was added to the methyl ester (0.9

g.) in absolute ether and the reaction mixture was refluxed for 4 hr. The resulted solution was worked up in a usual manner and then treated with phosphorous pentoxide in boiling benzene. The distillate (b.p. 130–40°/0.1 mm) was ozonized to give, after treatment in conventional procedure and subsequent esterification, methyl ester of (+)-(1*S*, 2*S*)-*trans*-(46); b.p. 133–4°/17 mm, n_D^{20} 1.5269, yield 0.3 g., $[\alpha]_D^{20} + 4.4^\circ$, ($c = 4.75$, in methanol). The i.r. and n.m.r. spectra were identical with those of the authentic sample.

***cis*-Bicyclo-[4, 1, 0]-heptan-2-ol (21) :**

According to the Dauben procedure, the bicyclic alcohol (21) was prepared in a 65 % yield from 2-cyclohexenol; b.p. 75–6°/17 mm, n_D^{20} 1.4890. About 3 % contamination of *trans*-(21) was detected in the crude product by g.l.p.c. analysis. Phenylurethan melted at 109–9.5°.

***cis*-Bicyclo-[4, 1, 0]-heptan-2-ol (21) from (58) :**

An identical procedure was followed for (58), b.p. 75–6°/17 mm, n_D^{20} 1.4590, and after subsequent reduction with lithium aluminum hydride of the reaction mixture, *cis*-(21) was obtained in a 23 % over-all yield. The product was contaminated by *trans*-(21), 5 %, as detected by g.l.p.c. analysis. The phenylurethan of *cis*-(21) had m.p. 109.5°. (Anal. *Calcd.* for $C_{14}H_{17}O_2N$, C, 72.70; H, 7.41; N, 6.06, *Found* C, 72.61; H, 7.45; N, 6.17). The phenylurethan of *trans*-(21) had m.p. 97.5–8° (*Anal. Found*, C, 72.74; H, 7.41; N, 6.24).

The identity of *cis*-(21) by this route was obtained by the comparison of i.r. spectrum and r.t. on g.l.p.c. and other physical properties and phenylurethan derivative with those of the authentic sample prepared by the Dauben procedure.

II-2. Preparation of a Chiral Simmons-Smith Reagent and the Reaction with Achiral olefins :

The accelerating and directing influence of the hydroxyl group on the steric course of the Simmons-Smith reaction has been pointed out in some cases (20) and (21), and it has been proved that in the reaction of olefinic alcohol, methyl-

Table 4.
Yields of 1-Methyl-2-hydroxymethylcyclopropane by the Reaction of Crotyl Alcohol and Sodium Crotylate with the Present^b and the Simmons-Smith Reagents

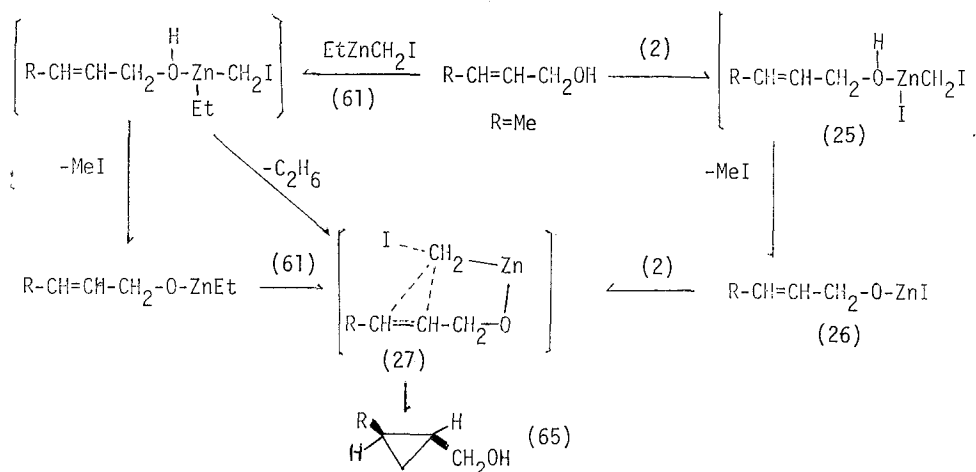
Run	Olefin	Mol equiv. of Simmons-Smith Reagent	Present Modif. (as EtZnCH ₂ I)	Reaction (hr)	Yield %
1	Crotyl Alc.	1		5	8
2	Crotyl Alc.	2.5		5	65
3	Sodium Crotylate	1		0.5	53
4	Crotyl Alc.		1	0.5	27
5	Sodium Crotylate		1	0.5	60

a; ref. 85, bp.131, n_D^{20} 1.4284; b; see the Part II-3

ene transfer occurs intramolecularly through either a zincate (27) or a merely coordinate complex (25), so that in any case the addition predominates only from the side of double bond nearest the oxygen atom.

