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Incorporating Transition Metal Organometallic Chemistry into the Introductory Organic Chemistry Course

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An abstract of
A thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
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Abstract

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Over the past fifty years, transition metal organometallic chemistry has become increasingly important in organic chemistry research. In contrast, the introductory organic chemistry curriculum has not been sufficiently updated to reflect the significant influence of discoveries in organometallic chemistry. To expand students' understanding of organic chemistry, this thesis proposes an integration of transition metal organometallic chemistry into the introductory organic chemistry course. This integration gradually builds from the basics of organic chemistry to four important transition metal-catalyzed organic reactions: the Heck reaction, the Suzuki reaction, olefin metathesis, and coenzyme B_{12}-catalyzed reactions.

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Acknowledgements

I would like to express my sincere gratitude to Dr. Jose Soria for his support and encouragement of my untraditional path. His willingness and enthusiasm to discuss chemistry education with me and advise me on this thesis has allowed me to explore chemistry from the viewpoint of an instructor and has given me many tools that I need to succeed as a chemistry instructor in the future. Without Jose, I would not have had the opportunity to explore chemistry education as much as I have.

I would also like to thank Dr. Liotta and Rev. Susan Henry-Crowe for the interest that they brought to my thesis defense. Their attentiveness and suggestions made my defense a positive experience that I will never forget.

Finally, I would like to thank my mom and dad for always believing in me and supporting me. I have achieved all I have today because of their support and guidance.

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Part 1

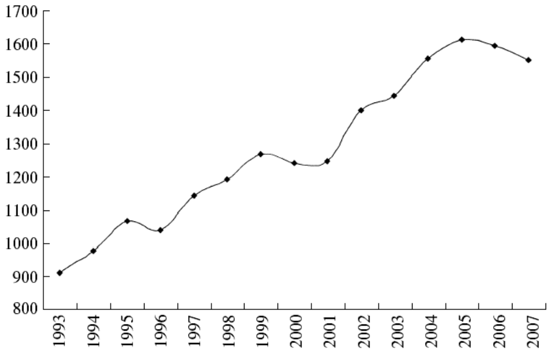
Introduction

Organic chemistry describes the study of carbon-containing compounds, particularly their structures, reactions and synthesis. Carbon is the fourth most abundant element in the universe by mass after hydrogen, helium and oxygen, respectively.[1] Additionally, it plays a large part in every known living organism and is vital for life. In particular, it is the second most abundant element by mass in the human body after oxygen.[2]

In addition to its high abundance in the universe, carbon atoms are involved in a range of structures and reactivity. Carbon can be connected to up to four separate atoms at the same time, most frequently hydrogen, oxygen, nitrogen and other carbon atoms. Additionally, carbon can be used as electron deficient centers (electrophiles), electron rich centers (nucleophiles), or free radicals. Changes in the polarity of carbon allow for the synthesis of a large quantity of new carbon-based molecules. Due to the high abundance and range of reactivity of carbon, the study of carbon-containing compounds is important in science, especially its overlap with other areas of science, particularly biology and physics.

1.1 Advances in Organic Chemistry

The overlap of biology and physics with organic chemistry forms various subsections of organic chemistry, for instance bioorganic chemistry and physical/theoretical organic chemistry. Additionally, within chemistry, inorganic chemistry intersects with organic chemistry in the area of organometallic chemistry. In bioorganic chemistry, there has been a linear increase of publications since 1993 (Graph 1.1).



Graph 1.1 Number of publications in bioorganic chemistry from 1993 to 2007.[3]

Similarly, the quantity of articles in journals about transition metal organometallic chemistry has significantly increased over the past 50 years.[4,5] The increase in the research in both bioorganic chemistry and organometallic chemistry demonstrates the increasing interest and future potential of these interdisciplinary subsections of organic chemistry. A summary of major past, present and future research in bioorganic chemistry, physical/theoretical organic chemistry and organometallic chemistry are provided in Table 1.1.

Table 1.1 Summary of the Past, Present and Future of Organic Chemistry Research

Type of Organic Chemistry Research	Past Research	Areas of Present and Future Research[4-8]
Bioorganic	● Synthesis of Urea [9] ● Fermentation of sucrose outside of the cell [10] ● Krebs cycle[11] ● Structure and function of ribosome (Yonath, Steitz, Ramakrishnan) [12,13,14] ● Molecular basis of eukaryotic transcription (Kornberg) [15]	● Green chemistry ● Bioorganometallic chemistry ● Medicine

Physical/Theoretical Organic	● Burgi-Dunitz angle [16] ● Huckel's rule[17] ● Theory of electron transfer reactions (Marcus) [18] ● Carbocation stability (Olah) [19] ● Orbital symmetry (Woodward, Hoffmann) [20] ● HOMO-LUMO (Fukui) [21]	● Biochemical process ● Chemistry of disease ● Design of molecular materials ● Green chemistry
Organometallic (a combination of organic and metallic chemistry)	● Zeize's salt (1831) [22,23] ●Grignard's reagents (1900) [24] ● Gilman reagents (1952) [25] ● Ferrocene (1952) [26] ● Ziegler-Natta catalyst[27] ● Heck reaction (1972) [28] ● Asymmetric hydrogenation and oxidation [29,30,31] ● Π-bond metathesis (Chauvin, Grubbs, Schrock) [32,33,34] ● Bioorganometallic chemistry with nickel (i.e. methyl coenzyme M reductase) (1998) [35,36]	● Catalysis (particularly asymmetric catalysis) ● Theoretical Studies ● Mechanistic Studies ● "Unconventional" solvents ● Materials and Superassemblies ● Bioorganometallic chemistry (particularly related to iron-based enzymes)

1.2 Introductory Organic Chemistry Curriculum

In comparison to the increasing potential of interdisciplinary organic chemistry research, the content in the introductory organic chemistry sequence has remained virtually unchanged over the years. Comparing a classic, internationally-used Organic Chemistry textbook from 1987 and a popular Organic Chemistry textbook from 2008 emphasizes these similarities (Table 1.2).

Table 1.2 Topics in Organic Chemistry Textbooks

Morrison and Boyd, *Organic Chemistry,* Fifth Edition (1987)[37]	**Bruice, *Organic Chemistry*, Fifth Edition (2008)**[38]
Structures and Properties	Electronic Structure and Bonding
Stereochemistry	Stereochemistry: The Arrangement of Atoms in Space; The Stereochemistry of Addition Reactions
Alkyl Halides	Substitution Reactions of Alkyl Halides Elimination Reactions of Alkyl Halides
Alkenes	Alkenes: Structure, Nomenclature, and an Introduction to Reactivity The Reactions of Alkenes
Conjugation and Resonance	Delocalized Electrons and Their Effect on Stability, Reactivity and pKa
Aromaticity	Aromaticity/ Reactions with Benzene
Alcohols	Reactions of Alcohols, Amines, Ethers, Epoxides and Sulfur-containing Compounds
Aldehydes and Ketones	Carbonyl Compounds
Carboxylic Acids	Carbonyl Compounds
Amines	Reactions of Alcohols, Amines, Ethers, Epoxides and Sulfur-containing Compounds More about Amines
Biomolecules	Biomolecules

The American Chemical Society describes the concepts important to organic chemistry in the organic chemistry supplement to the ACS Guidelines and Procedures for Bachelor Approved Programs.[39] It particularly addresses the following areas as important in an introductory organic chemistry course sequence:

(1) Scientific understanding comes from experiments

(2) Functional groups

(3) Stereochemistry and conformational analysis

(4) Effects of electronic, steric, and orbital interactions on molecules and chemical reactions
(5) Bonding and its consequences on molecular structure and reactivity
(6) Dependence of reaction on surrounding environment
(7) Acid-base chemistry
(8) Addition, elimination, substitution, and rearrangement mechanisms
(9) Organic Synthesis

These concepts, described by the ACS supplement, help provide students with the basics of organic chemistry and its subsections (bioorganic chemistry, physical organic chemistry, organometallic chemistry).

The organic chemistry curriculum has also often been heavily influenced by MCAT/medical school standards. This influence has developed due to the large population of pre-medical students in the classroom. A list of the parts of organic chemistry considered important for pre-medical students are listed as part of a content outline for the MCAT.[40] The organic chemistry section of this supplement is summarized below:

1) Sigma and pi bonding
2) Stereochemistry
3) Organic experimental analysis

4) Physical and chemical properties of hydrocarbons, alcohols, aldehydes, ketones, carboxylic acids, keto acids, esters, amines, carbohydrates, amino acids, proteins and lipids
    a. Acidity/Basicity
    b. Steric effects
    c. Electronic effects
    d. Strain
5) Reactions involving hydrocarbons alcohols, aldehydes, ketones, carboxylic acids, keto acids, esters, amines, carbohydrates, amino acids and proteins

There are many overlaps between the information deemed necessary in the organic chemistry sections of the ACS and MCAT supplements, particularly stereochemistry, acid-base chemistry, and chemical reactions. The similarities in these supplements emphasize what is considered to be the essential information and reactions that students need to understand in organic chemistry.

However, the material from the organic chemistry requirements for ACS and MCAT as well as organic chemistry textbooks do not discuss in detail the interdisciplinary subsections of organic chemistry – bioorganic chemistry, physical organic chemistry and organometallic chemistry. In particular, in these resources, organometallic chemistry is only discussed in detail through Grignard reagents; transition organometallic chemistry, particularly organocuprate reactions, is only mentioned in passing. The lack of transition metal organometallic chemistry in both MCAT and ACS guidelines as well as organic chemistry textbooks demonstrates that it is not normally considered part of the typical introductory organic chemistry curriculum. Therefore, if a professor wants to incorporate more advanced organometallic chemistry into their organic chemistry course, they would have to rely on materials other than textbooks for the class, particularly organometallic chemistry research papers.

1.3 Problems in the Introductory Organic Chemistry Curriculum

One of the most frequently noted problems in organic chemistry is the tendency of students to solely memorize information rather than recognize patterns. [41,42] Grove found that many times students realize that they would learn better if they did not just memorize the material but also tried to learn the concepts behind it as well.[41] However, students often choose the prior, particularly due to time constraints as the semester goes on.

These time constraints are probably partially due to the lack of connection of organic chemistry to both other areas of science and to the outside world itself. If students cannot see the importance in the material and/or the relevance of it in their lives, they do not find it worth giving as much time. Also, many times students do not see the relationship of organic chemistry to other areas of science, including the science subjects they had already studied. In particular, Grove noted that many students struggled to make connections between what they learned in general chemistry and organic chemistry.[41] If more students understood the implications of organic chemistry in other sciences, in the world and/or in their lives, they may be more apt to focus on learning the concepts rather than just memorizing the material to pass the class.

1.4 The Psychology behind Memorization and Associations

Students can process information in two different ways: shallow and deep processing. In shallow processing, the brain processes information based on the senses.[43,44] For example, a student writes a mechanism on a piece of paper to learn it. Because the student does not make any strong connections to the new information, shallow processing usually leads him or her to remember the material for a short period of time. If the student repeatedly writes the mechanism on a piece of paper though, the student could remember the information for a longer period of time. Although this method is effective and useful in particular parts of organic chemistry, it is not productive to use it alone in an organic chemistry course. Students need to additionally make connections in the material to increase their understanding of the material.

In deep processing, the information is processed by making associations.[43,44] There are several types of associations that can be made with the new information. One type of association describes finding a pattern in the information that is being studied.[43,44] For example, if several unknown organic substances were being identified in a lab, a student could better remember what they were if he or she had realized that they all had carbonyl groups. Another type of association that can be made occurs between the new data and previously learned information.[43,44] By relating current knowledge to what the students already know, students ferment their understanding in both the new and old material. This deep processing often leads students to remember the material for a longer period of time than with rote memorization alone and thereby gives them a deeper understanding of the material.

