SIX-MEMBERED TRANSITION STATES IN ORGANIC SYNTHESIS

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Department of Chemistry

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INTERSCIENCE

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To my sons,
Walt and Larry

CONTENTS

PREFACE

When I was a graduate student in the Department of Chemistry at the University of Pittsburgh, I took organic chemistry courses taught by Professors Craig S. Wilcox and Dennis P. Curran. One of the most amazing topics that I learned about from their lectures was stereoselective synthesis in organic chemistry.

Stereochemistry is a concept of paramount importance in chemistry. Stereoselective reactions, be they diastereoselective or enantioselective, are therefore a valuable tool in producing compounds of the desired stereochemistry. Every stereoselective reaction has an energetically preferred transition state that can explain the formation of the major stereoisomer. A reasonable transition state is very important not only in rationalizing the experimental results, but also in further advancing the chemical system that one is studying.

Since the seminal proposal in 1957 by Howard E. Zimmerman and Marjorie D. Traxler regarding the stereoselective Ivanov reaction, six-membered chairlike transition states have been recognized as one of the most convincing methods used in organic chemistry to describe the course of reactions that have a well-organized molecular ensemble geometry. In this book I describe organic reactions that go through well-defined six-membered transition states. The reactions are classified into four categories: [3,3]-sigmatropic rearrangements, aldol reactions, metal allylation reactions, and stereoselective reductions. Each chapter begins with a section on general considerations in which I gather all the computational studies known to me that support the proposal of a six-membered transition state. Each reaction has a brief introduction, a description of the six-membered chairlike transition state, and applications selected from natural product synthesis. In presenting reactions and transition states, I have tried to deliver the arguments and conclusions exactly the way they are outlined in the original references. When questions arise or further information on a transition state is sought, readers are strongly encouraged to study the references listed at the end of each section.

This book will serve as a starting point in learning the amazing features of six-membered chairlike transition states in stereoselective organic reactions. With this book, I hope that students and practitioners alike will be able to propose reasonable transition states for the description of newly discovered stereoselective reactions.

Comments and suggestions from readers are always welcome. I can be reached by email at bizibeaver@yahoo.com.

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Without the many people who have helped me, this book could not have appeared. I would like to thank Professor Tom Livinghouse of Montana State University for his critical reading of the entire manuscript. Drs. Rohan Beckwith, Xing Dai, Tim Peelen, and Janelle Thompson each read portions of the manuscript and provided a number of helpful comments. Thanks are also due to graduate students Elisa Leonardo and Bryce Sunsdahl at the Livinghouse Laboratory for their invaluable editorial assistance. Thanks also to the anonymous reviewers who read sample chapters and gave me invaluable suggestions. I have one very special person to whom I would like to express my sincere gratitude: Walt Harris, head football coach at the University of Pittsburgh between 1996 and 2005. Not only has coach Harris been a constant source of inspiration to me, he has also been a big part of my family's life, and I truly thank him for that.

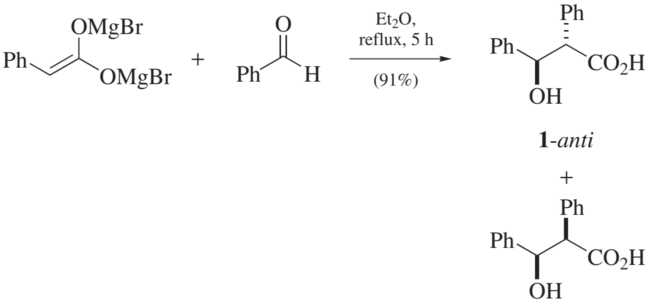
Finally, I would like to thank my wife, Wenjing Xu, for her criticisms, encouragement, and suggestions over the course of writing the book.

