Name Reactions for Carbocyclic Ring Formations

Edited by

Jie Jack Li
Bristol-Myers Squibb Company

Foreword by

E. J. Corey
Harvard University

WILEY

A JOHN WILEY & SONS, INC., PUBLICATION

This page intentionally left blank

Name Reactions for Carbocyclic Ring Formations

Wiley Series on Comprehensive Name Reactions

Jie Jack Li, *Series Editor*

Name Reactions in Heterocyclic Chemistry
Edited by Jie Jack Li

Name Reactions of Functional Group Transformations
Edited by Jie Jack Li

Name Reactions for Homologation, Part 1 and Part 2
Edited by Jie Jack Li

Name Reactions for Carbocyclic Ring Formations
Edited by Jie Jack Li

Name Reactions for Carbocyclic Ring Formations

Edited by

Jie Jack Li
Bristol-Myers Squibb Company

Foreword by

E. J. Corey
Harvard University

WILEY

A JOHN WILEY & SONS, INC., PUBLICATION

Published by John Wiley & Sons, Inc., Hoboken, New Jersey.

Published simultaneously in Canada.

Library of Congress Cataloging-in-Publication Data:

Name reactions for carbocyclic ring formations / edited by Jie Jack Li ; foreword by E.J. Corey.
p. cm.
Includes index.
ISBN 978-0-470-08506-6 (cloth)
1. Ring formation (Chemistry) I. Li, Jie Jack.
QD281.R5N36 2010
547'.2—dc22 2010008429

Printed in the United States of America.

10 9 8 7 6 5 4 3 2 1

Dedicated to Professor Keith R. Fagnou

June 27, 1971–November 11, 2009

This page intentionally left blank

Contents

Foreword

Part of the charm of synthetic organic chemistry derives from the vastness and multidimensionality of the intellectual landscape. First, there is the almost infinite variety and number of possible target structures that lurk in the darkness waiting to be made. Then there is the vast body of organic reactions that serve to transform one substance into another, now so large in number as to be beyond credibility to a nonchemist. There is the staggering range of reagents, reaction conditions, catalysts, elements, and techniques that must be mobilized in order to tame these reactions for synthetic purposes. Finally, it seems that new information is being added to that landscape at a rate that exceeds the ability of a normal person to keep up with it. In such a challenging setting, any author or group of authors must be regarded as heroic if through their efforts, the task of the synthetic chemist is eased.

This volume on methods for formation of carbon rings brings to the attention of practicing synthetic chemists and students of chemistry a wide array of tools for the formation of such rings by synthesis. Since cyclic structures are among the most useful molecules, it is a valuable addition to the literature that will prove its merit for years to come. The new knowledge that arises with its help will prove to be of great benefit to humankind.

E. J. Corey
February 1, 2010

This page intentionally left blank

Preface

This book is the fifth volume of the series *Comprehensive Name Reactions*, an ambitious project conceived by Professor E. J. Corey of Harvard University in the summer of 2002. Volume 1, *Name Reactions in Heterocyclic Chemistry*, was published in 2005. Volume 2, *Name Reactions for Functional Group Transformations* was published in 2007. Volumes 3 and 4 on homologations were both published in 2009. They have been warmly received by the organic chemistry community. After this Volume 5, *Name Reactions on Carbocyclic Ring Formations* is out in 2010, we will roll out the final volume, Volume 6 on *Name Reactions in Heterocyclic Chemistry—Part II*, in 2011. Continuing the traditions of the first four volumes, each name reaction in Volume 5 is reviewed in seven sections:

1. *Description,*
2. *Historical Perspective,*
3. *Mechanism,*
4. *Variations and Improvements,*
5. *Synthetic Utility,*
6. *Experimental, and*
7. *References.*