1.5 Creating Associations within Organic Chemistry

1.5.1 Arrow Formalism

Although the curriculum of organic chemistry has no significant changes in content over several decades, there has been a significant change in how organic chemistry mechanisms have been presented to students. A couple of decades ago, textbooks emphasized which part of the molecule interacts with the other part of the molecule using boxes or color coding. In particular, the fifth edition of Morrison and Boyd's Organic Chemistry demonstrates how molecules interact using color coding (Figure 1.1).[37]

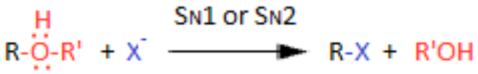


Figure 1.1 Color Coding

This mechanism demonstrates what reacts with what, but does not really explain how the interaction occurs. Arrow formalism, on the other hand, helps students see why the reaction occurs the way it does: the donation of electrons from a nucleophile to an electrophile. An example of an S_N2 mechanism with arrow formalism is shown in Figure 1.2.

Figure 1.2 Arrow Formalism

In contrast to Figure 1.1, the arrow formalism in Figure 1.2 shows the structures of the molecules rather than just their condensed or Lewis structure.

Expanding on arrow formalism, orbital overlap is also emphasized during organic chemistry. Orbitals are used as a representation to demonstrate where the electrons are. Bonding molecular orbitals, which create highly stable bonds, emphasize where there is maximum constructive overlap between orbitals. On the other hand, antibonding orbitals emphasize where there is minimum constructive overlap electrons overlap of orbitals. Electrons in the antibonding orbital increase the instability of the molecule. Orbital overlap is useful in emphasizing why a bond would form in a particular place and to explain sterics. Figure 1.3 shows the molecular orbital diagram which describes the formation of a bonding orbital oxygen-carbon σ bond and an antibonding oxygen-carbon σ* bond in an S_N2 reaction

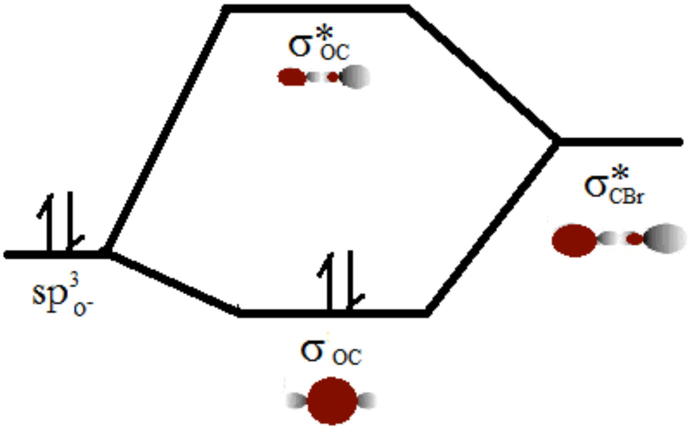


Figure 1.3 Molecular Orbital Diagram of a S_N2 reaction

By being able to see the structure and how the molecules interact through arrow formalism and orbital overlap, students are able to visualize the orientation and reactions of the molecules in space rather than just memorizing which molecules interact.

1.5.2 Integration

For organic chemistry education to be improved, students need to be able to make more associations with the new information they are learning, both by seeing connections in the information being processed and connections between the new and prior knowledge. Over the past two decades, curriculum integration has been used to address this issue. Curriculum integration is a term that describes the interrelationship between two different types of knowledge. This term is very general and, for that reason, many different types of integration exist.[45]

One type of integration already appears in the organic chemistry classroom, the connected methodology of integration. In connected methodology, connections are made by the instructor within a particular subject.[45] For example, stereochemistry, which is discussed in organic chemistry about three-eighths of the way through the first semester, is often referenced again at a later point when discussing the Diels alder reaction. By making connections to what was learned before, students are able to review older material. However, one of the main downsides of using connected integration by itself is that it does not relate to other disciplines.[45] For this reason, students are not able to process the information as well as they could if an association was made to another discipline.

In response, many educators have made changes to their introductory organic chemistry course using a cross-disciplinary method of integration. A cross-disciplinary integration involves the incorporation of one discipline into another.[46] Specifically, for organic chemistry, cross-disciplinary integration involves the incorporation of another science discipline into an introductory organic chemistry course. Although this is a very vague definition, successful cross-disciplinary integration has a couple of key components as demonstrated by articles on integration in organic chemistry education.[47-56] First of all, the integrated material must be smoothly connected into the specific section of organic chemistry being learned. If not, students will not be able to see the connection between the two areas and/or may develop faulty logic. Secondly, the integrated material should encourage investigation and/or reference research, thereby increasing student interest in the material. Thirdly, the integrated material must be incorporated in a way that challenges the students to think, thereby allowing them to form associations and to apply the information to solve future problems.

Besides these components, the particular methods of cross-disciplinary integration vary. In some methods, a different discipline is integrated gradually into the curriculum throughout the semester while, in other methods, it is integrated as a special topic. In addition, some integrations involve a college-wide curriculum change while others occur only in a particular class.

Not only are there many methods of cross-disciplinary integration, but there are also a range of disciplines that can be integrated into organic chemistry. The cross-disciplinary integration has been proposed for integrating biochemistry, environmental chemistry, physical chemistry, computational chemistry, and general chemistry into the undergraduate organic chemistry course. Biochemistry, in particular, has often been integrated into the undergraduate organic chemistry curriculum over the past decade, partially due to its importance in medical school and for biochemistry research.[47] Olefin College started a curriculum which gives students the choice between the second semester of organic chemistry (for students interested in research) and biochemistry (for future doctors and biochemists). To adjust for this choice, the curriculum for the first semester was later changed so that some of the reactions typically covered second semester in the traditional organic chemistry course would be discussed first semester. In particular, carbonyl group chemistry was introduced into first semester because of its importance in both chemistry research and biochemistry.

Computational chemistry has also been integrated successfully into introductory organic chemistry. In an integration of computational chemistry into an organic chemistry course, students used computer software to make molecules, and find the ideal conformations using thermodynamics.[48] From there, students were able to develop their own definition of the Markovnikov rule and the "anti-Markovnikov" rule, which allowed students to experience this concept rather than just memorize a definition.

Also, this method has been suggested and/or implemented for integrating other disciplines into introductory organic chemistry laboratory experiments as well. In particular, there are many organometallic reactions that have been integrated into the organic chemistry laboratory.[49-54] One such experiment uses the Heck reaction.[49] In this experiment, o-bromocinnamic acid was synthesized from different bromoiodobenzenes using a palladium catalyst. The students verified the structure of their final product using NMR and IR spectroscopy. By exploring the Heck reaction for themselves, students were able to learn more about this organometallic reaction, which was not discussed in their lecture classes. In particular, by discovering how different ligands on the bromoiodobenzene affect the reaction, they could understand the mechanism from a more conceptual point of view rather than from memorization.

As shown by the research discussed and referenced above, cross-disciplinary integration in organic chemistry has been highly popular within the past decade and has had many successes. It has been considered so successful that the American Chemical Society (ACS) and the National Science Foundation (NSF) have developed resources, including grants, to support the cross-disciplinary integration in college science classrooms.[57,58]

1.6 Objective of Thesis

As shown previously, the main purpose of integration in an organic chemistry course is to help students see connections in the material, which will ideally help them to recognize and understand concepts rather than solely memorize information. The key factors observed for a successful integration of another subject into organic chemistry are (1) integrated material must be smoothly connected, (2) the material should be based off of new discoveries and developments, (3) the material must be integrated in a way that challenges the students to think, and (4) students must be able to apply the material they have learned to solve problems. Because transition metal organometallic chemistry has these characteristics, it can be integrated into an introductory organic chemistry course effectively. However, despite its rising importance in research, many students do not learn about transition metal organometallics in traditional organic chemistry courses or their other chemistry courses. In high school and general chemistry, students learn the basics of d orbital shapes, which are fundamental to understanding carbon-metal interactions. However, d orbitals are only talked about once or twice a year in these courses, often in collaboration with s and p orbitals. Because more emphasis is often placed on s and p orbitals, students never really come to have a deep understanding of d orbitals. Likewise, in the traditional organic chemistry course sequence, students see transition metal organometallics, notably Gilman reagents, once or twice a year but do not often explore the mechanism in depth; rather, they are just expected to memorize the reactants and products. For this reason, although students may have seen the material, they do not understand the role of it in organic chemistry. To address this deficiency, this paper will:

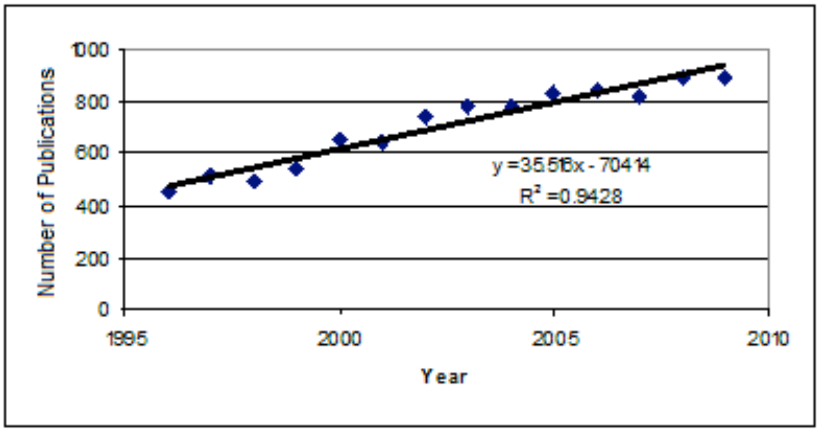
(1) Discuss the advantages and applications of transition metal organometallic chemistry for students.

(2) Propose where transition metal organometallic chemistry can be successfully integrated into an introductory organic chemistry curriculum throughout a two-semester sequence. This integration will ideally (a) introduce organometallic concepts, (b) reinforce and/or strengthen understanding of organic chemistry, (c) deepen overall understanding of chemistry and (d) help students to see connections of transition metals and organic chemistry to the world outside of the classroom, particularly in regards to biochemistry and modern research.

Part 2

Advantages of Transition Metal Organometallic Chemistry

As mentioned previously, over the past few years, transition metal organometallic chemistry has had an increasing role in organic synthesis, polymerization, and materials science.[4,5] Multiple Noble Prizes have been given to acknowledge the significance of this research, particularly to Chauvin, Grubbs and Schrock for their work on metal catalyzed olefin metathesis and to Ernst Fischer and Geoffrey Wilkinson for their work on metallocenes. [59] Graph 2.1 reflects the increased role of transition metal organometallic chemistry publications in the *Journal of Organic Chemistry*, *Organic Letters*, *Organic Process Research and Development* and *Organometallics* between 1996 and 2009.



Graph 2.1 Number of transition metal organometallic chemistry publications in *Journal of Organic Chemistry*, *Organic Letters*, *Organic Process Research and Development* and *Organometallics* between 1996 and 2009. [60]

As emphasized by the increasing number of transition metal organometallics in organic research, organometallic chemistry has a large impact in organic chemistry as well as other disciplines like biology and physics. Because of the interdisciplinary nature of organometallic chemistry, its incorporation into the introductory organic chemistry classroom provides opportunities for students to expand their chemical knowledge and relates organic chemistry to real-world applications or other scientific subjects.

The type of associations formed by the students is shaped by their background in chemistry. All organic chemistry students have taken an introductory course in chemistry, whether as AP chemistry in high school or general chemistry in college. This course provides them with the basics necessary for organic chemistry, particularly acidity, basicity and Lewis structures. Additionally, a majority of organic chemistry class consists of pre-medical or pre-health students who are only taking the course as a requirement for medical school. For this reason, many pre-medical students tend to rely on memorizing the material rather than forming associations.

