1

Introduction of Computational Organometallic Chemistry

This chapter provides a brief introduction of computational organometallic chemistry, which usually focuses on the reaction mechanism of homogeneous organometallic catalysis.

1.1 Overview of Organometallic Chemistry

In this section, the historical footprint of organometallic chemistry is concisely given, which would help the readers better understand the role of computation in the mechanistic study of organometallic chemistry.

1.1.1 General View of Organometallic Chemistry

Creating new material is always entrusted with the important responsibility for the development of human civilization [1–3]. In particular, synthetic chemistry becomes a powerful tool for chemists, as it exhibits great value for the selective construction of new compounds [4–8]. Various useful molecules could be prepared by the strategies of synthetic chemistry, which provides material foundation, technological support, and drive force for science [9–20]. Synthetic chemistry is also the motivating force for the progress of material science, pharmaceutical science, energy engineering, agriculture, and electronics industry [21–41]. In this area, organic synthesis reveals broad interests from a series of research fields, which could target supply to multifarious functional molecules.

The synthetic organic chemistry usually focuses on "carbon" to widen related research, which could afford various strategies for the building of molecular framework, functional group transformations, and controlling stereochemistry in more sophisticated molecules [9, 22, 42–50]. Therefore, selective formation of new covalent bond between carbon atom and some other atom involving nitrogen, oxygen, sulfur, halogen, boron, and phosphorus becomes one of the most important aims for synthetic organic chemistry. In particular, nucleophiles and electrophiles are important for the construction of new covalent bonds.

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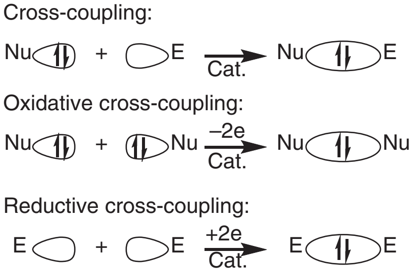
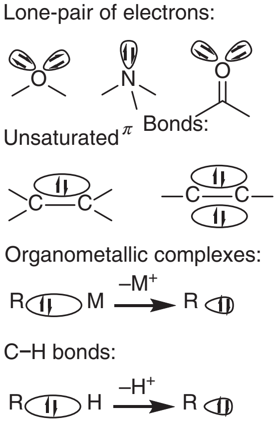
A nucleophile, which is a molecule with formal lone-pair electrophiles, can donate two electrons to its reaction partner for the formation of new covalent bond. Alternatively, an electrophile, which is a molecule with formal unoccupied orbitals, can accept two electrons from its partner for the formation of new covalent bond. Thereinto, coupling reactions could be categorized as redox-neutral cross-coupling with an electrophile and a nucleophile, oxidative coupling with two nucleophiles, and reductive coupling with two electrophiles (Scheme 1.1).



Scheme 1.1 Cross-coupling reactions with nucleophiles and electrophiles.

In organic chemistry, the nucleophile is an electron-rich molecule that contains a lone pair of electrons or a polarized bond, the heterolysis of which also could yield a lone pair of electrons (Scheme 1.2). According to this concept, organometallic compounds, alcohols, halides, amines, and phosphines with a lone pair of electrons are nucleophiles. Some nonpolar π bonds, including olefins and acetylenes, which could donate the π-bonding electrons, are often considered to be nucleophiles. Moreover, the C—H bonds of hydrocarbons can be considered to be nucleophiles because the electronegativity of carbon is higher than that of hydrogen, which could deliver a proton to form a formal carbon anion. Correspondingly, the electrophile is an electron-deficient molecule that contains unoccupied orbitals or



Scheme 1.2 Some selected examples of nucleophiles.

low-energy antibonding molecular orbital, which could accept the electrons from nucleophiles. In this chemistry, cationic carbons, which usually come from the heterolysis of carbon—halogen bonds, are electrophile. Polar π bonds, including carbonyl compounds and imines, also could be considered to be electrophile, which involve a low-energy π antibond. Interestingly, Fisher-type singlet carbene has an electron pair filling one sp^2 hybrid orbital and an unoccupied p orbital, which could be considered to be either nucleophile or electrophile in coupling reactions.

Superficially, at least, the reaction between nucleophile and electrophile could construct a covalent bond undoubtedly. However, the familiar nucleophiles and electrophiles, used in cross-coupling reactions, are usually inactive, which could not react with each other rapidly. Moreover, when more active nucleophiles and electrophiles are used in coupling reactions, it would become out of control, which would not selectively afford target products. In effect, introducing transition metal catalysis can perfectly solve this problem. The appropriate transition metal can be employed to selectively activate the nucleophiles and electrophiles and stabilize some others, which led to a specially appointed cross-coupling reaction.

High-valence transition metal can obtain electrons from nucleophile, which led to the transformation of nucleophile into electrophile. The newly generated electrophile can couple with other nucleophiles to form covalent bond, which is named oxidative coupling reaction [51–53]. Meanwhile, the reduced transition metal can be oxidized by exogenous oxidant for regeneration. Correspondingly, low-valence transition metal can donate electrons to electrophile leading to the transformation of electrophile into nucleophile, which can react with another electrophile to form covalent bond. Accordingly, it is named reductive coupling reaction. The oxidized transition metal also can be reduced by exogenous reductant.