To make a choice between (25) and (27), the following experiments are worthwhile noting, to which the author will return again in connection with the improvement of the reaction procedure (*vide infra*).

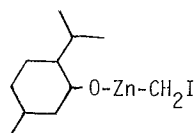
When crotyl alcohol was allowed to react with equimolar of (2), 1-methyl-2-hydroxymethylcyclopropane (65) was just sparingly produced (8 %, run 1), whereas with the use of an excess of the reagent (run 2) a much higher yield (65 %) of (65) was obtained. A similar trend was observed in run 3 where sodium crotylate was employed instead of the free alcohol with equimolar of (2). This observation suggests that unsaturated alcohol primarily contacts with zinc atom in the reagent to form a coordinate complex (25) which in turn dissociates predominantly to give (26) together with elimination of methyl iodide so far as alcoholic hydrogen is available. It then seems likely that the salt (26) thus formed, (or sodium crotylate in run 3) undergoes a spontaneous substitution with surplus methylene transfer reagent to form a zincate, iodomethylzinc crotylate (27), which decomposes eventually to afford cyclopropane product (65). The runs 4 and 5 stand for this postulation.



Now the modification of the Simmons-Smith reagent in type of R-O-ZnCH₂I⁽⁸⁷⁾ is feasible. In this connection it seems of interest to undertake the reaction of this reagent, in particular, involving a chiral R- group, with achiral olefins in expectation of the possible asymmetric induction⁽⁸⁹⁾ of cyclopropanes.

The Simmons-Smith reaction of various achiral olefins in the presence of 0.3 mole equivalent of free (-)-menthol under the standardized conditions afforded the corresponding cyclopropane products with optical activity (Table 5). The achievement of partial asymmetric synthesis obviously corroborates the active species to be (-)-menthoxyiodomethylzinc (66) in the present system and shows the stereochemical participations of the chiral moiety of menthoxy group in transition state leading to the chiral products.

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(66)

This mechanistic requirement can be met only by the one-step methylene-transfene mechanism³³⁾ involving a three-center intermediate (4) and not by the two-step mechanism.³²⁾ According to the latter mechanism, the addition of (66) first formed to the double bond of the substrate can not be the asymmetric induction in these cases of runs 7, 8 and 9. And the subsequent cyclization, (intramolecular nucleophilic displacement) also would proceed under no significant influence of zinc (-)-menthoxylate cation, so that asymmetric induction would not be expected.

Both the reaction and optical yields in the present systems were found poor amounting to 18 and 3.4 % respectively at most, but the sign of rotation found for the cyclopropane products of fully substantiated structures is decisive for the assignment of the absolute configuration. As can be seen from the data in Table 5, the present reaction afforded unexceptionally the levorotatory cyclopropanes of the (*R*)- and (1*R*, 2*R*)-configurations. Although the transition state geometry has not been elucidated as yet, the present data seem to permit one to formulate an empirical correlation between the absolute configuration of (-)-menthol employed here and those of the resulting chiral cyclopropane products. This may provide one with a useful means of predicting absolute configuration of cyclopropanes in general.

An attempt of the asymmetric synthesis in the Simmons-Smith reaction in a chiral medium, (-)-menthylmethylether, was doomed to failure, since the reagent

Table 5.

Simmons-Smith Reaction of Achiral Olefins in the Presence of (-)-Menthof

Run	Olefin	Cyclopropane Product	Yield, %	$[\alpha]_D^{25}$ (neat) deg	Optical yield, %	Abs. Confign.
1		(48)	6.0	-1.2	1.9	<i>R,R</i>
2		(46)	7.0	-1.2	0.7	<i>R,R</i>
3		(45)	5.0	-6.8(MeOH)	3.4	<i>R,R</i>
4			9.0	-2.3(MeOH)	1.1	<i>R,R</i>
5		(47)	12.0	-3.2		<i>R,R</i> ^a
6		(55)	18.0	-0.3		<i>R,R</i>
7		(51)	12.0	-0.28	0.3	<i>R</i>
8		(62)	18.0	-0.2		<i>R</i>
9			15.0	-0.7		<i>R</i>

a; ref. 86

can only be formed with great difficulty in this solvent.