Transition metal organometallic chemistry and its applications in the human body give students the opportunity to make connections between metals, organic chemistry and biology. For example, coenzyme B_{12}, which is derived from vitamin B_{12}, acts as a cofactor in several enzymatic reactions.[61] Also, carbon monoxide dehydrogenase acts as a catalyst for the transformation of carbon monoxide into carbon dioxide in the body.[35] The discoveries of the reactions of coenzyme B_{12} and carbon monoxide dehydrogenase along with other bioorganometallic enzymes, coenzymes and proteins have made major contributions to biochemistry within the past fifty years. The outcome of these discoveries suggests that organometallic chemistry may have a much larger role in the body than currently recognized.[4]

Transition metal organometallic chemistry can also demonstrate the overlap between metals, organic compounds and pharmaceutical drugs. Many organometallic deviations of drugs are being made to overcome resistance to the original drug. For example, many types of bacteria have become resistant to the antibiotic penicillin over time due to adaptation.[62] In response, Edwards, Epton and Marr synthesized a penicillin inhibitor with a ferrocenyl moiety, which prevented the activity of the otherwise resistant bacteria.[62] By discussing this topic in the introductory organic chemistry classroom, both pre-medical students in particular could gain a deeper understanding of the properties and importance of organometallic drugs in modern medicine.

In addition to its relationship to biology, organometallic chemistry can also be advantageous to students because it overlaps two areas of chemistry. *Topics of Organometallic Chemistry* describes "organometallic chemistry is a well established research area at the interface of organic and inorganic chemistry."[63] The inherent intradisciplinarity of transition metal organometallic chemistry has significant potential in organic chemistry classroom to relate inorganic chemistry with organic chemistry.

Because organometallic chemistry is based off of inorganic chemistry, organometallic chemistry can also be used to connect inorganic concepts discussed in general chemistry into organic chemistry. Students often view general chemistry and organic chemistry as two separate subjects with few overlapping concepts. However, by integrating organometallic chemistry into an organic chemistry course, students can take the knowledge about metals, particularly d orbitals, that they received in general chemistry and can apply it into their organic chemistry knowledge. Making associations between organic chemistry and general chemistry will enable students to reinforce what they have already learned in both classes and create a deeper, rather than short-term, understanding of the material.

Studying organometallics also allows students to see chemistry that they have not experienced before. In particular, it introduces topics covered typically in inorganic chemistry and organometallic chemistry courses. This exposure is especially advantageous to large amount of students who will not take upper level courses in inorganic chemistry because it is not required for their major or for medical school.

By making connections between both other science disciplines and other areas of chemistry itself while learning new information, students will be able to deeply process what they learned. This deep processing will provide students with a better understanding of the material because they associate the information with their previous knowledge and/or interests.

Part 3

Proposed Method for the Integration of Transition Metal Organometallic Chemistry

3.1 Background for Introducing Transition Metals into Organic Chemistry

To successfully introduce new material into the curriculum, associations between the material and the curriculum must be made. de Vos and Verdonk have found that the best way to introduce concepts is to integrate them gradually over time by setting a foundation and then expanding on it.[59] Transition metal organometallic chemistry can be successfully introduced into the classroom by systematically building on previous material to culminate with four important transition metal catalyzed reactions.

3.1.1 Organic Chemistry Fundamentals

Primarily, a basic understanding of organic chemistry is necessary to introduce transition metals into organic chemistry. Below is a proposed selection of organic background necessary before these transition metals can be introduced in depth.

1. Orbitals and Bonding
2. Stereochemistry
3. Addition Reactions
4. Elimination Reactions
5. Substitution Reactions
6. Grignard and Organolithium Reactions
7. Reactive Intermediates

8. Aromaticity and Heterocycles
9. Oxidation and Reduction
10. Carbonyl Chemistry
11. Cyclo Additions
12. Phosphorus Reactions

A basic understanding of oxidation and reduction, which can primarily be introduced through the reduction of carbon in carbonyl reactions, is necessary because oxidation and reduction occur frequently in transition metal chemistry. Additionally, phosphorus reactions need to be discussed before discussing organometallic chemistry reactions because phosphorous, similar to transition metals, has an expanded octet that allows it to have more than four bonds at one time.

In the organic chemistry course, several transition metal-catalyzed organic reactions are typically introduced where students are required to know the reactants, products, and conditions but not to understand the direct mechanism by which it occurs. A list of frequently-discussed transition metal-catalyzed reactions is below.

1. Chromium oxidations
2. Permanganate oxidations
3. Hydrogenation using metal catalysts
4. Organocopper Reactions (using Gilman reagents)

Metal-catalyzed hydrogenation, permanganate oxidations and chromium oxidations are often introduced while discussing alkene/alkyne addition. Organocopper reactions are often discussed around the same time as Grignard reactions because they both deal with carbon-carbon bond formation.

These transition metal-catalyzed organometallic reactions reinforce the use of catalysts in organic synthesis. Transition metal catalysts present students with alternate pathways for the construction of target molecules. The alternate pathways are often shorter than non-metal organic synthesis pathways, making them more consistent with the strategy of saving energy and resources.

3.1.2 Orbitals

To further build the background for organometallic chemistry, metal-orbital interactions need to be introduced. Although students often have a background in metals from general or high school chemistry, they often do not remember enough of that information to apply it into their knowledge of organic chemistry. For this reason, it is important to review some basic principles of metals before discussing organometallic reactions in detail. It is imperative that students review d orbitals shapes because these orbitals appear in transition metals as well as phosphorus (Figure 3.1).

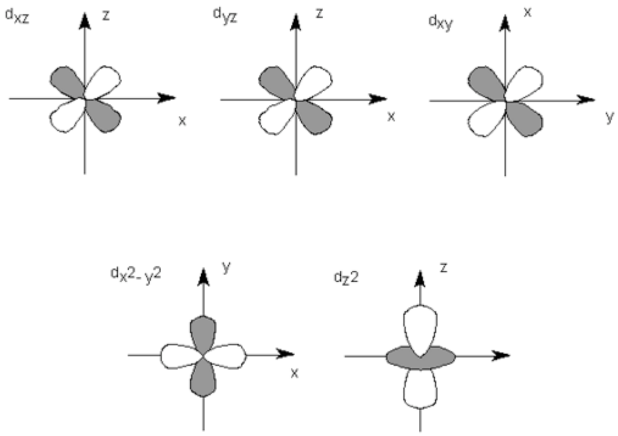


Figure 3.1 d orbital shapes

By emphasizing d orbitals, students can incorporate d orbitals into their understanding of orbital overlap.

Hybridization of s, p and d orbitals can introduce orbital overlap of metals and organic ligands in an introductory organic chemistry class. The type of hybridized orbitals particularly important in organometallic chemistry is sp^3d^2 orbitals (Figure 3.2).

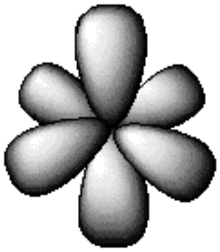


Figure 3.2 sp^3d^2 hybridization

Six sp^3d^2 hybrid orbitals form an octahedral molecule (2 axial and 4 equatorial orbitals). Octahedral molecules also have three unhybridized d orbitals.

Hybridization is the best theory to introduce into an introductory organic chemistry course in comparison to other theories, particularly molecular orbital theory. Students often have a background in s and p hybridization both from general chemistry and the first semester of organic chemistry. Because students are more familiar with hybridization and hybridization is less complex than molecular orbital theory, sp^3d^2 hybridization is easier to integrate into the organic chemistry curriculum.

3.1.3 Eighteen Electron Rule[60]

The eighteen electron rule is used to describe the amount of electrons in the outer shell of a transition metal when it is most stable. It can be compared to the octet rule, with which students are familiar from first semester of organic chemistry and general chemistry. In the octet rule, carbon contains several occupied s and p orbitals and is usually most stable when its outer shell is filled. Transition metals are similarly most stable when its outer shell is full. However, in comparison to carbon, they also have d orbitals in addition to s and p orbitals, so they require eighteen electrons rather than eight to fill its outer shell. It is important to mention that, like the octet rule, there are exceptions to the eighteen electron rule. These exceptions are particularly important in the transition metal catalyzed organic reactions for understanding oxidation and reduction. The exceptions to the eighteen electron rule discussed in class will have less than eighteen electrons in the metal's outer shell.

There are two methods which can be used to determine if the organometallic compound follows the eighteen electron rule: the neutral atom method and the ionic atom method. The neutral atom method treats each ligand as a neutral atom. The ionic atom method treats each ligand and the metal as its corresponding ion. Although either method will allow students to determine the number of electrons in the outer shell, using the ionic atom method in particular can reinforce oxidation and reduction in metals.

3.1.4 Preface to Transition Metal-Catalyzed Organic Reactions

With this foundation in organometallics, students have enough background knowledge to learn about four reactions in depth – the Heck reaction, the Suzuki reaction, olefin metathesis and coenzyme B_{12}-dependent reactions. These reactions will be introduced in a way that builds on each other and expands the knowledge students already have.

3.2 The Heck Reaction[35,66]

The Heck reaction is a transformation where an organic halide or triflate is coupled with an alkene under basic conditions using a palladium catalyst to yield a trans substituted alkene (Figure 3.3).

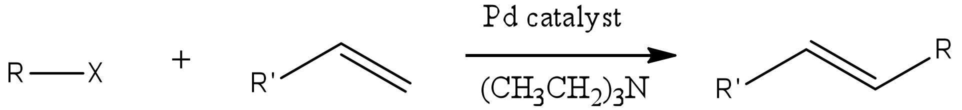


Figure 3.3 Heck Reaction

The Heck reaction has played a vital role in organic synthesis since its creation in 1972. There have been over 2500 articles published by the American Chemical Society within the past five years that use the Heck reaction.[62] As an increasingly useful reaction in synthesis, the Heck reaction would give students an understanding of the importance of transition metals in organic synthesis.

To introduce the Heck reaction successfully into an organic chemistry course, students should have background knowledge of chemical structure and reactivity. In particular, they should have an understanding of the following concepts:

1. Hybridization and sigma and pi bonding
2. d orbitals, oxidation and reduction
3. Functional groups, sterics and electronic interactions
4. S_N2 reactions
5. 1,2 hydride shift
6. 1,2 hydride elimination

3.2.1 The Heck Reaction in the Organic Chemistry Classroom

The Heck reaction belongs to a class known as coupling reactions. Coupling reactions are reactions in which two groups (alkyl, aryl or vinyl groups) join together through a carbon-carbon bond formation. By discussing coupling reactions, the structures and reactivity of alkyl, aryl or vinyl groups can be reinforced. The particular steps of the Heck reaction cycle are shown in Figure 3.4.

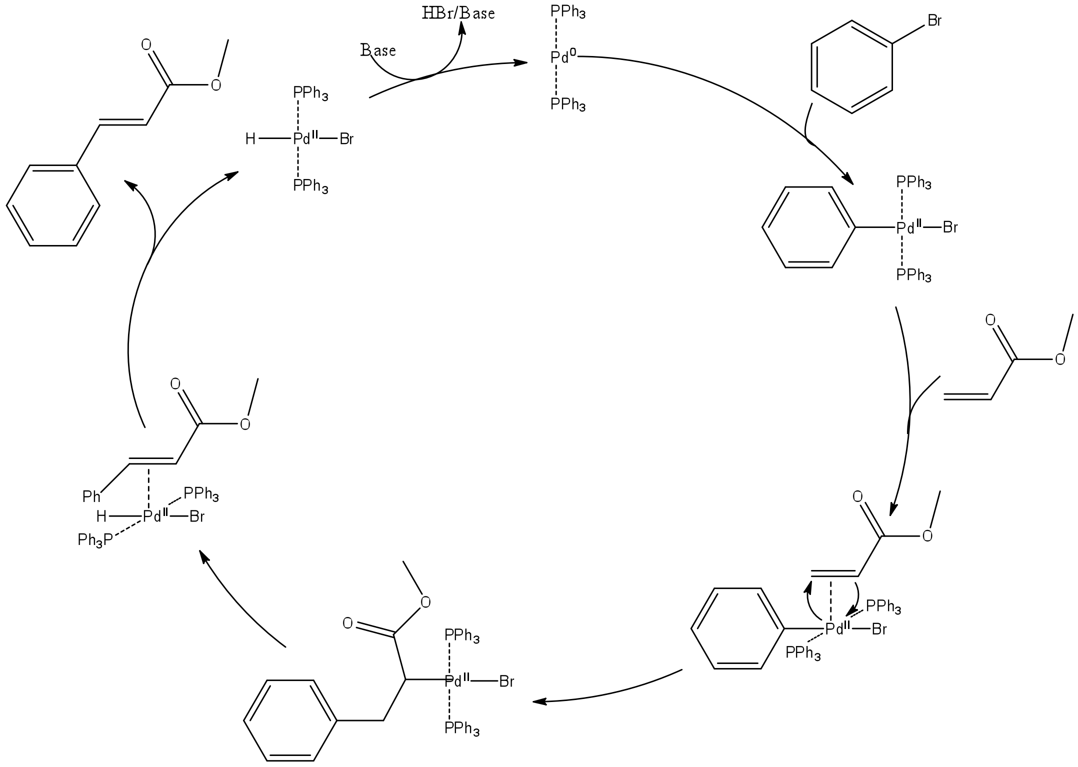


Figure 3.4 Heck Reaction Cycle

Step 1: Oxidative Addition

The first step of the Heck reaction involves the oxidative addition of an organic halide or triflate to the palladium catalyst (Figure 3.5).