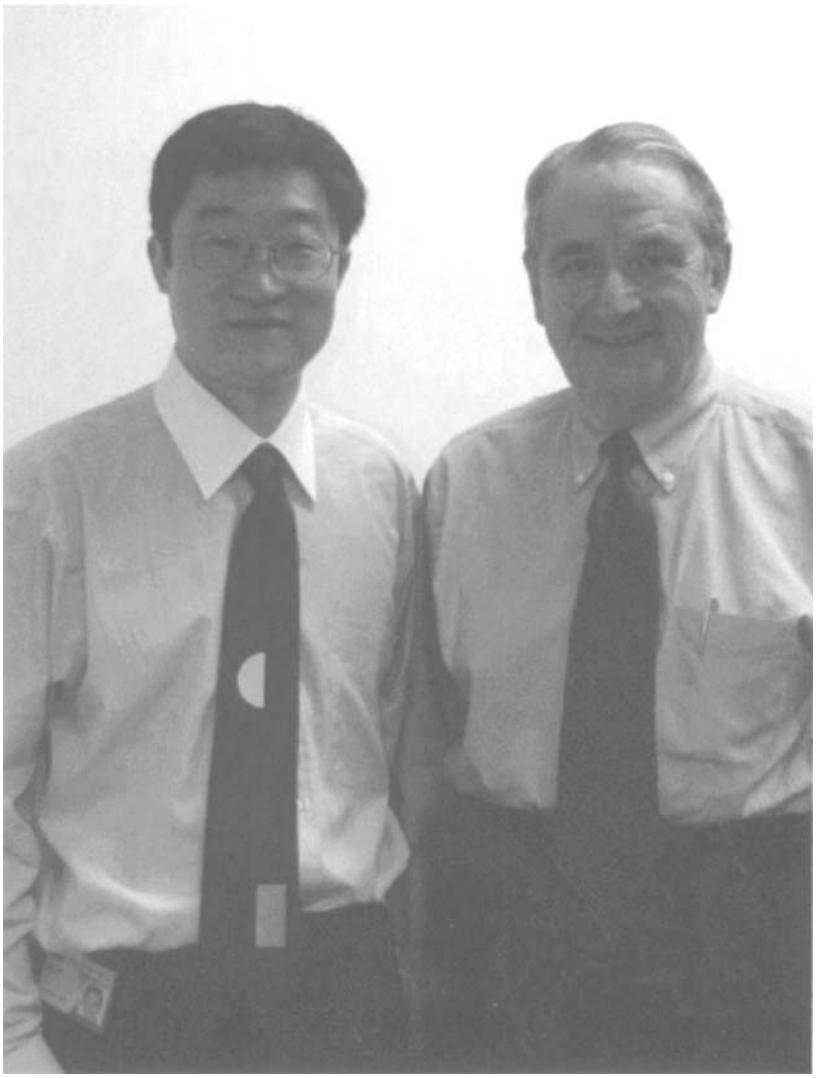
I also introduced a symbol [R] to highlight review articles, book chapters, and books dedicated to the respective name reactions.

I have incurred many debts of gratitude to Professor E. J. Corey. What he once told me — "The desire to learn is the greatest gift from God" — has been a true inspiration. Furthermore, it has been my great privilege and a pleasure to work with a collection of stellar contributing authors from both academia and industry. Some of them are world-renowned scholars in the field, some of them have worked intimately with the name reactions that they have reviewed, some of them even discovered the name reactions that they authored in this series. As a consequence, this volume truly represents the state-of-the-art for *Name Reactions for Carbocyclic Ring Formations*.

I welcome your critique.

Jack Li
February 1, 2010

This page intentionally left blank



Jie Jack Li and E. J. Corey, circa 2002

This page intentionally left blank

Contributing Authors:

Dr. Nadia M. Ahmad
Takeda Cambridge
418 Cambridge Science Park
Cambridge
CB4 0PA
United Kingdom

Dr. Jeffrey A. Campbell
Department of Chemistry
Lehigh University
Bethlehem, PA 18015

Dr. Louis S. Chupak
Discovery Chemistry
Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

Dr. Timothy T. Curran
Chemical Development
Vertex Pharmaceuticals
130 Waverly Street
Cambridge, MA 02139

Professor Roman Dembinski
Department of Chemistry
Oakland University
2200 North Squirrel Road
Rochester, MI 48309

Dr. Matthew J. Fuchter
Department of Chemistry
Imperial College London
London SW7 2AZ

Dr. Paul Galatsis
Medicinal Chemistry
Pfizer Global Research & Development
Eastern Point Road
Groton, CT 06340

Professor Brian Goess
Department of Chemistry
Furman University
3300 Poinsett Highway
Greenville, SC 29613

Dr. Martin E. Hayes
Medicinal Chemistry
Abbott Bioresearch Center
381 Plantation Street
Worcester, MA, 01605

Professor Nessan Kerrigan
Department of Chemistry
Oakland University
2200 North Squirrel Road
Rochester, MI