In experiments with various molar ratios of (-)-menthol to achiral olefins, no remarkable change was observed, but the yield of the products decreased with increasing amount of alcohol.

Experimentals for II-2:

Partial asymmetric synthesis of cyclopropanes by the Simmons-Smith reaction with achiral olefins in the presence of (-)-menthol is illustrated by a typical procedure. Identical procedure was followed for other runs with the substrate olefin varied.

(-)-(*R*)-1, 1-Diphenyl-2-methylcyclopropane (51):

Zinc-copper couple (13 g., 0.2 atom, in powder), and methylene iodide (27 g., 0.1 mole) in 150 ml of absolute ether were stirred for 0.5 hr and then (-)-menthol (5 g., 0.03 mole) in 20 ml of ether was added to the preformed solution of the reagent, when a mild exothermic reaction took place. After the reaction ceased, 1, 1-diphenyl-1-propene (b.p. 100-5°/0.5 mm., n_D^{25} 1.5990, m.p. 45-8°, 10 g., 0.05 mole) in 20 ml of ether was added together with a few drops of boron trifluoride etherate. The reaction mixture was refluxed for 30 hr and then was decomposed, washed several times with aqueous thiosulfate, and dried over anhydrous sodium sulfate. After removal of ether, the residue was ozonized in carbon tetrachloride solution to remove the unreacted olefin. After usual work-up of the ozonide, the neutral fraction was eluted on alumina to give pure (-)-(*R*)-(51), completely free from (-)-menthol and benzophenone as indicated by i.r. and g.l.p.c. spectra b.p. 104-5°/0.1 mm., n_D^{20} 1.5764, $[\alpha]_D^{20}$ -0.28° (neat) yield 1.2 g..

Table 6.

Physical Properties and Analytical Data of Cyclopropanes^a

Cyclopropane	Bp, C (mm)	n_D^{25}	Mp, C	Molecular formula	Calcd, %		Found, %	
					C	H	C	H
(68)			220	C ₇ H ₁₀ O ₄	53.16	6.37	52.94	6.47
(47)	95(17)	1.5142		C ₁₀ H ₁₂	90.85	9.15	89.12	10.33
(55)	99-100(0.1)	1.5980		C ₁₅ H ₁₄	92.74	7.26	92.47	7.53
(51)	104-105(0.1)	1.5764		C ₁₆ H ₁₆	92.26	7.74	92.51	7.70

^aFor other cyclopropane the data were identical with those of Pare I. Compound, (67) was identified by i.r. spectrum and also by the conversion in to (62).

II-3. A Novel Improvement of the Simmons-Smith Reaction:

In search for a more active reagent and/or effective procedure for the cyclopropane synthesis, many attempts to improve the Simmons-Smith reaction have been carried out. In general, reagents of the type-(1) are known to transfer the methylene ligand to carbon-carbon unsaturation. The alteration of metal in the complex has been achieved by Wittig over a wide range of normal potential of metals³⁰⁾ without any available evidence for successful cyclopropane formation.

Furukawa and his collaborators^{57,59)} have modified the reaction by replacing

zinc-copper couple with diethylzinc, which has brought about remarkable improvements in the reaction yield.

In practical performance of a cyclopropane synthesis by means of either the conventional reaction procedure originated by Simmons and Smith and subsequently developed by many workers²⁸⁾ or the recent modification introduced by Furukawa, inconvenience the worker encounters is the sluggishness and fluctuation in reactivity of the prepared reagent, which necessitates longer reaction period not less than 50 hr usually in the former procedure, and the dangerous explosion hazards on handling diethylzinc in the latter modification.

Substantial improvement of the reaction is duly desirable and it is natural that the present author's attention was directed to the above-mentioned defects; *i.e.* he aimed at such modifications as to enable one to ensure the preparation of the reagent with a high and constant reactivity from commoner reagents in a usual manner, and to obtain better yields of the cyclopropane products in a more shortened reflux period, suppressing any possible side reactions.

It seems to be not the metal atom itself, though essential for the complex-formation, but the other ligands that is responsible for the cyclopropane formation in the reaction of (1) with olefins and affects delicately the reactivity of the intermediate complex. The variety of the ligand Y in ICH_2MY (1) has been iodide, iodomethyl, benzoxy^{30-f)} and ethyl⁵⁷⁾ groups in the literature.