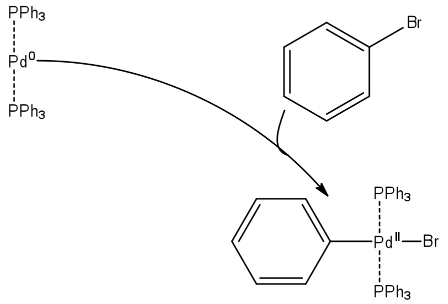


Figure 3.5 Oxidative Addition

In oxidative addition, a substrate molecule is added to a transition metal complex, oxidizing the metal from the *x* to the *x+2* oxidation state. This addition results in a new ligand becoming attached to the metal. This step gives the opportunity to discuss a particular application of oxidation and reduction in organic chemistry and challenges students to understand why it is called "oxidative addition."

There are several different mechanisms for oxidative addition. In the Heck reaction, a metallacycle intermediate is formed and then breaks apart to reform the aromatic ring, kicking off the halide in the process (Figure 3.6). The second part of this step resembles an E2 reaction.

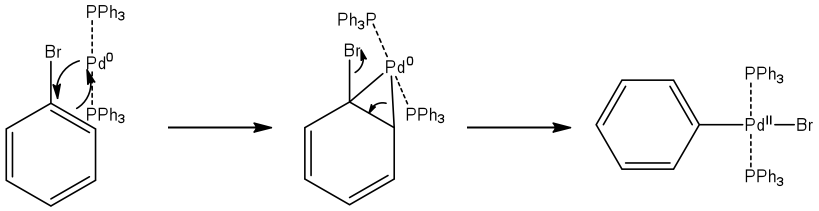


Figure 3.6 Arrow Formalism for Oxidative Addition

The step can be further analyzed by comparing it to the formation of the Grignard reagent. Similar to step 1 of the Heck reaction, the formation of a Grignard reagent occurs by oxidative addition. However, in contrast with the Heck reaction, this oxidative addition occurs through single electron transfer (Figure 3.7).

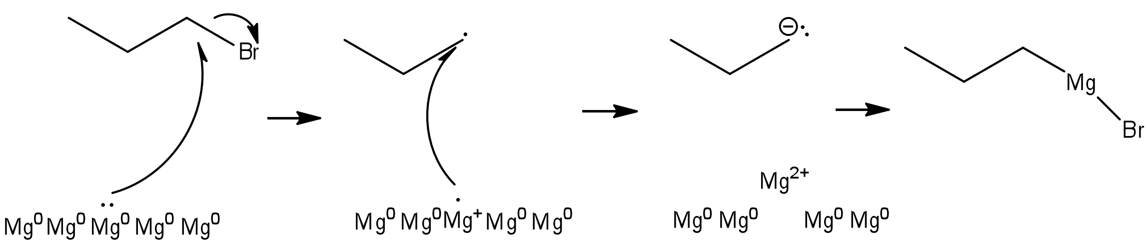


Figure 3.7 Grignard Reagent Formation

By comparing Grignard reagent formation to the first step of the Heck reaction, students can learn that just because two reactions occur by oxidative addition does not necessarily mean that their mechanisms are the same.

Step 2: Formation of a Pi Complex

In the second step of the Heck reaction, a pi complex is formed by the coordination of an alkene and the palladium(II) intermediate formed previously (Figure 3.8).

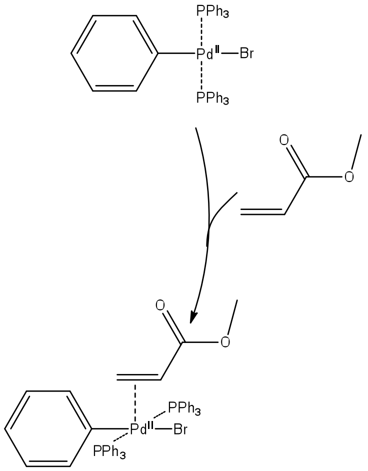


Figure 3.8 Formation of a Pi Complex

In this type of bonding described by the Dewar-Chatt-Duncanson model, a sigma-like bond and a pi backbond are both formed. A sigma-like bond is formed when electrons from a filled pi-orbital are donated into an empty d-orbital (Figure 3.9).

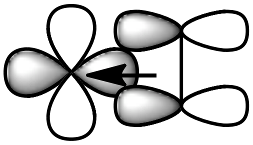


Figure 3.9 Sigma Bond Formation

A pi backbond is formed when electrons from a filled d-orbital are donated into an empty π* orbital (Figure 3.10).

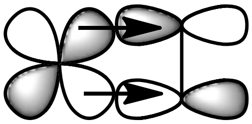


Figure 3.10 Pi Backbond Formation

The sigma and pi backbond reinforce each other. In other words, when there is increased sigma donation to the metal, there is increased pi-backbonding. To expand on this discussion, the electronic and/or steric factors that affect the stability of pi complexes could be discussed.

Step 3: Olefin (Alkene) Insertion

In the third step in the Heck reaction, the metal and alkyl group that make up the pi complex react by olefin insertion, creating a metal-carbon sigma bond (Figure 3.11). Olefin is another term for an alkene.

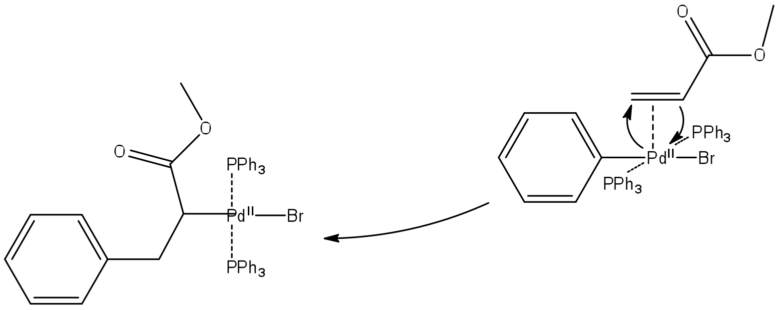


Figure 3.11 Olefin Insertion

In the olefin insertion in Figure 3.11, the electrons from the carbon-palladium bond attack the empty π* orbital on the alkene and the electrons from the pi bond on the alkene attack the empty d orbital of the palladium. This insertion can be examined further by using Markovnikov's rule to discuss the effect of the alkene's electron withdrawing group on the regioselectivity of the reaction.

Step 4: β-Hydride Elimination

In the fourth step of the Heck reaction, a new pi complex is formed by β-hydride elimination (Figure 3.12).

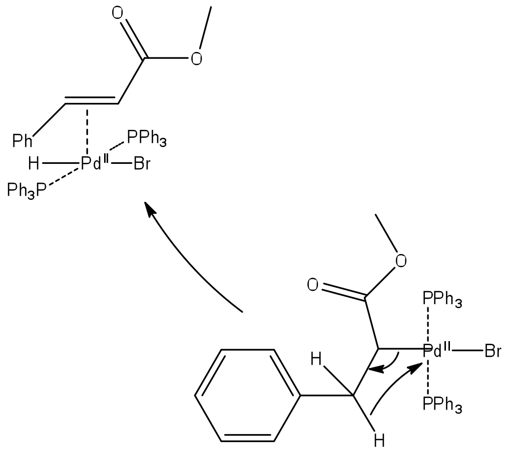


Figure 3.12 β-Hydride Elimination

In β-hydride elimination, a hydride is transferred from the beta-carbon to an open-coordination site on the metal. To introduce this step, the terms "beta position" and "hydride" should be referenced. By doing so, students will be able to make the connection that a hydride is transferred from the beta carbon to the metal in β-hydride elimination. It is important to accentuate that this is a syn elimination rather than an anti elimination, with which students are more familiar.

Step 5: Dissociation of the Pi Complex

The final product of the Heck reaction is generated through the dissociation of the pi complex. In this step, the pi complex breaks a ligand apart from the metal (Figure 3.13).

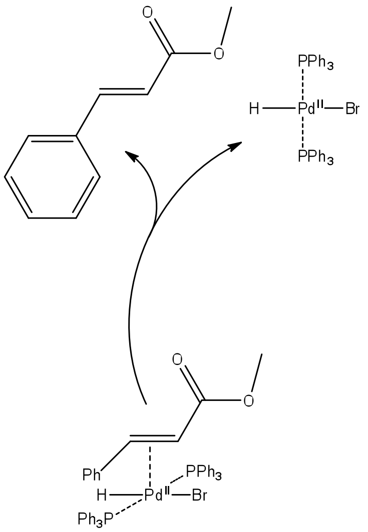


Figure 3.13: Dissociation of the Pi Complex

This step essentially is the opposite of step 2, the formation of a pi complex. To discuss this step, it is therefore important for them to make this connection. However, this step is not exactly the same. Using their new knowledge of back bonding as well as their previous understanding that a better overlap is key to stronger bonds, students can hypothesize why this pi complex would dissociate. The dissociation of this complex can be explained by the little to no back bonding or, in other words, the less overlap between the metal and carbon. For that reason, this step can be used to reinforce what was learned earlier in the lecture about pi complexes as well as what was learned throughout organic chemistry about orbital overlap.

Step 6: Reductive Elimination

In the Heck reaction, reductive elimination is used to regenerate the catalyst. Reductive elimination is the inverse of oxidative addition (Figure 3.14).

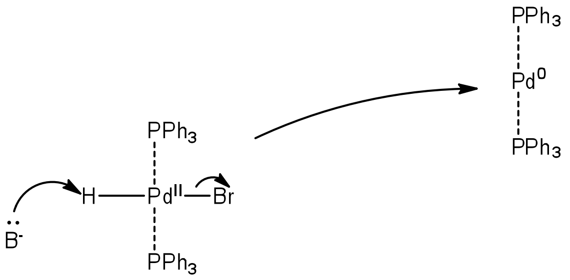


Figure 3.14: Reductive Elimination

In reductive elimination, the metal center is reduced from the *x+2* to the *x* oxidation state, which is the opposite of oxidative addition. In Figure 3.14, the base removes a hydrogen from the palladium, causing the palladium to be reduced and the bromide to be eliminated. It is particularly important to emphasize that reductive elimination does not go through the reverse mechanism of oxidative addition in the Heck reaction. By comparing the similarities and differences between the oxidative addition and reductive elimination in the Heck reaction (steps 1 and 6 respectively), student understanding of both steps can be reinforced.