Jaemoon Yang

Bozeman, Montana

INTRODUCTION

In 1957, Zimmerman and Traxler published their study on the reaction of benzaldehyde with the magnesium enolate of phenylacetic acid: namely, the *Ivanov reaction*[1] (Scheme I). The major product from the reaction is an *anti*- or *threo*-isomer of 2,3-diphenyl-3-hydroxypropionic acid, and the minor product is a *syn*- or *erythro*-isomer.[2] Although in 1957 the Ivanov reaction had been known for quite some time, no reasonable proposal had been put forward to explain the stereochemical outcome observed for the reaction. In explaining the ratio of the two stereoisomers, the authors made a seminal proposal that the condensation reaction would go through a six-membered transition state (Scheme II). The coordination of benzaldehyde carbonyl group with magnesium brings the two reactants in close contact in both chairlike transition state **A** and boatlike transition state **B**. The authors speculated that the particular spatial arrangement of the four substituents in the transition state could determine the stereochemistry of the products. For the Ivanov reaction of benzaldehyde, transition state **A** would be favored over **B** because transition state **A** involves a lower-energy approach to bonding than that of the alternative transition state **B**, which experiences an energetically unfavorable gauche interaction between the two phenyl substituents[1] (Scheme III).



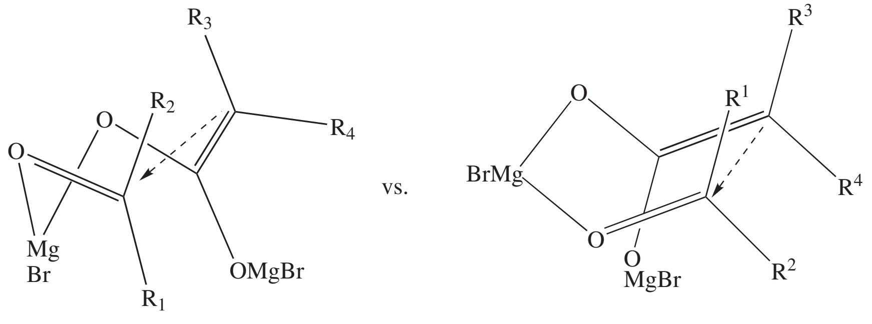
1-*anti*

1-*syn*

anti/*syn* = 76:24

Scheme I

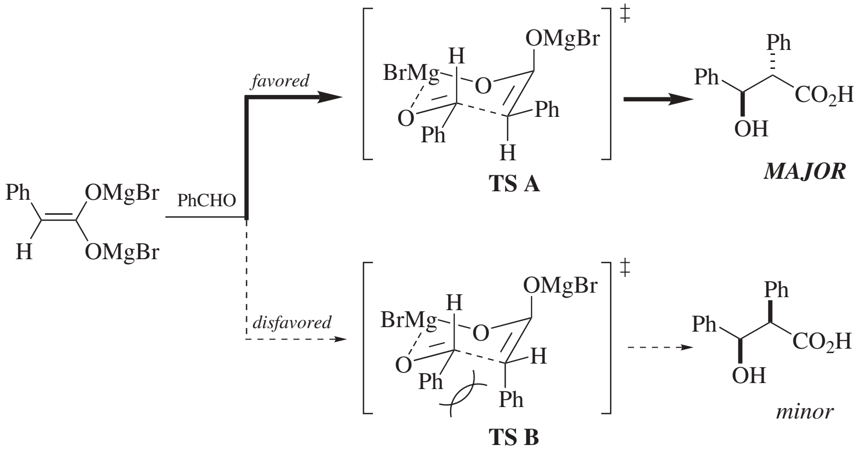
Six-Membered Transition States in Organic Synthesis, By Jaemoon Yang