As has been detailed in Introduction I-1, the complexes containing the groups-II and -III metals other than zinc are inactive or just poorly effective for the methylene transfer reaction to give cyclopropane products. For example, both (14) and (15) obtained by substitution³⁴⁾ of isopropylmagnesium iodide with methylene iodide at dry ice-temperature failed to react with olefins under the conditions to afford cyclopropane. The former (14) however, reacted at -70°C with cyclohexene to give norcarane in the presence of equimolar zinc iodide or cadmium iodide (8 or 5% yield respectively).

Having been suggested by the analogy with those described above, some further modifications of the procedure were devised. The present work is consisted in the reaction of ethyl iodide with zinc-copper couple which gave ethylzinc iodide in an equilibrium with diethylzinc plus zinc iodide, and subsequent introduction of methylene iodide and olefin as substrate. A mild reaction took place upon the addition of methylene iodide and olefin under stirring at room temperature. After the period (0.5-5 hr) the reaction mixture was worked up as usual to give the corresponding cyclopropane products. In Table 7, were summarized the yields of cyclopropane obtained by the present procedure in comparison with those by the Simmons-Smith method and by the Furukawa modification.

The treatment of enamine (run 12) with the present organozinc reagent in ether-tetrahydrofuran (1:1) solution resulted in the formation of 1-piperidion-bicyclo-[4, 1, 0]-heptane without any separation of gelatinous precipitate.⁵⁵⁾





















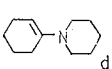

An equilibrium as schemed below is conceivable for the present system and the operating species responsible for methylene-transfer may be either ethyliodo-methylzinc (61), (3) or (2).

Both the reactivity and the yield in the present modification surpassed those

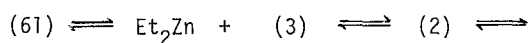
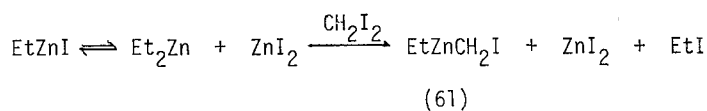
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Table 7.

Yields of Cyclopropanes by the Present Procedure in comparison with Those by the Simmons-Smith Reaction and the Furukawa Modifn.

Run	Olefin ^a	Cyclopropane product	Reaction period, hr	Yield, %		
				Present work	Simmons-Smith	Furukawa ⁱ
1			2	92	61 ^e	79
2			1	80	65 ^e	
3			3	78	32 ^e	76
4		 (47)	3	68	54 ^e	
5		 (55)	3	13		
6	 b	 (55)	3	48	18 ^f	
7	 b	 (51)	3	45	17 ^f	
8	π -Hex- 	π -Hex- 	3	77	70 ^e	60
9	π -Bu-O- 	π -Bu-O- 	1	15		92
10	 c	 (48)	3	24	9 ^e	
11	}  d		1	15	(8) ^h	
12			1	28		

a; mol ratio of olefin: CH_2I_2 : EtZnI =1:1:2 in all runs except 6, 10 and 12. b; ratio=1:3:6. c; mol ratio=1:2:2, d; solvent composition, ether: T.H.F=1:1. e; ref. 23. f; see the Present work II-g. g; by g.l.p.c. analysis, ref. 57. h; ref. 55.



in the conventional Simmons-Smith procedure and compared well with those in the Furukawa modification except the induction of olefin polymerization as easy as in the conventional procedure (run 9), so that the active intermediate may reasonably be looked upon as being (61). Thus the reaction mechanism may be essentially the same as in the Furukawa method.

The present modification offers the advantages over the procedures hitherto employed in that one is able to obtain (1) the better yields of cyclopropanes (2) in a far shorter reaction period and (3) to conduct the reaction in a homogeneous phase with the constant reactivity, and (4) to avoid the risk of explosion hazard of diethylzinc in the Furukawa procedure.

Experimentals for II-3:

The cyclopropane synthesis in the present modification is exemplified by the typical run with cyclohexene to give norcarane (run 1) and essentially the same procedure except in runs 6 and 12, was followed for other runs in the mol ratio of olefin: EtZnCH₂I=1:1.