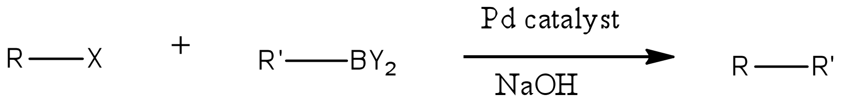
3.2.2 Applications

Coupling reactions as well as the Heck reaction can be expanded further by describing their impact in the research and production of consumer products. Coupling reactions are used in pharmaceutical production to help decrease the number of steps involved in the synthesis of drugs, lessening the environmental impact of the synthesis.[67] Additionally, coupling reactions are used to convert natural gas into liquid fuels and are also used to construct highly efficient organic solar cells.[68,69]

The Heck reaction's role in biochemical research can be discussed. For example, one particular paper by Haberli and Leumann describes the use of the Heck reaction to develop a novel synthesis of *C*-nucleosides.[70] Additionally, many commonly used products that are also made using the Heck reaction can be mentioned. For instance, Naproxen is a popular anti-inflammatory drug produced via the Heck reaction.[71] Another molecule that is synthesized using the Heck reaction is octyl methoxycinnamate, the main ingredient in sunscreen.[71] This ingredient is responsible for absorbing UV-B rays. Without the Heck reaction, these products would be significantly harder, if not impossible, to make. By discussing these and/or other applications, students can make associations between what they learn in the classroom and what they see in the outside world, helping them find more relevance in the material.

3.3 The Suzuki Reaction[35,74,75]

The Suzuki reaction is a coupling reaction where an organic halide is coupled with an organoborane in basic conditions using a palladium catalyst (Figure 3.15).



$$R{-}X + R'{-}BY_2 \xrightarrow[\text{NaOH}]{\text{Pd catalyst}} R{-}R'$$

Figure 3.15 Suzuki Reaction

By learning about this reaction, students can apply their new knowledge about the Heck reaction as well as analyze the interaction between a palladium organometallic catalyst and an organoborane.

The necessary background for the Suzuki reaction is similar to the Heck reaction because both are palladium catalyzed coupling reactions. However, the Suzuki reaction also requires students to have an understanding of hydroboration and boron oxidation because it uses an organoborane as a reactant.

3.3.2 The Suzuki Reaction in the Organic Chemistry Classroom

The general reaction described above can be used to introduce this carbon-carbon bond forming reaction made from an organic halide and organoborane. Because the Suzuki reaction is a coupling reaction, similar to the Heck reaction, it can be introduced after the Heck reaction. One particular similarity is that they both have palladium catalysts and aryl, benzylic or vinylic halide reagents. In contrast to the Heck reaction, the Suzuki reaction uses an organoborane reagent rather than an alkene-containing reagent. The knowledge that students gain from discussing the Heck reaction as well as their knowledge of hydroboration gives them the necessary background to learn about the

Suzuki reaction in detail. The Suzuki reaction can be introduced as a catalytic cycle displayed in Figure 3.16.

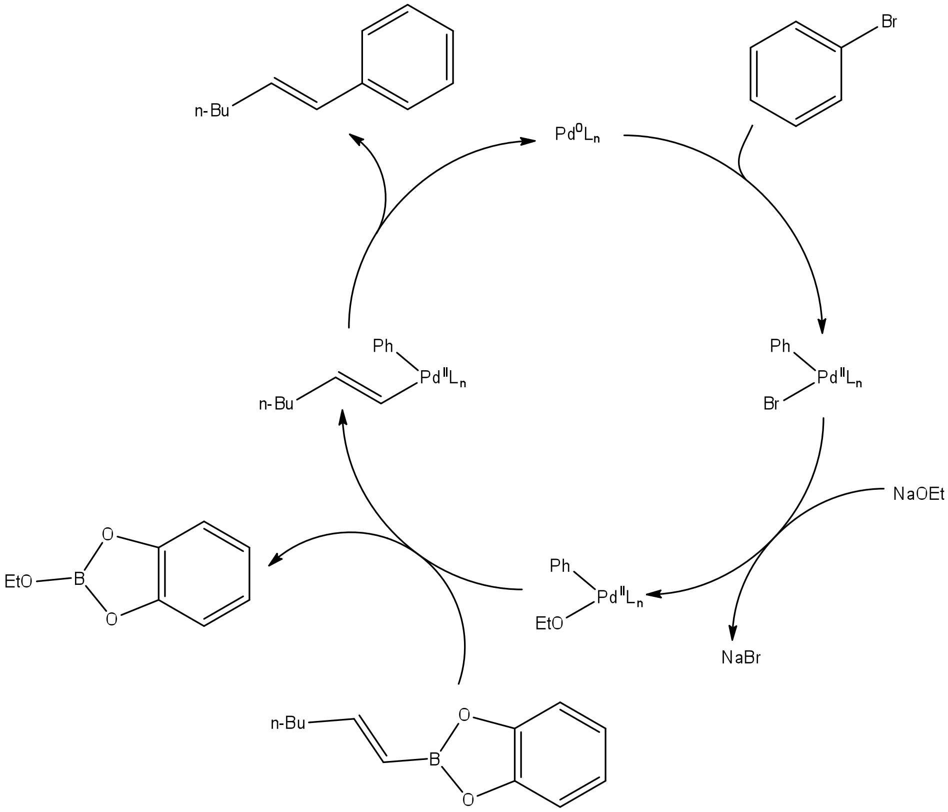


Figure 3.16 Suzuki Reaction Cycle

Step 1: Oxidative Addition

The first step of the Suzuki reaction involves the oxidative addition of an organic halide or triflate to the palladium catalyst (Figure 3.17).

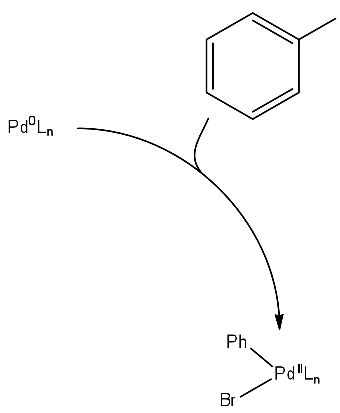


Figure 3.17: Oxidative addition

As mentioned previously, oxidative addition occurs when the palladium metal is oxidized from the *x* to the *x+2* oxidation state. The similarities between this step and the first step in the Heck reaction gives students the chance to apply their new organometallic knowledge to a different reaction, thereby reinforcing what they learned previously.

Step 2: Metathesis (Ligand exchange)

In the second step of the Suzuki reaction, the halide on the palladium is exchanged with the alkoxide (Figure 3.18).

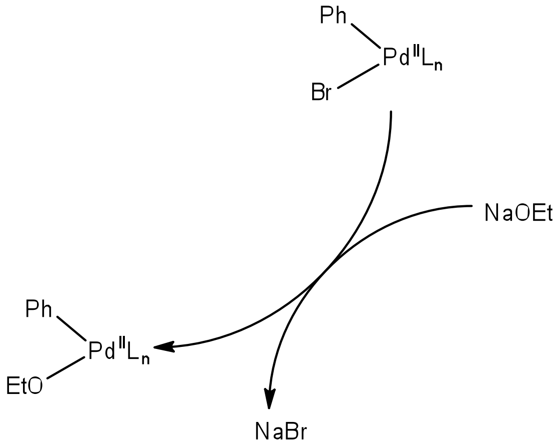


Figure 3.18: Metathesis in the Suzuki Reaction

This exchange of ligands between the reacting chemical species that concludes in a similar interaction in the products as in the reactants is called metathesis.

Step 3: Transmetalation

3,3-butenyl group (R group) is exchanged with the alkoxyl group so that the R group becomes attached to the palladium metal in a step called transmetalation (Figure 3.19).

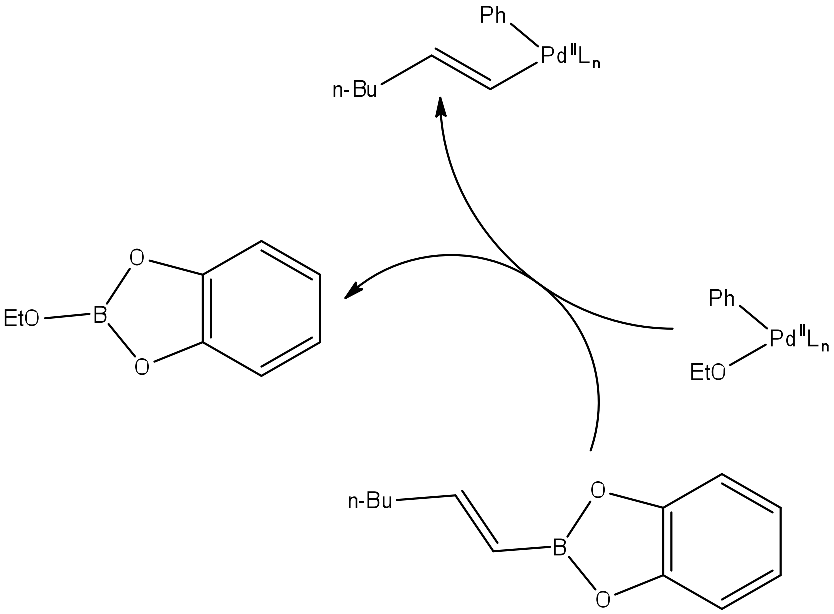


Figure 3.19: Transmetalation

Transmetalation is the exchange of ligands between two metal centers. However, the definition of transmetalation will probably leave students wondering where the second “metal” is. In this difficulty, there is an opportunity to discuss how boron acts “metal-like” based on what they know about metals and about boron. Boron is a metalloid with an empty p orbital. This empty p orbital, allows it to exchange ligands with organometallics, similar to the exchange metals with empty d orbitals can do.

Transmetallation in the Suzuki reaction occurs through a four atom cycle transition state (Figure 3.20).

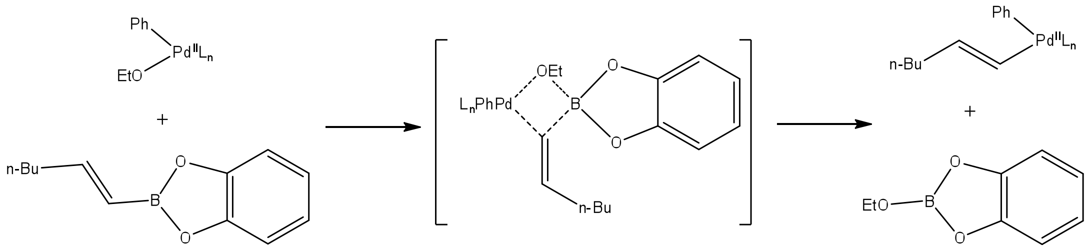


Figure 3.20: Transmetalation Transition State

This transition state is formed while the electrons from the boron-carbon sigma bond are attacking the empty d orbital on the palladium and the electrons from the oxygen-palladium single bond are attacking an empty p orbital on the boron. This step adds to student knowledge of the reactivity of boron.

Step 4: Reductive Elimination

In reductive elimination in the Suzuki reaction, the Pd-alkene bond attacks the sigma star orbital from the Pd-aryl bond, causing a gain of electrons on the palladium from the Pd-aryl bond (Figure 3.21).

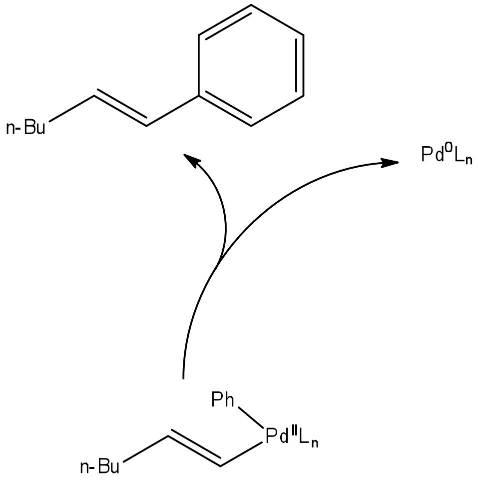


Figure 3.21 Reductive Elimination

As mentioned previously in the Heck reaction, reductive elimination, the inverse of oxidative addition, occurs when the palladium is reduced from the *x+2* to the *x* oxidation state. However, it is particularly important to discuss that unlike in the Heck reaction, the reductive elimination in the Suzuki reaction not only regenerates the catalyst, but also forms the product.