TS A: chairlike transition structure

TS B: boatlike transition structure

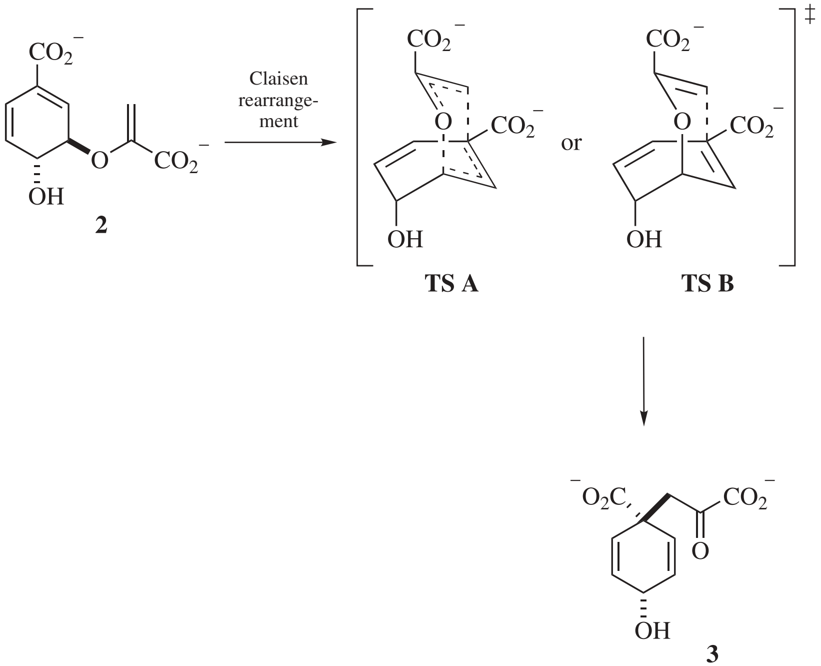
Scheme II



Scheme III

Due to its simplicity and outstanding prediction power, the *Zimmerman–Traxler transition state* has frequently been used in explaining the stereochemical outcome of certain stereoselective reactions. The characteristics of the Zimmerman– Traxler transition state can be summarized as follows:

1. The transition state is for a six-atom system and thus is six-membered.
2. The transition state involves six electrons and thus exhibits the aromatic character of benzene.[3]
3. A chairlike transition state is favored over a boatlike transition state. There are, however, exceptions.

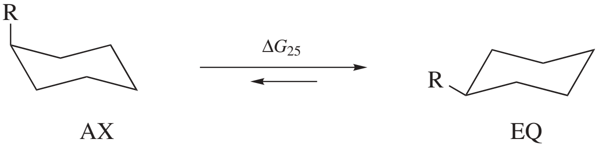


2

3

Scheme IV

TABLE 1 Conformational Energies of Monosubstituted Cyclohexanes



R	$-\Delta G$ (kcal/mol)	EQ/AX
Me	1.74	19:1
Et	1.79	19:1
i-Pr	2.21	42:1
t-Bu	4.7	>99:1
C_6H_5	2.8	>99:1
OMe	0.55	2.5:1

4. When two chairlike transition states compete, the transition state in which a bulky substituent occupies an equatorial position is favored over the state that has the same substituent in an axial position. The free-energy difference between the two potential transition states can be approximated by using the ΔG or A-values of the monosubstituted cyclohexanes[4] (Table 1).

In the following four chapters, readers will find some of the most frequently cited and most synthetically relevant examples of the Zimmerman–Traxler or six-membered transition state. In presenting reactions that go through a six-membered chairlike transition state, I pay special attention to including computational studies, in an effort to prove the existence of a six-membered chairlike transition state. Although not all six-membered transition states have been studied computationally, recent interest in using computers in studies of stereoselective reactions would certainly confirm the legitimacy of Zimmerman–Traxler transition states for many more reactions.[5]

Before we embark on our journey into the world of six-membered transition states, I would like to speak briefly about one reaction, to illustrate how a transition state is drawn throughout the book. The enzyme-catalyzed transformation of chorsimate (**2**) to prephenate (**3**) is a classic example of a [3,3]-sigmatropic *Claisen rearrangement*[6] (Scheme IV). As an old bond is being broken and at the same time a new bond is formed in the transition state, the transition state for the Claisen rearrangement of chorismate to prephenate would look more like transistion state **A** than like **B**. Still, for the convenience of following the bond connection event clearly, I prefer to draw the transition state like **B**.