Dr. Ewa Krawczyk
Department of Heteroorganic Chemistry
Centre of Molecular & Macromolecular Studies
Polish Academy of Sciences
Sienkiewicza 112
90-363 Łódź, Poland

Dr. Jie Jack Li
Discovery Chemistry
Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

Noha S. Maklad
Medicinal Chemistry
Pfizer Global Research & Development
Eastern Point Road
Groton, CT 06340

Professor Richard J. Mullins
Department of Chemistry
Xavier University
3800 Victory Parkway
Cincinnati, OH 45207-4221

Dr. Kevin M. Peese
Discovery Chemistry
Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

Dr. Frank Rong
ChemPartner
No. 2 Building, 998 Halei Road
Zhangjiang Hi-Tech Park, Pudong
Shanghai, China 201203

Professor Kevin M. Shea
Department of Chemistry
Clark Science Center
Smith College
Northampton, MA 01063

Professor Nicole L. Snyder
Hamilton College
198 College Hill Road
Clinton, NY 13323

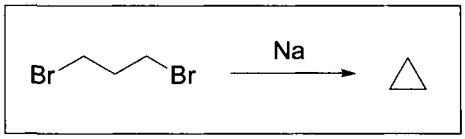
Dr. Stephen W. Wright
Medicinal Chemistry
Pfizer Global Research & Development
Eastern Point Road
Groton, CT 06340

Dr. Yong-Jin Wu
Discovery Chemistry
Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

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]

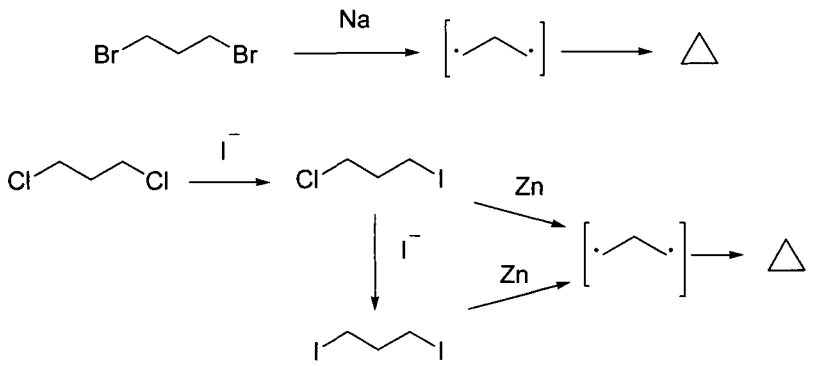
1.1.2 Historical Perspective

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]



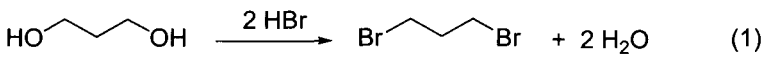
1.1.4 Variations and Improvements

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.

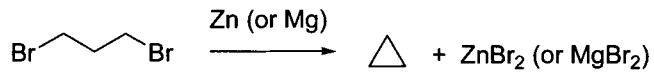
Hass has further modified the Gustavson reaction condition.[4] By using a large excess of zinc dust and by raising the temperature of the reaction mixture with high-boiling solvents, the rate of conversion was increased materially. When sodium iodide was added to a refluxing mixture of zinc dust, ethanol, 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.



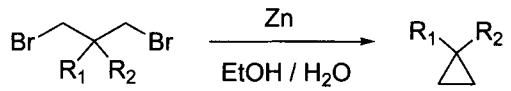
(1)



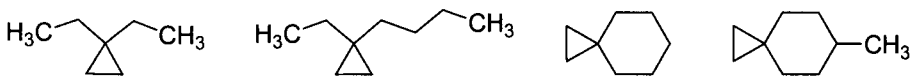
(2)

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.

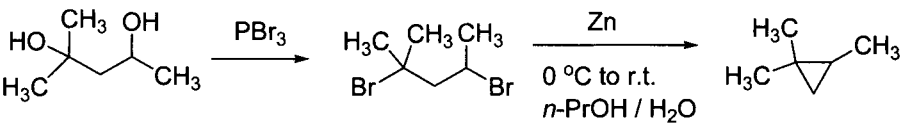
Shortridge and co-workers reported an extension of the Gustavson method for the synthesis of cyclopropane and its derivatives.[6] They successfully prepared spiranes containing a cyclopropane ring and provide an easy, straightforward way of producing this type of hydrocarbon in quantity and in a good 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%

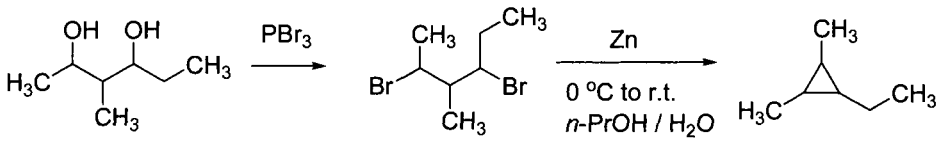


7 **8** **9**

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.