3.3.2 Applications

To conclude a discussion of the Suzuki reaction and of reactions in general, it is important to emphasize what it gives to organic chemistry. As in the Heck reaction and other coupling reactions, the Suzuki has played an increasingly significant role in material production and pharmaceutical chemistry. The Suzuki reaction in particular is superior because of its high selectivity as well as the low toxicity of boron in comparison to other elements like tin. It can also be performed in an aqueous environment. The Suzuki reaction has been used to produce non-linear optical (NLO) materials and as an alternate pathway to form Losartan, an angiotensin II receptor antagonist drug used to treat high blood pressure.[76,77]

3.4 Olefin Metathesis[79,80]

In 2005, Grubbs, Schrock and Chauvin won the Nobel Prize in chemistry for their work on olefin metathesis.[59] In olefin metathesis, the substituents of different olefins are rearranged by the breaking of carbon-carbon double bonds to form new olefins using a metal catalyst (Figure 3.22). This reaction is often catalyzed by nickel, tungsten, ruthenium and molybdenum.

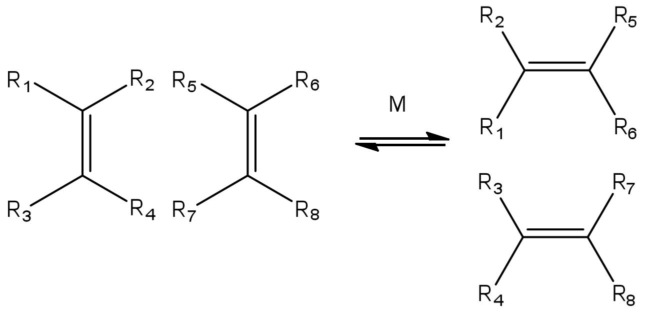


Figure 3.22: Olefin Metathesis

By learning about olefin metathesis, students can build on their knowledge of carbon-carbon bond forming reaction.

To introduce olefin metathesis successfully into an organic chemistry course, students should have background knowledge of alkene reactions and interactions. In particular, they should have an understanding of the following concepts:

1. Hybridization and sigma and pi bonding
2. d orbitals, oxidation, reduction and eighteen electron rule
3. Functional groups, sterics and electronic interactions
4. Alkene addition
5. Wittig reaction
6. Carbene chemistry

3.4.1 Olefin Metathesis in the Organic Chemistry Classroom

Olefins are compounds that contain carbon-carbon pi bonds and are also commonly referred to as alkenes. Metathesis, as discussed previously in the Suzuki reaction, is a transformation where ligands are exchanged intermolecularly to form products with a connectivity similar to the original molecules (Figure 3.23).

$$AX + BY \rightarrow AY + BX$$

Figure 3.23: Metathesis

By understanding the name of the reaction, it will be easier for students to understand what occurs in olefin metathesis.

Olefin metathesis can be discussed in more detail using a full reaction cycle (Figure 3.24).

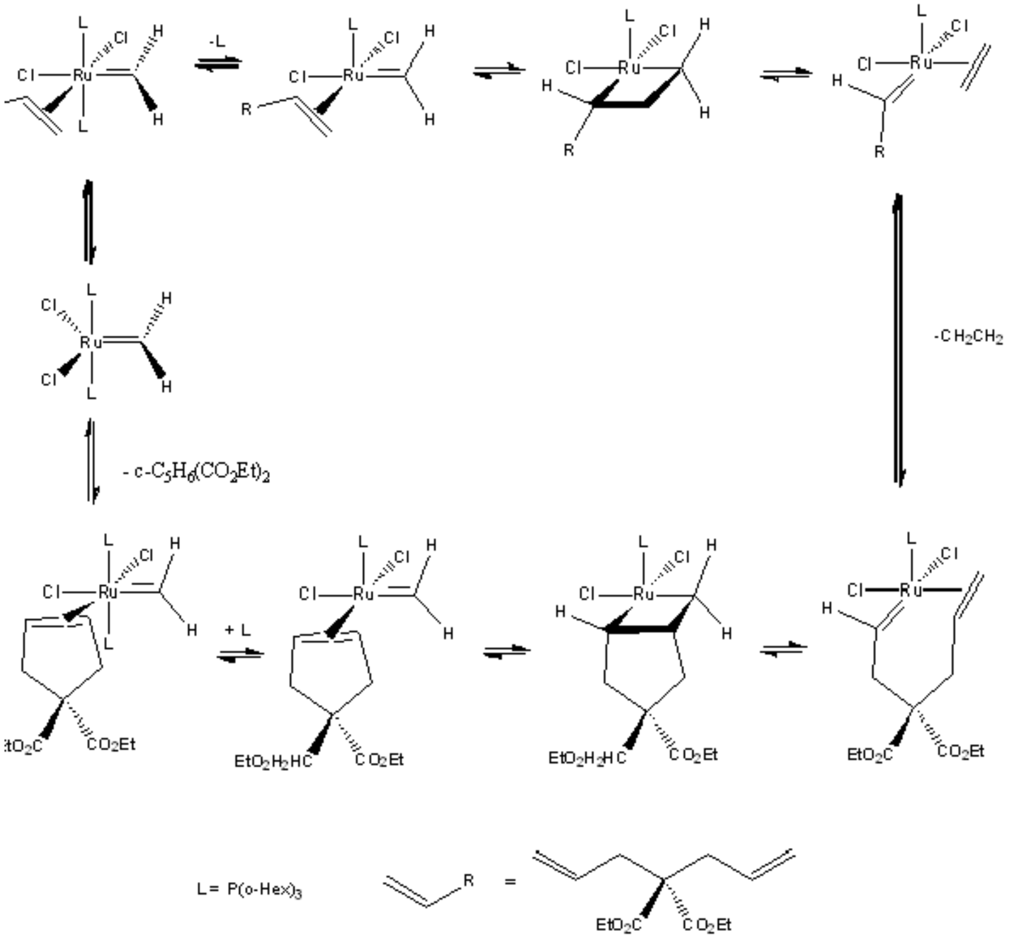


Figure 3.24 Olefin Metathesis Cycle

Step 1: Formation of a Pi Complex

The first step of olefin metathesis begins with the formation of a pi complex from the reaction of an olefin and the organometallic catalyst (Figure 3.25).

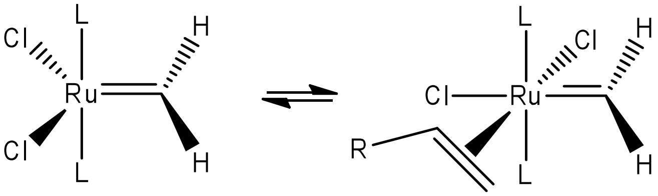


Figure 3.24 Formation of a Pi Complex

In this type of bonding, a sigma-like bond and a pi backbond are both formed. A sigma-like bond is formed when electrons from a filled π bond on the alkene attack an empty d-orbital on the ruthenium (Figure 3.26).

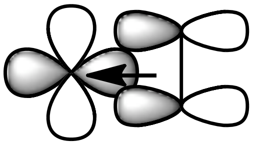


Figure 3.26 Sigma Bond Formation

A pi backbond is formed when electrons from a filled d-orbital on the ruthenium attack an empty π* alkene orbital (Figure 3.27).

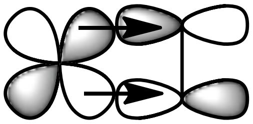


Figure 3.27 Pi Backbond Formation

The pi complex formation that occurs in the Heck reaction can be referenced when discussing this step, thereby making a connection between what students have learned previously.

Step 2: Dissociation of the Ligand

In this step, the ligand breaks away from the catalyst (Figure 3.28).

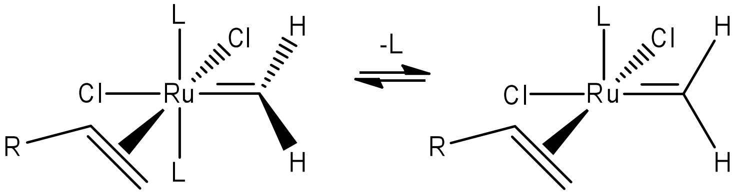


Figure 3.28 Dissociation of the Ligand

This dissociation causes a change in the electrons on ruthenium. To reinforce student understanding of this step as well as the eighteen electron rule, the amount of electrons on the ruthenium in the reactant and the product could be calculated using the ionic atom method. This analysis can emphasize that the reactant is an eighteen electron ruthenium complex and the product is a sixteen electron ruthenium complex.

Steps 3-4: Formation and Dissociation of a Ruthenium Metallacycle

In steps 3 and 4, the first alkene exchange occurs (Figure 3.29).

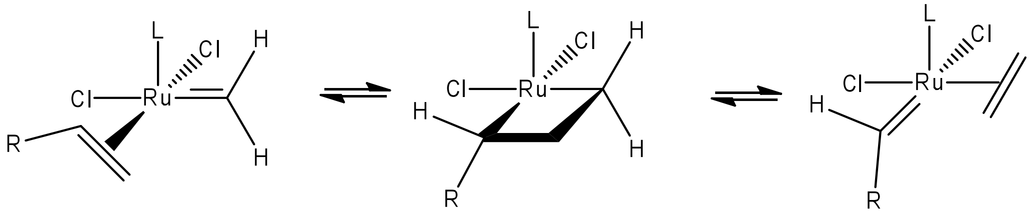


Figure 3.29 Formation and Dissociation of a Ruthenium Metallacycle

In step 3, electrons from the metal-carbene bond attack the pi star orbital of the alkene and the pi electrons of the alkene attack an empty d orbital in the ruthenium concurrently, resulting in a ruthenium metallacycle. In step 4, the metallacycle dissociates, creating a new alkene and transition metal transition metal-carbene complex. The arrow mechanism for these steps is shown in Figure 3.30.

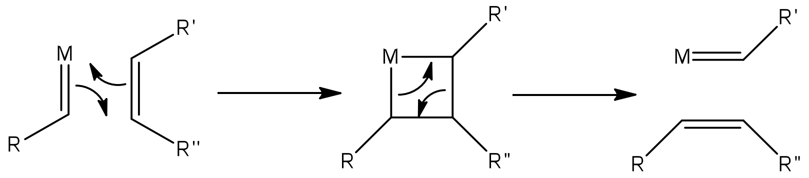


Figure 3.30 Arrow Mechanism of the Formation and Dissociation of a Metallacycle

The mechanism of this step can be reemphasized by comparing it to the Wittig reaction, in which a similar four-atom cyclical intermediate is made and dissociated with an organophosphorus compound (Figure 3.31).

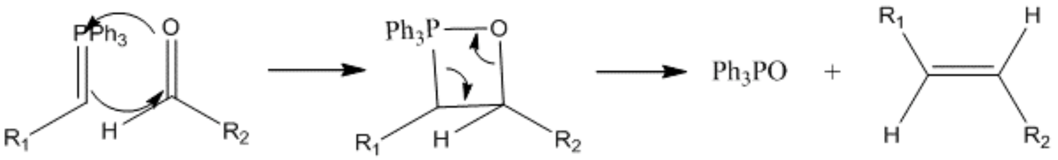


Figure 3.31 Arrow Mechanism of the Wittig Reaction

Step 5: Dissociation and Formation of a Pi Complex

In the first part of step 5, an olefin is made by a dissociation of the olefin-ruthenium pi complex (Figure 3.32). In the second part, a pi complex is formed between the ruthenium and a different olefin, similar to step 1 (Figure 3.32).

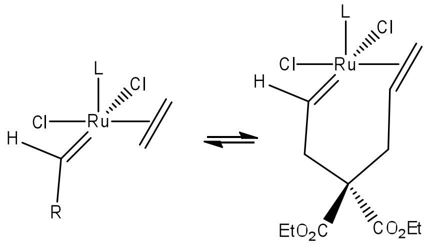


Figure 3.32 Dissociation and Formation of a Different Pi Complex

It is important to emphasize that an alkene is produced as product and a different alkene couples with it, rather than the same alkene. This step can be expanded further by discussing possible methods to remove the dissociated alkene from the solution so it does not react with the catalyst. Additionally, the rate of reaction of the new intramolecular alkene could be compared to the rate of reaction in step 1 of the separate alkene, emphasizing the importance of proximity in reactions.