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1 [3,3]-Sigmatropic Rearrangements

GENERAL CONSIDERATIONS

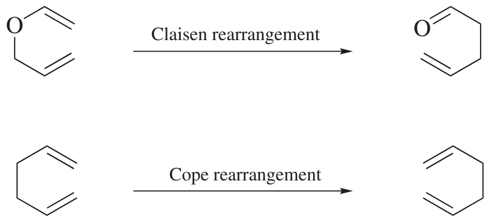
The Claisen and Cope rearrangements are two of the best known sigmatropic rearrangements in organic chemistry[1] (Scheme 1.I). As the rearrangement involves six electrons in a six-atom system, these two reactions serve as excellent examples of the ubiquitous existence of a six-membered transition state in organic chemistry.

In 1912, Ludwig Claisen discovered that the allyl ether **1** of ethyl acetoacetate underwent a reaction to afford **2** upon heating in the presence of ammonium chloride[2] (Scheme 1.II). Similarly, the allyl naphthyl ether **3** transformed into 1-allyl-2-naphthol (**4**) in 82% yield at 210°C. The reaction, now known as the *Claisen rearrangement*, is general for a variety of aliphatic and aromatic ethers and is recognized as one of the most synthetically useful reactions in organic chemistry.[3]

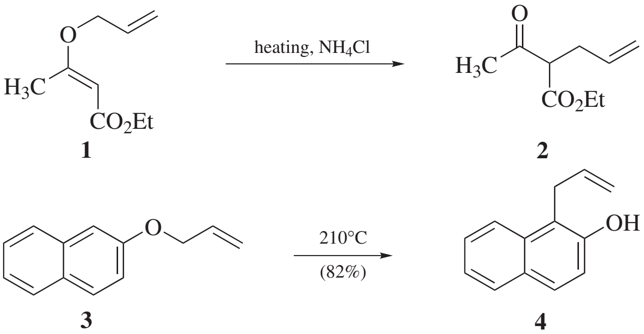
The Claisen rearrangement is a thermally induced [3,3]-sigmatropic rearrangement of allyl vinyl ethers to form γ,δ-unsaturated carbonyl compounds.[4] Due to the concerted nature and synthetic utilities of the Claisen rearrangement, much effort has been devoted to understanding the mechanism of the reaction.[5] Although the extent of delocalization of the six electrons involved in the transition state may depend on the nature of the substrates, it is believed that the rearrangement goes through a six-membered aromatic transition state[6] (Scheme 1.III).

To uncover the transition-state structures for Claisen rearrangement of the parent allyl vinyl ether,[7] Vance et al. performed ab initio quantum mechanical calculations[8] (Scheme 1.IV). When the transition structures were calculated using the 6-31G* basis set, the partially formed C_1-C_6 bond length is 2.26 Å and the partially broken C_4-O bond length is 1.92 Å in chairlike transition structure **A**. These two bond lengths were confirmed by Meyer et al. in a later study employing different-level calculations.[9] Another important finding in Vance et al.'s study is that chairlike transition structure **A** is more stable than boatlike structure **B**, by 6.6 kcal/mol. The conclusion thus supports the proposals of chairlike transition structures for the stereoselectivities observed for the Claisen rearrangement reactions of substituted molecules.

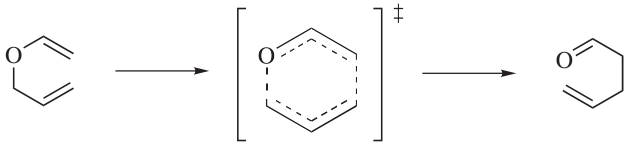
Six-Membered Transition States in Organic Synthesis, By Jaemoon Yang