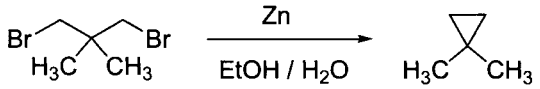
The 1,2-dimethyl-3-ethylcyclopropane **12** was similarly synthesized from 3-methyl-2,4-dibromohexane **11**.[7] A yield of 90% was obtained in the ring closure step. The secondary–tertiary and secondary–secondary 1,3-dibromides, **8** and **11**, were prepared in 90% yields by the reaction of phosphorus 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.

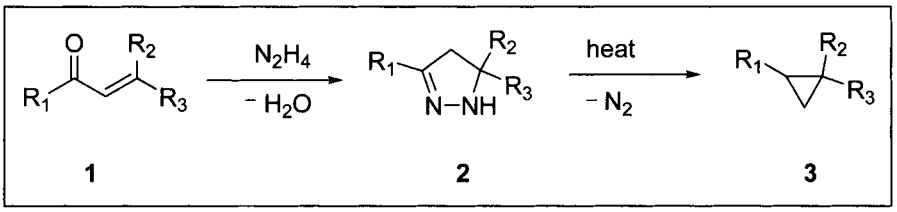
1.1.7 References

1. Freund, A. *Monatsh.* **1882**, *3*, 625–635.
2. Gustavson, G. *J. Prakt. Chem. (2)* **1887**, *36*, 300–303.
3. Gustavson, G.; Popper; J. *J. Prakt. Chem. (2)* **1898**, *58*, 458.
4. Hass, H. B.; McBee E. T.; Hinds, G. E.; Gluesenkamp, E. W. *Ind. Eng. Chem.* **1936**, *28*, 1178–1181.
5. Galasso, *Anesth. and Analges.* **1936**, *15*, 32.
6. Shortridge, R. W.; Craig, R. A.; Greenlee, K. W.; Derfer, J. M.; Boord, C. E. *J. Am. Chem. Soc.* **1948**, *70*, 946–949
7. Bartleson, J. D.; Burk, R. E.; Lankelma, H. P. *J. Am. Chem. Soc.* **1946**, *68*, 2513–2518.

1.2 Kishner Cyclopropane Synthesis

Frank Rong

1.2.1 Description



1 **2** **3**

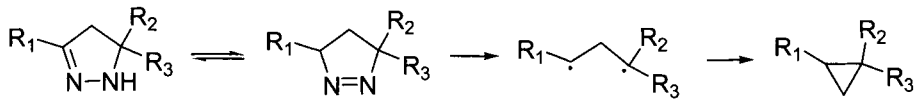
Kishner cyclopropane synthesis refers to the formation of cyclopropane derivatives **3** by decomposition of pyrazolines **2** formed by reacting α,β-unsaturated ketones or aldehydes with hydrazine.[1]

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

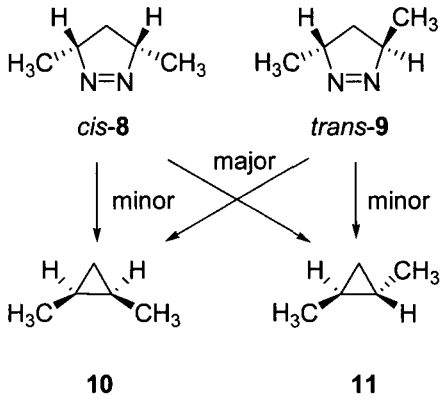
It is believable that the pyrazoline, **4** or **5**, undergoes thermolytic decomposition and gives the diradical **6** first. Then, the diradical formed a bond quickly to give the cyclopropane **7**.[2,3] This could be a reversible reaction between the diradical **6** and the cyclized product **7**.