Step 6-7: Formation and Dissociation of a Different Ruthenium Metallacycle

In this step, an intermolecular exchange of alkene substituents occurs between the transition metal-carbene complex and the alkene (Figure 3.33).

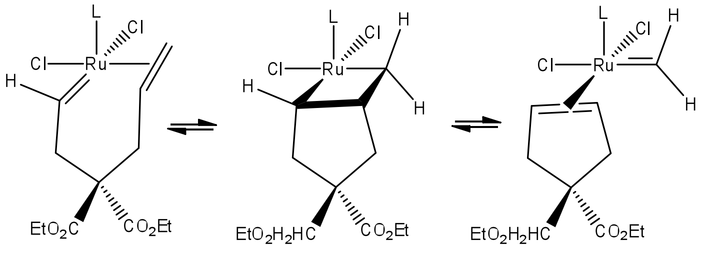


Figure 3.33 Formation and Dissociation of a Different Ruthenium Metallacycle

These steps occur through the same mechanism as steps 3-4. However, in comparison, this reaction involves a different transition metal-carbene complex and alkene.

Step 8: Attachment of the Ligand

In step 8, the ligand bonds with the ruthenium complex, reducing it from sixteen electrons to eighteen electrons (Figure 3.34). This step is the reverse of step 3.

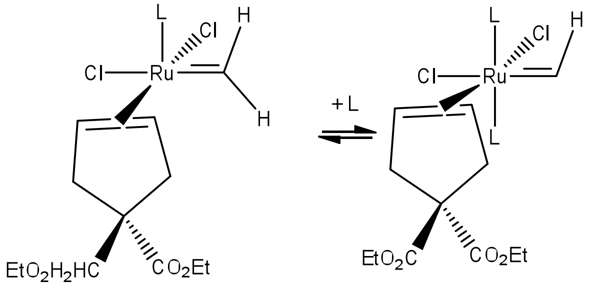


Figure 3.34. Attachment of the ligand to the catalyst

Step 9: Dissociation of Product from the Catalyst

In the final step, the second olefin product is formed and the catalyst is regenerated by the dissociation of the pi complex (Figure 3.35).

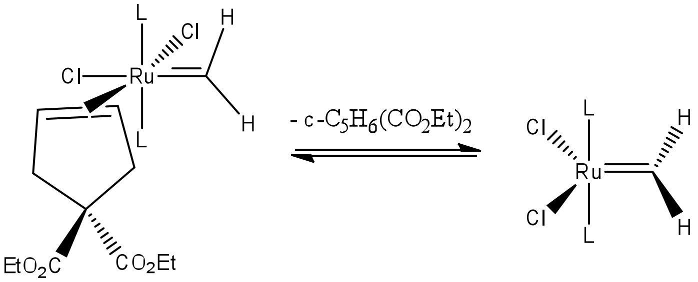


Figure 3.35 Dissociation of the Pi Complex

The second olefin product is formed and the catalyst is regenerated. This step is the reverse of step 1, in which a substrate binds to the catalyst.

3.4.2 Applications

As with the previous reactions, discussing the applications of organoruthenium olefin metathesis can show its importance in organic chemistry synthesis. Similar to the Suzuki reaction, olefin metathesis is easy to scale. In particular, pheromones have been produced less expensively in the laboratory using olefin metathesis.[81] Ruthenium complexes are good catalysts for these reactions because they react with carbon-carbon double bonds well and do not react with other functional groups. Students can expand their understanding of olefin metathesis by postulating why this reaction is cheaper, easier and more reactive than many non-metal organic reactions.

3.5 Coenzyme B_{12} Catalyzed Reactions[35,60]

Vitamin B_{12} is crucial for the formation of blood and functioning of the brain. Inside the body, vitamin B_{12} is transformed into coenzyme B_{12}, which is used to catalyze reactions. In reactions that require coenzyme B_{12}, a group on one carbon changes places with a hydrogen on an adjacent carbon (Figure 3.36). This exchange occurs through radicals.

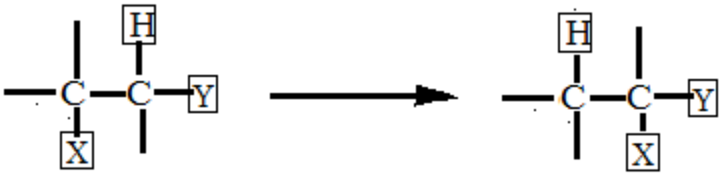


Figure 3.36 Coenzyme B_{12} Catalyzed Reactions

By learning about coenzyme B_{12}-cataylzed reactions in the human body, students can learn how a cobalt-organic compound can work as a radical catalyst inside the human body.

Students should have background knowledge in radical chemistry before B_{12} coenzyme catalyzed reactions are introduced into the classroom. In particular, they should have an understanding of the following concepts:

1. d orbitals and hybridization
2. Oxidation and reduction
3. Functional groups, sterics and electronic interactions
4. Radical structure and stability
5. Radical reactions
6. Carbonyl chemistry
7. Heterocycles

These concepts will provide them with the background that they need to understand organometallic catalyzed radical chemistry.

3.5.1 Coenzyme B_{12}-Catalyzed Reactions in the Organic Chemistry Classroom

Students have often seen "enzymes" whether in high school or college biology. However, many students probably have not come in contact with the term "coenzyme." A coenzyme is an organic molecule substance that assists enzymes in catalyzing reactions. Discussing this definition will help students understand the function of coenzyme B_{12} in the body, particularly if they have not seen/understood this word before.

After introducing the term coenzyme, coenzyme B_{12} can be introduced. Coenzyme B_{12} is a cobalt-organic coenzyme, which is derived from vitamin B_{12}. Vitamin B_{12} is not found naturally in the human body; rather, it is introduced into the body indirectly from bacteria in the form of fish, eggs and milk. It has also been recently synthesized by Woodward and Eschenmoser.[79] Without vitamin B_{12}, and coenzyme B_{12} respectively, people would develop pernicious anemia.

One way to introduce coenzyme B_{12} into the classroom is to compare it to the structure of vitamin B_{12}. Relating the coenzyme B_{12} to the vitamin B_{12} will not only emphasize the shape of both molecules but will also emphasize that coenzyme B_{12} is derived from the ingested vitamin B_{12}. The structure of vitamin B_{12} and coenzyme B_{12} are shown in Figure 3.37.

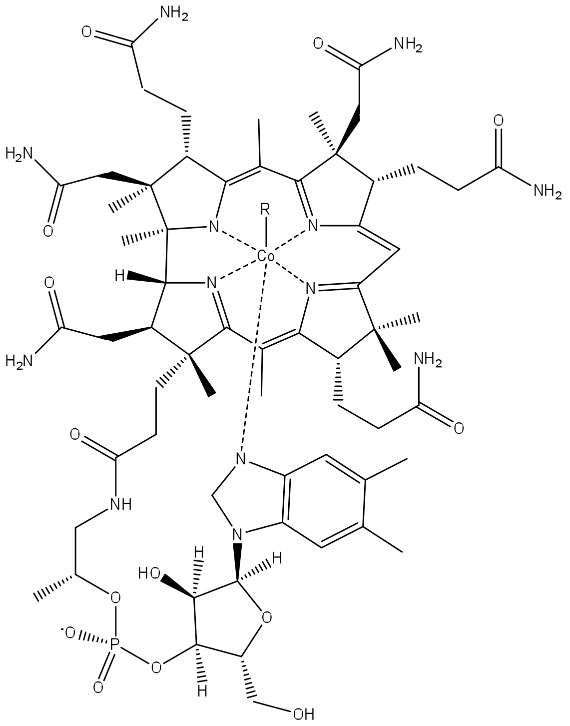


Figure 3.37 Vitamin B_{12} (R=OH) and Coenzyme B_{12} (R=5’-deoxyadenosyl)

As shown in Figure 3.37, vitamin B_{12} and coenzyme B_{12} are octahedral. According to hybdrization theory, they have six sp^3d^2 orbitals and 3 empty d orbitals. Both groups are attached to four nitrogens in equatorial positions and attached by a nitrogen in the axial position. In the other axial position, coenzyme B_{12}contains a 5’-deoxyadenosyl group while vitamin B_{12} has a hydride or water molecule attached. The enzyme is responsible for holding the coenzyme in this orientation. By discussing the structure of the coenzyme B_{12} based on what students know about octahedral molecules, the coenzyme B_{12}-catalyzed reactions are easier to introduce.

There are many different types of reactions in which coenzyme B_{12} could assist, any of which can be introduced into the classroom. The particular mechanism discussed below is when diol dehydratase is the enzyme. Diol dehydratase in combination with coenzyme B_{12} catalyzes the removal of oxygen and hydrogen from a molecule in the form of water. The coenzyme B_{12}-dependent diol dehydratase-catalyzed reaction is shown in Figure 3.38.

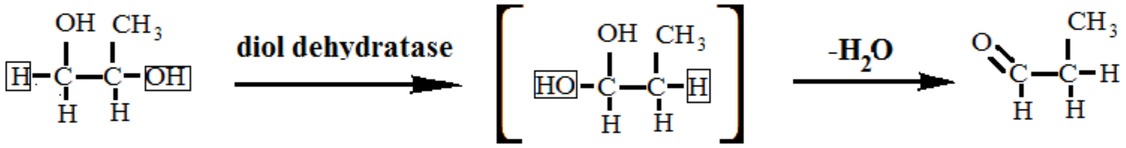


Figure 3.38 Coenzyme B_{12}-Dependent Diol Dehydratase-Catalyzed Reaction

The full mechanism for this reaction is shown in Figure 3.39.

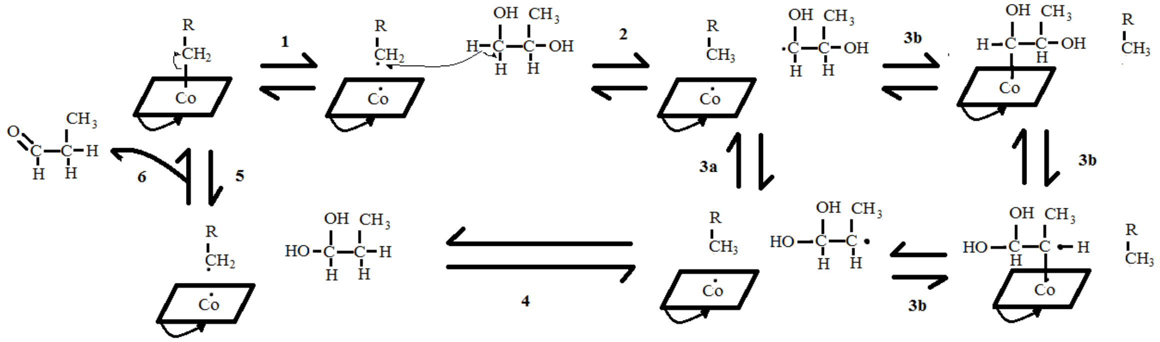


Figure 3.39 Coenzyme B_{12}-Dependent Diol Dehydratase-Catalyzed Reaction Cycle

As seen above, this reaction is reversible. The reversibility of this reaction gives the opportunity to analyze what factors of this reaction make it reversible, in particular radical stability. The radical chemistry of this reaction can be explored further by discussing the initiation, propagation and termination steps in detail.

Step 1: Initiation

The most important step to discuss is the first step, the radical initiation step, which is also the catalyzing step. In this step, the sp^3d^2-sp^3 cobalt-carbon bond is homolytically cleaved or split to form two radicals, catalyzing the reaction (Figure 3.40).