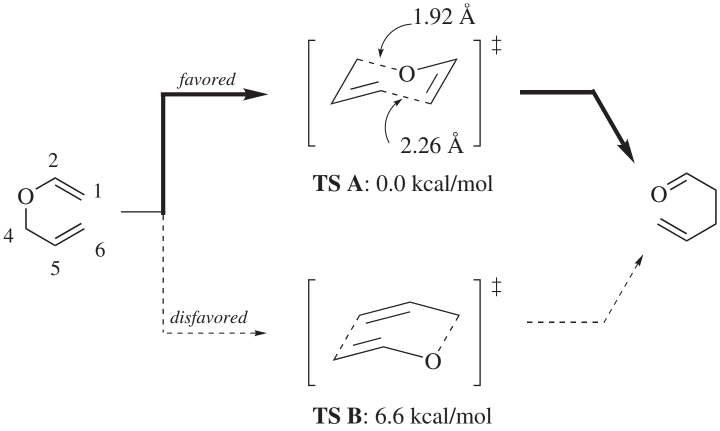
Scheme 1.I



Scheme 1.II

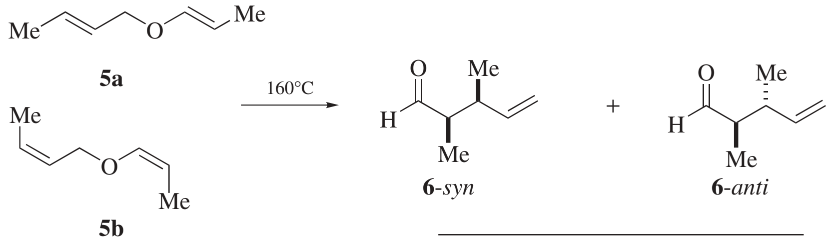


Scheme 1.III



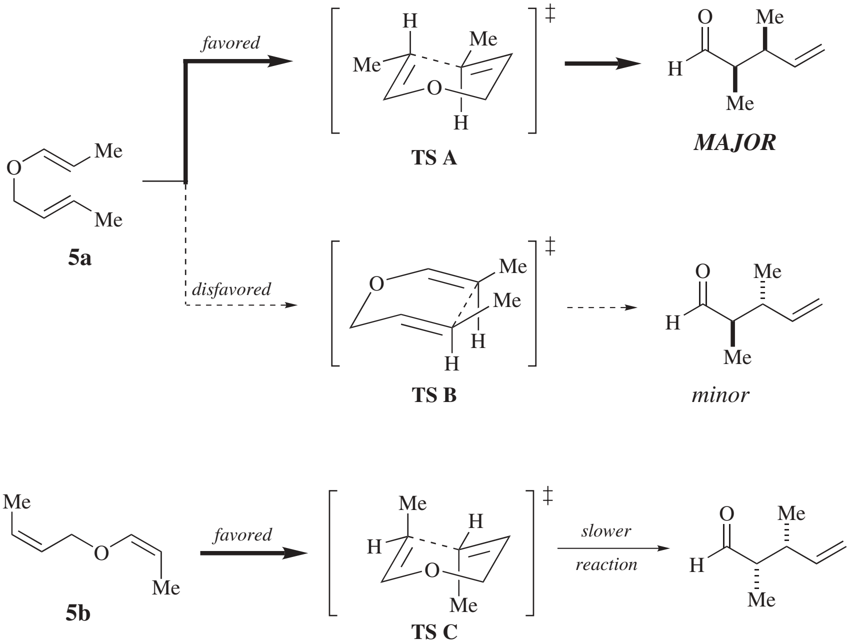
Scheme 1.IV

One classic example that confirms the preference of Claisen rearrangement for a chairlike transition state was provided by Hansen and others. In 1968, they investigated the Claisen rearrangement of the crotyl propenyl ethers **5a** and **5b** to examine the stereochemistry of the rearrangement in the gas phase at 160°C[10] (Scheme 1.V). Both the *E*,*E*- and *Z*,*Z*-isomers rearrange to afford a *syn*-isomer as the major product. The stereochemical outcome of the reaction can be explained



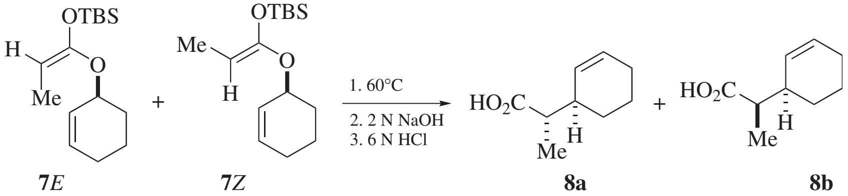
Ether	*syn*/*anti*	Rel. Rate
5a	95.9:4.1	9
5b	94.7:5.3	1