Synthesis of norcarane (run 1): Methylene iodide (15 g., 0.055 mole) was added to an aliquot of the stock solution (100 ml) containing 2 mole equivalent of active ethylzinc iodide and the reaction mixture was stirred at 30-35° for 1 hr. To the chilled solution, cyclohexene (4.1 g., 0.05 mole) was added and the mixture was refluxed under stirring and after 2 hr, *ca.* 50 ml of ether was distilled off. The resulting mixture was decomposed with water and hydrochloric acid solution and the organic layer was separated, washed several times with water, sodium thiosulfate solution and again water, and dried over anhydrous magnesium sulfate. The solution which contained norcarane in a 92 % yield as determined by g.l.p.c. analysis was ozonized to remove unreacted cyclohexene. After drying over anhydrous magnesium sulfate the solution was distilled to give norcarane boiling at 115-7°, n_D^{25} 1.4540. The i.r. and n.m.r. spectra were identical in every respect with those of the authentic specimen, yield 2.8 g.. Additional amount of norcarane (1 g.) was recovered by the rectification of the forerun (b.p. 70-115°), totalizing the yield as 3.8 g. (88 %).

The cyclopropane product in each run was identified by g.l.p.c., i.r. and n.m.r. spectral comparisons with the respective authentic specimen. The yields were estimated by g.l.p.c. analysis except in runs 2, 9, 11 and 12, where actually isolated.

Stock solution of ethylzinc iodide: Ethyl iodide (156 g., 1 mole) was allowed to react with zinc copper couple (70 g., 1 atom) in absolute ether (900 ml), and the mixture was stirred at room temperature overnight. The supernatant liquid was withdrawn free from sludge and stored in a stoppered flask carrying a drying tube. After storage at room temperature for a week, no precipitate formed and the activity of the solution was kept unchanged.

Synthesis of 1-(1-piperidino)-bicyclo-[4, 1, 0]-heptane (run 12): Methylene iodide (6 g., 0.02 mole) was allowed to react with ethylzinc iodide (40 ml of the stock solution, 0.04 mole) and 40 ml of absolute tetrahydrofuran was added to the solution. After 1 hr stirring, 1-(1-piperidino)-cyclohexene (b.p. 120°/17 mm., n_D^{20} 1.5120,⁸⁸) 3 g., 0.018 mole) was introduced at 30-40° and the mixture was refluxed for an additional hr. The reaction mixture was hydrolyzed with hydrochloric acid and then was made alkaline with sodium carbonate. The organic layer, which exhibited a single peak of the product on g.l.p.c. analysis and indicated the absence of the parent enamine, was washed with saturated solution and dried over anhydrous magnesium sulfate. After removal of the solvent, the residual oil was distilled to give 1-(1-piperidino)-bicyclo-[4, 1, 0]-heptane, b.p. 115°/17 mm., n_D^{25} 1.4889. *Anal. Found:* C, 80.10; H, 11.93; N, 7.66; *Calcd.* for C₁₂H₂₁N: C, 80.38; H, 11.81; N, 7.81. Yield 0.9 g. (28 %).

II-4. Summary

Partial asymmetric synthesis was for the first time achieved in the Simmons-Smith reaction which involved the methylene transfer of the achiral reagent toward (-)-menthyl esters of α , β - and β , γ -unsaturated carboxylic acids to give the corresponding (+)-(*S*)- and (+)-(*1S, 2S*)-cyclopropanecarboxylic acids, with the exception of the cinnamate system where (-)-(*1R, 2R*)-acid was produced.

In an alternative way, the reaction of a chiral reagent of iodomethylzinc (-)-menthoxyolate with achiral olefins resulted in the formation unexceptionally of (-)-(*R*)- and (-)-(*1R, 2R*)-cyclopropane products. Both asymmetric reactions unequivocally confirmed the operation of the one-step and three-center mechanism in this type of reaction.

The steric course of the former system was successfully accounted for by the coordination of ester carbonyl oxygen with zinc atom in the reagent at the transition state. The latter asymmetric induction provides one with a useful means of assigning the absolute configuration to cyclopropane in general.

Substantial improvement has been introduced for the procedure of the cyclopropane synthesis, which consisted of a prior reaction of ethyl iodide with zinc-copper couple and subsequent addition of methylene iodide and substrate olefins to the preformed organozinc solution. The present modification may involve the operation of ethyliodomethylzinc as the active species and is advantageous over the hitherto reported procedures in enabling one to conduct the reaction in a homogeneous phase with a constantly secured reactivity of the reagent in shorter reaction periods and even to obtain much-improved yields.

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