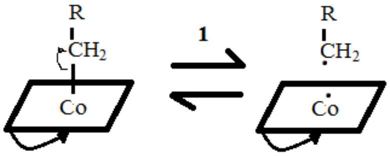


Figure 3.40 Initiation Step

The cobalt-carbon bond only requires 26 kcal/mol to break apart. This bond dissociation energy provides a way to discuss why coenzyme B_{12} is such a good catalyst. The weak bond dissociation energy of Br-Br (46 kcal/mol) and the high dissociation energy of C-H (98 kcal/mol) can be used in comparison to emphasize how easy it is for this step to occur and catalyze the reaction. It is also important to emphasize that because of this cleavage the cobalt changes from +3 to +2; in other words, it gains an electron.

Steps 2-4: Propagation

Steps 2 through 4 are the propagation steps, in which both a new bond and radical are created. They lead to the isomerization, or formation of an isomer, of the original substrate. In step 2, the 5’-deoxyadenosyl radical removes a hydrogen atom from a primary carbon on the substrate, forming a radical on that carbon (Figure 3.41).

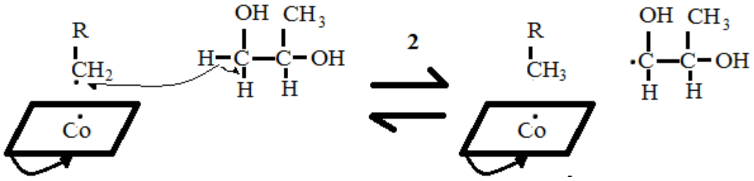


Figure 3.41 Step 2

For step 3, there are two radical pathways proposed to form a radical substrate (Figure 3.42). Analyzing both the “accepted” and proposed pathways emphasizes that mechanisms are proposed based on experimental results and that there is not always, if ever, an obvious mechanism. 3a is the most popular explanation of these radical pathways and is the pathway to emphasize if only one is discussed in the classroom. In pathway 3a, the hydroxyl radical shifts from an adjacent carbon to the primary carbon, creating a radical on the adjacent carbon.

In comparison to pathway 3a, pathway 3b is a three step pathway. First, the primary carbon substrate radical combines with the cob(II)alamin. Next, it is suggested that the cobalt on the switches with the hydroxyl group on the primary via a Co(III)-olefin pi complex. Finally, the cobalt-carbon bond dissociates, forming cob(II)alamin and a carbon radical on the substrate. In this pathway, the cobalt is oxidized to cobalt III and then reduced back to cobalt II. By emphasizing this particular oxidation and reduction, students can expand their understanding of oxidation and reduction in organometallics to include radical oxidation and reduction as well as reinforce what they learned in the initiation step.

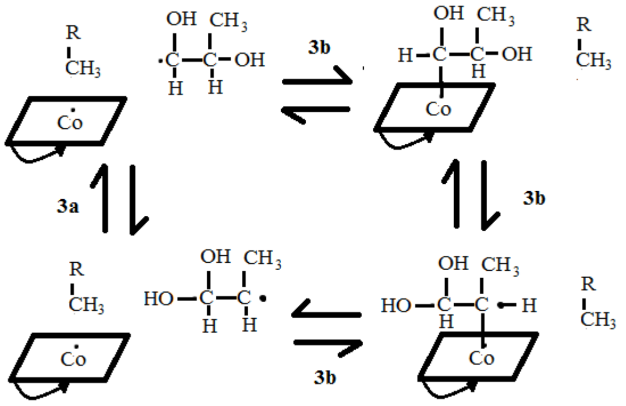


Figure 3.42 Step 3

In step 4, the adjacent carbon radical removes a hydrogen atom from the 5'-deoxyadenosine, making a 5'-deoxyadenosine radical (Figure 3.43).

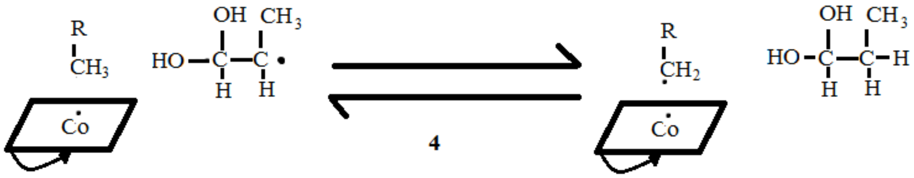


Figure 3.43 Step 4

Analyzing the steps 2 through 4 can reemphasize radical organic chemistry learned previously in the year. In particular, the rate of reaction can be discussed relatively for each step based on radical stability. If the radical is more stable, then it takes a longer amount of time it takes for the radical to react.

Step 5: Termination

The catalyst is regenerated by the termination step. In this step, the cob(II)alamin and carbon radical combine to make a cobalt-carbon bond (Figure 3.44). This step is the inverse of step 1.

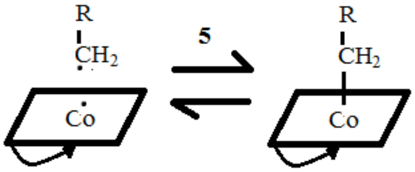


Figure 3.44 Termination Step

Step 6: Dehydration

In this step, hydrogens and oxygen are removed from the hydrate in the form of water to form an aldehyde (Figure 3.45).

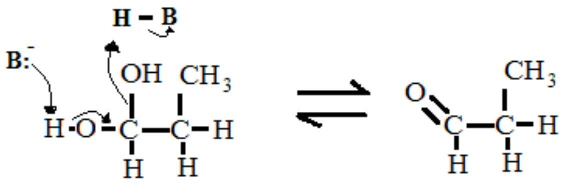


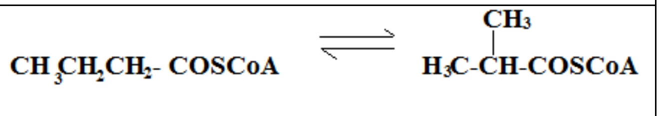
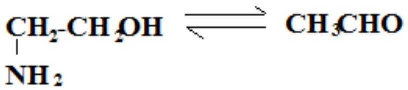
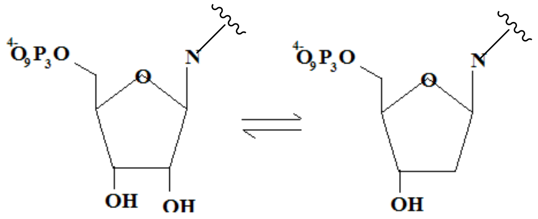
Figure 3.45 Dehydration

Analyzing the mechanism of this step gives students the opportunity to apply their knowledge of carbonyl chemistry in a biological setting.

3.5.2 Other Coenzyme B_{12}-Catalyzed Reactions

To conclude this discussion, other coenzyme B_{12}-dependent reactions can also be introduced. A list of some of these reactions, as described in *The Organic Chemistry of Enzyme-Catalyzed Reactions*, is provided below (Table 3.1).

Table 3.1 Coenzyme B_{12}-dependent reactions

Enzyme	**Class of Reactions**	**Reaction**
Isobutylryl-CoA mutase	Carbon Skeletal Rearrangements	 $CH_3CH_2CH_2\text{- }COSCoA \rightleftharpoons H_3C\text{-}\overset{CH_3}{\overset{\vert}{C}H}\text{-}COSCoA$
Ethanolamine ammonia lyase	Elimination	 $\underset{NH_2}{\underset{\vert}{C}H_2}\text{-}CH_2OH \rightleftharpoons CH_3CHO$
Ribonucleotide reductase	Reduction	

Each of these enzymes in combination with coenzyme B_{12} catalyzes a reaction through a similar radical mechanism. The last step of each enzyme-catalyzed reaction however varies based on the type of enzyme to which the coenzyme B_{12} is attached and the type of substrate that is affected by this reaction. For example, coenzyme B_{12} attached to a dehydratase causes a particular substrate to loose a water molecule. In comparison, coenzyme B_{12} attached to an aminomutase solely causes a change in isomerization of another substrate; it changes the location of the amine group. A coenzyme B_{12} attached to mutase moves a carbon from the main chain to form a side chain. While it is not important to introduce every single one of these examples, they show that the radical mechanisms that coenzyme B_{12} initiates occur frequently inside the human body.

Part 4

Conclusion

This proposed integration has many positive aspects that will make it successful. Primarily, the material itself, particularly the Heck, Suzuki and olefin metathesis reactions, has been successfully integrated into the introductory organic chemistry laboratory, emphasizing that students have been able to learn the information and apply it.[46-51]

Additionally, the proposed integration of organometallic chemistry builds on students' chemical knowledge. The organometallic examples discussed in this proposal are frequently related back to concepts learned in both general and organic chemistry. By combining the concepts learned in general and organic chemistry into a discussion of organometallics, students are able to see several connections between these two subjects. Furthermore, organometallic chemistry introduces students to an important area of organic chemistry research that they will probably not have the chance to experience otherwise.

Not only does the material build on what students know, but it also does so in a way that enables students to learn it better. The proposed curriculum builds from organic chemistry to basic metal-based chemistry to transition metal-catalyzed organic reactions, allowing for a smooth integration. As it builds, many concepts are discussed repeatedly, reinforcing the important aspects of organometallic chemistry and catalysis and thereby deepening student understanding of the material.

Although there are many positives in this integration, there also are some challenges that may arise for students. Primarily, one difficulty with this integration is that some concepts were simplified to introduce the material at a level students could understand within a certain period of time. In particular, hybridization is being introduced instead of molecular orbital theory, which is the more accurate of the two in the study of transition metal chemistry. However, because of the level at which the students are discussing organometallic chemistry, hybridization does not affect the main concepts the students are learning and therefore should not be a large concern.

Additionally, there is a lack of resources (textbooks or websites) available about the subject for an undergraduate enrolled in an introductory organic chemistry course. This makes it more difficult for students to study and amplify their knowledge of the material discussed in class. An attempt to reduce this problem would be to provide specific references students could use, including books, websites and sample problems. The sample problems give students the ability to apply their newfound knowledge. A list of possible references for students and example problems on the eighteen electron rule are provided in the appendix.

Despite these potential hurdles, these resources in conjunction with the interdisciplinarity of the material will help students to increase and apply their knowledge of chemistry. This proposed integration does this by taking what students consider the traditional boundaries of organic chemistry - mainly carbon, hydrogen, oxygen and nitrogen atoms – and expanding them to include transition metals. By increasing their knowledge in both general chemistry and organic chemistry using organometallic chemistry, students are challenged to make associations between these subjects, and thereby promoting an overall understanding rather than a segmented knowledge of chemistry.

Part 5

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Part 6

Appendix

6.1 References for Students

Eighteen Electron Rule

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Heck Reaction

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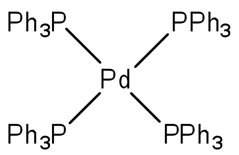
6.2 Eighteen Electron Rule Problem Set with Answers

Determine the oxidation state of each metal and electron count of the following compounds. Use the ionic atom method to determine the electron count.

1.

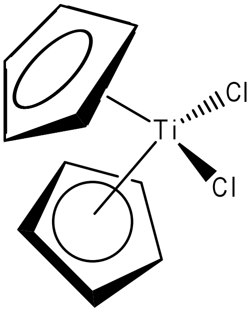


Oxidation State: 0

Electron Count:

Pd	$10e^-$
4 PPh_3	$8e^-$
Total	**18 e^-**

2.

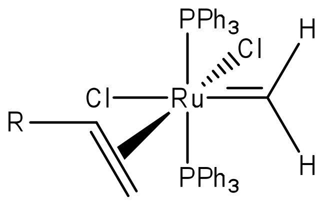


Oxidation State: +4

Electron Count:

Ti	0 e^-
2 Cl^-	4 e^-
2 Cp^-	12 e^-
Total	**16 e^-**

3.



Oxidation State: +4

Electron Count:

Ru	4 e^-
2 PPh_3	4 e^-
2 Cl^-	4 e^-
Carbene	4 e^-
Alkene	2 e^-
Total	**18 e^-**