Scheme 1.V



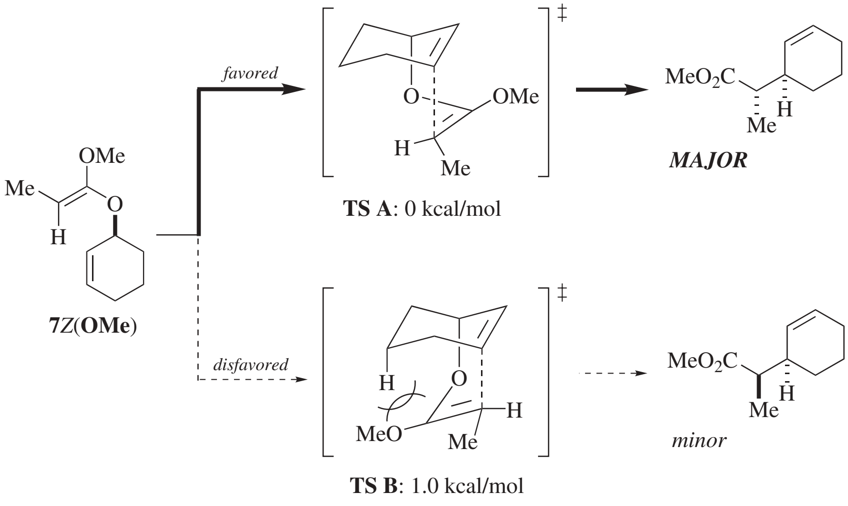
Scheme 1.VI

in terms of a six-membered transition state[10] (Scheme 1.VI). Between the two transition states for **5a**, chairlike transition state **A** is favored over boatlike state **B** to afford a *syn*-isomer as the major product. Chairlike transition state **C** can explain the formation of the *syn*-isomer that is enantiomeric to **6**-*syn*. Other indirect evidence for the existence of a chairlike transition state is the fact that the *E*,*E*-isomer **5a** reacts nine times faster than the *Z*,*Z*-isomer **5b**. This difference in the reaction rate can be understood by examining transition states **A** and **C**: Transition state **C** for **5b** is of higher energy than transition state **A** for **5a**, due presumably to the 1,3-diaxial interactions arising from the axial methyl groups in transition state **C**.