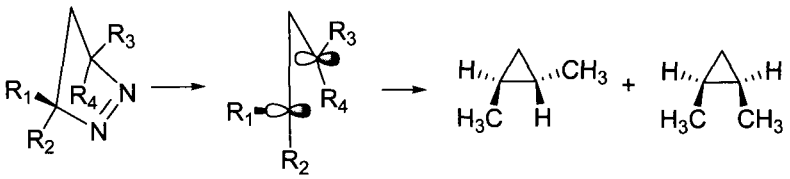
4 **5** **6** **7**

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.

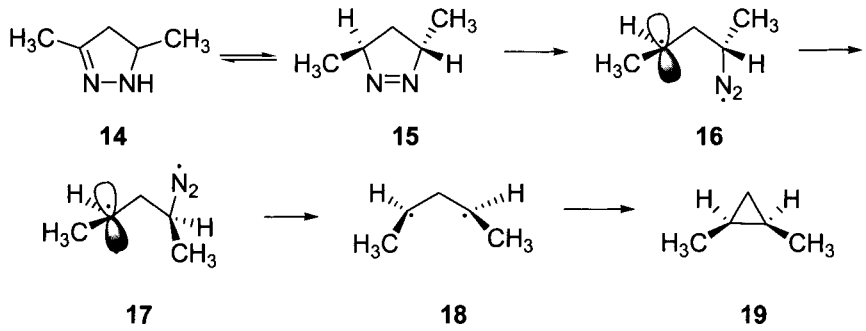


The research groups of McGreer[5,6] and Crawford[7–11] have done comprehensive investigation on the cyclic azo compounds thermal decomposition. Crawford's group investigated the stereochemistry problem in the thermal decomposition of *cis*- and *trans*-3,5-dimethylpyrazolines (**12** and **13**).[7] 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]



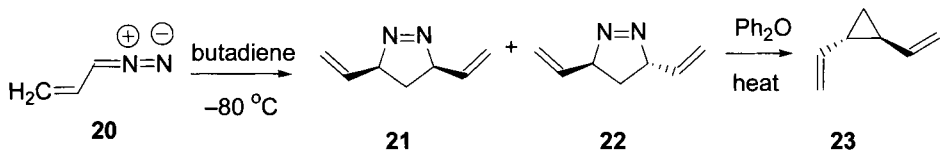
12) $R_1 = R_3 = CH_3$ and $R_2 = R_4 = H$ *trans*- 66.1% *cis*- 33.2%
13) $R_1 = R_4 = CH_3$ and $R_2 = R_3 = H$ *trans*- 25.4% *cis*- 72.6%

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]



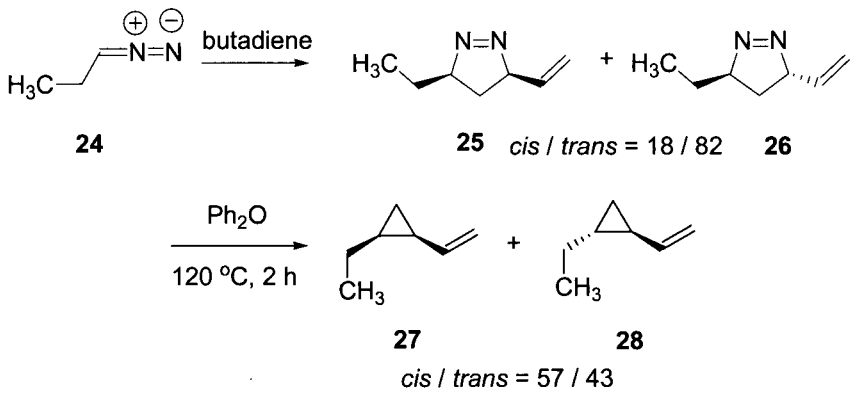
1.2.4 Variations and Improvements

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.