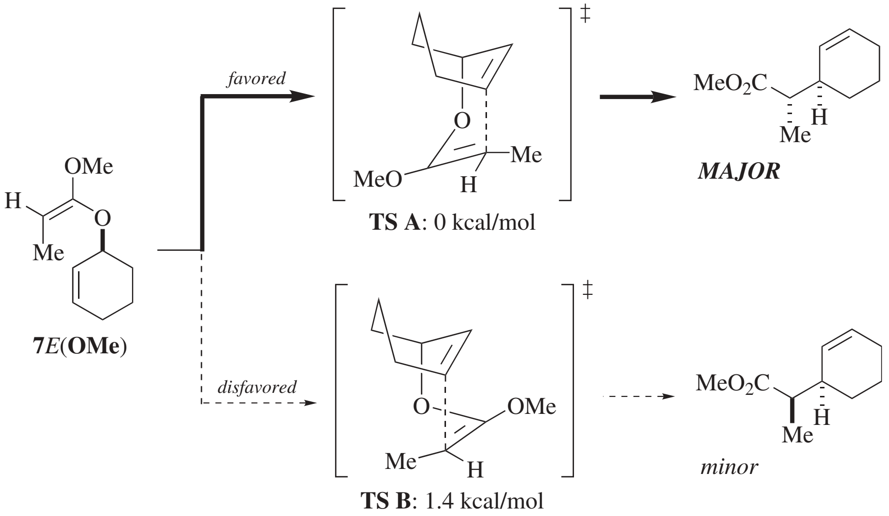


7*E*/7*Z*	**8a/8b**	Yield, %
83:17	84:16	79
4:96	72:28	91

Scheme 1.VII



Scheme 1.VIII



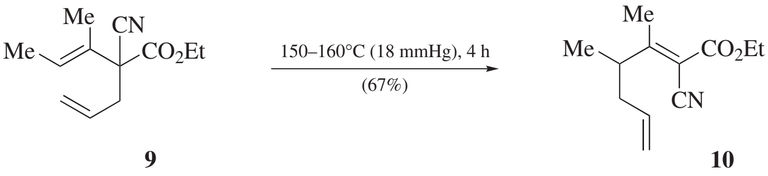
Scheme 1.IX

Although a chairlike transition state is favored for the Claisen rearrangement reactions of acyclic substrates, this is not always the case with cyclic systems. For example, Bartlett and Ireland independently studied the rearrangement reactions of cyclohexenyl silylketeneacetals and found that there was competition between the chairlike and boatlike transition states[11] (Scheme 1.VII). Clearly, the *E*-isomer **7***E* gives **8a** via a chairlike transition state, whereas the *Z*-isomer **7***Z* affords the same product (**8a**) via a boatlike transition state.

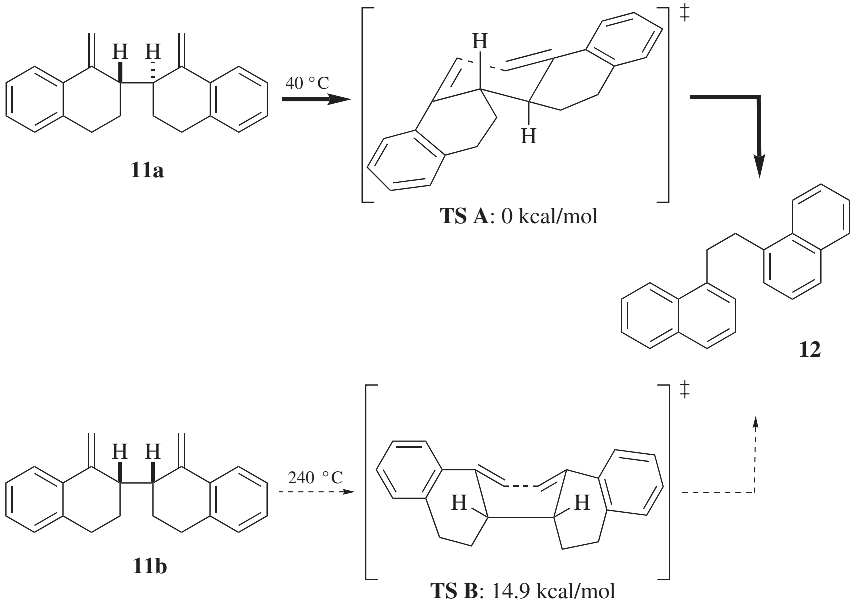
To quantitatively understand the preference for the chairlike and boatlike transition states of the Claisen rearrangement, Houk et al. carried out a computational study[12] (Scheme 1.VIII). In the theoretical treatment two methyl acetals, **7***Z*(**OMe**) and **7***E*(**OMe**), were used as a model system instead of the *tert*-butyldimethylsilyl (TBS) ketene acetal. Calculations locate four transition states for the rearrangement of **7***Z*(**OMe**), among which boatlike transition state **A** is of the lowest energy that leads to the formation of the major isomer observed experimentally. Chairlike transition state **B** is disfavored, due to steric repulsion between the axial hydrogen of the cyclohexenyl unit and the methoxy substituent of the alkene.

For the reaction of **7***E*(**OMe**), chairlike transition state **A** is favored over boatlike transition state **B**[12] (Scheme 1.IX). These computational results provide a solid theoretical rationalization of the original proposal by Bartlett and Ireland that the boatlike transition state is favored for the Claisen rearrangement of **7***Z*, and the chairlike transition state is preferred for **7***E*.