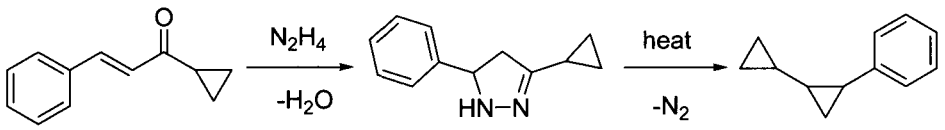
24 **25** *cis* / *trans* = 18 / 82 **26**

27 **28**

cis / *trans* = 57 / 43

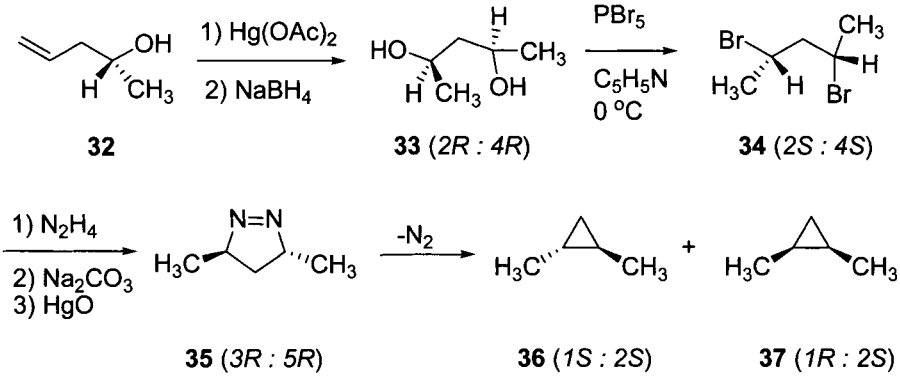
1.2.5 Synthetic Utility

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**

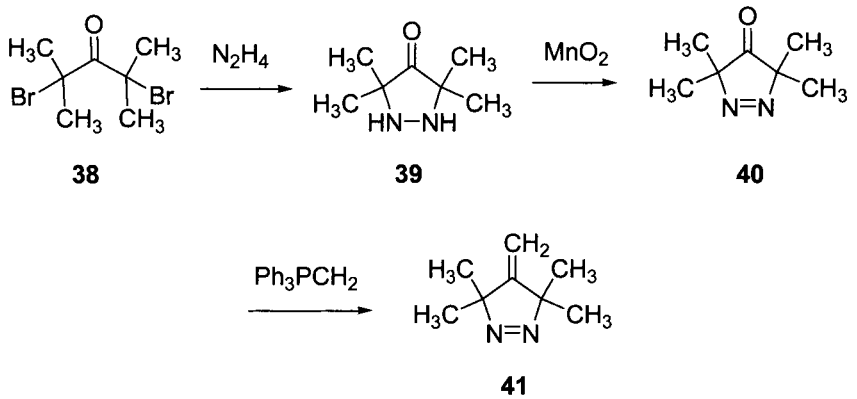
Mishra and Crawford reported the synthesis of (*3R,5R*)-(+)-*trans*-3,5-dimethyl-1-pyrazoline **35** by different approach starting from alcohol **32**.[7] The pyrazoline **35** undergoes thermolysis, producing 25.6% of *trans*-1,2-dimethyl-cyclopropane **36**, processing 23% optical purity, and having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



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

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

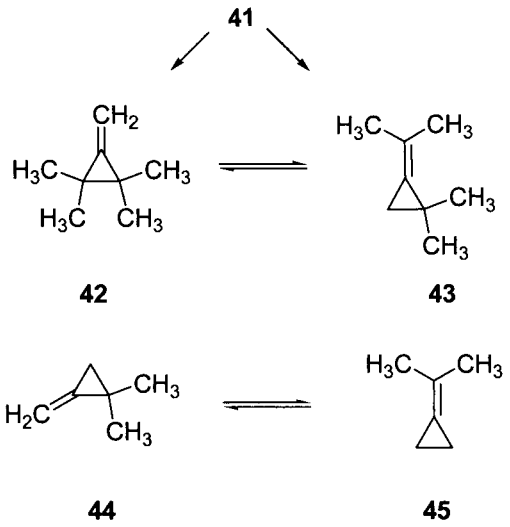
Crawford and Tokunaga synthesized 3,3,5,5-tetramethyl-4-methylene-1-pyrazoline **41** by a different approach.[10] The tetramethyl-4-pyrazolidone **39** was prepared by the reaction of hydrazine with α,α'-dibromodiisopropylketone **38**. Then oxidizing **39** by MnO_2 gives intermediate **40**, which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



38 **39** **40**

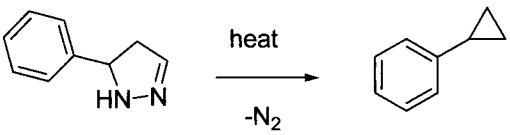
41

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**.



1.2.6 Experimental

Preparation of phenylcyclopropane 47.[15]



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