Another important [3,3]-sigmatropic rearrangement is the *Cope rearrangement*, a carbon analog of the Claisen rearrangement. At the eighth National Organic Chemistry Symposium in 1939, Arthur C. Cope and Elizabeth M. Hardy presented their exciting discovery of this new reaction in which an allyl group



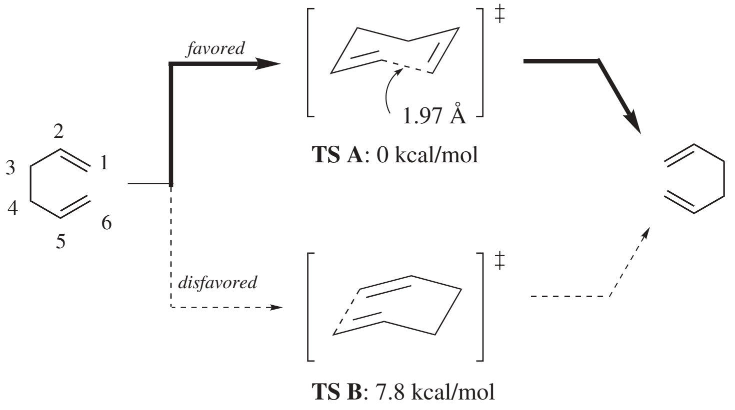
Scheme 1.X



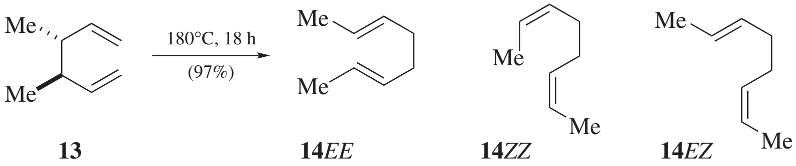
Scheme 1.XI

migrated in a three-carbon system[13] (Scheme 1.X). The discovery of the reaction was made possible by careful analysis of the product (**10**) that formed during vacuum distillation of the diene **9**.

The Cope rearrangement, which is the conversion of a 1,5-hexadiene derivative to an isomeric 1,5-hexadiene by the [3,3]-sigmatropic mechanism, has been studied extensively.[14] As is the case for the Claisen rearrangement, the Cope rearrangement prefers to go through a six-membered chairlike transition state. Shea et al. demonstrated elegantly the preference for the chairlike over the boatlike transition state by carrying out Cope rearrangements of racemic (**11a**) and meso (**11b**) naphthalenes[15] (Scheme 1.XI). It was determined that the racemic 1,5-diene **11a** underwent Cope rearrangement 7 million times faster than the meso diene **11b**. The energy difference between transition states **A** and **B** is calculated to be 14.9 kcal/mol.

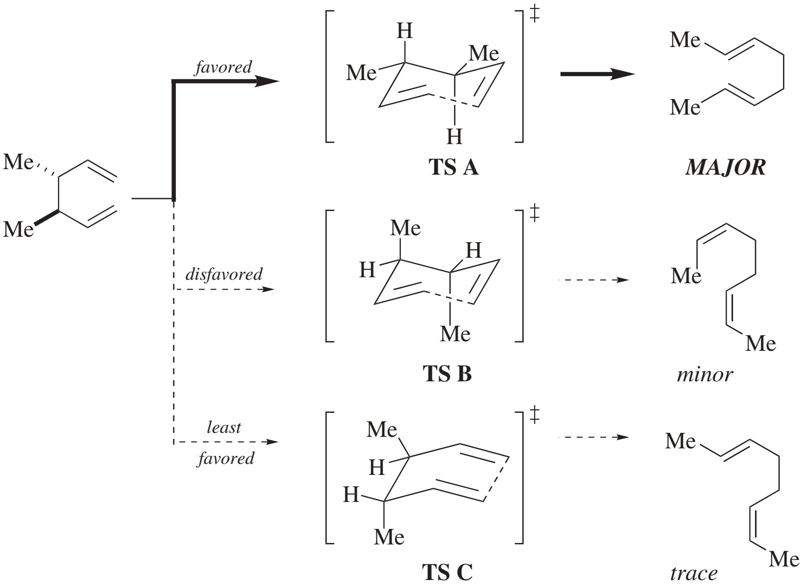


Scheme 1.XII



14*EE*/**14***ZZ*/**14***EZ* = 90:9:<1

Scheme 1.XIII



Scheme 1.XIV