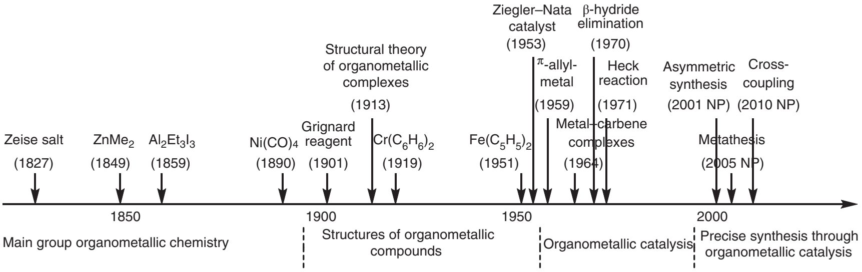
The d orbital of some transition metals could be filled by unpaired electrons, which led to a unique catalytic activity in radical-involved reactions. The homolytic cleavage of transition metal–carbon (or some other atoms) bond is an efficient way for the generation of a radical species, which can promote further transformations. On the other hand, free radical can react with some transition metal leading to the stabilization of radical, which can cause further radical transformations [54–57]. Moreover, nucleophiles and electrophiles, activated by transition metals, also can react with radical to form new covalent bonds.

Although there is no electron barrier due to the appropriate symmetry of frontier molecular orbitals, a great deal of uncatalyzed pericyclic reactions would occur under harsh reaction conditions, which could be often attributed to the low-energy level of highest occupied molecular orbitals (HOMOs) and high-energy level of lowest unoccupied molecular orbitals (LUMOs) in reacting partners. Transition metals can play as a Lewis acid, which could significantly reduce the LUMO of coordinated organic moiety. Therefore, it has been widely adopted to catalyze pericyclic reactions, which leads to moderate reaction conditions and adjustable selectivity [58–62]. Moreover, the node of d orbital can change the symmetry of a conjugative compound, which involves a transition metal. Therefore, transition metal itself also could participate in a pericyclic reaction to reveal unique catalytic activity.

As an overview of organometallic chemistry, the core is the formation of a metal–carbon bond and its further transformation. Different from organocatalysis, organometallic catalysis process usually goes through multiple steps as well as complicated catalytic cycles, which originated from the complex bonding pattern of metallic catalyst and the variation of valence state for the central metal element. Consequently, improving the reaction efficiency and yield for organometallic catalysis encountered more difficulty than conventional organocatalysis. Moreover, the design of catalysis and ligand for transition metal-catalyzed reaction is still facing both opportunities and challenges. To solve the above-mentioned issues, the understanding of reaction mechanism is imperative, which could give more information for the detailed reaction process, and help to improve the reaction efficiency and yield.

1.1.2 A Brief History of Organometallic Chemistry

As an interdiscipline of organic and inorganic chemistry, organometallic chemistry has a history of almost 200 years since the first complex $K[(C_2H_4)PtCl_3]\cdot H_2O$ was reported by Zeise when he heated ethanol solution of $PtCl_4/KCl$ [62]. The history of organometallic chemistry can be roughly divided into four stages. The chemists majorly focused on main group organometallic compounds in the nineteenth century. Later in the first half of the twentieth century, chemists paid more attention to understanding the structures of organometallic compounds involving transition metals. Then in the latter half of the twentieth century, various transition metal-catalyzed reactions had been widely reported. Since this century, chemists have been keen on using transition metal catalysis to selectively construct more complex organic compounds. The outlined history of organometallic chemistry could be concluded in Scheme 1.3 [63].



Scheme 1.3 A brief history of organometallic chemistry. Source: Based on Didier [63].

The nineteenth century could be considered as the enlightenment era of organometallic chemistry. Frankland first systemically investigated organometallic chemistry and prepared a series of alkyl metal compounds in 1850s. In the late nineteenth century, $ZnMe_2$ (in 1849 by E. Frankland), $Sn(C_2H_5)_4$ (in 1859 by E. Frankland), $PbEt_4$ (in 1853 by C. Löwig), $Al_2Et_3I_3$ (in 1859 by W. Hallwachs and

A. Schafarik), and RMgX (in 1900 by V. Grignard) had been prepared, and the chemical property of those compounds also had been studied [64–68].

In 1890, $Ni(CO)_4$ was found as the first metal carbonyl complex by L. Mond et al. in the study of the corrosion of stainless steel valves by CO [69]. Next year, $Fe(CO)_5$ was also found by the same group [70]. It could be considered as the beginning of the structural study of organometallic complexes. Two years later, Werner proposed structural theory of organometallic complexes involving the tetrahedral, octahedral, square planar, etc. which won him the Nobel prize in chemistry in 1913 [71]. In 1919, $Cr(C_6H_6)_2$ was prepared by Hein using MgPhBr to react with $CrCl_3$ [72]. However, the sandwich-like structure of this complex was proved by Fischer 36 years later. In 1951, $Fe(C_5H_5)_2$ had been synthesized by Kealy and Pauson individually [73]. The sandwich-like structure of that complex was confirmed by G. Wilkinson the following year, which aroused chemists' enthusiasm for the study of transition metal organic compounds. In 1964, tungsten carbene complex was reported by Fischer, who shared 1973 Nobel prize in chemistry with G. Wilkinson [74]. By the 1950s, with the appearance of representational methods, involving X-ray crystallography, infrared spectrum, and nuclear magnetic resonance spectrum, means of characterizing transition metal compounds were becoming more and more mature. Therefore, organometallic chemistry became an independent discipline.

From the middle of the twentieth century, organometallic compounds were gradually considered as a catalyst in organic reactions. In 1953, Ziegler and Natta found that $TiCl_4/AlEt_3$ could promote atmospheric polymerization of olefins, which helped them share 1963 Nobel prize in chemistry [75, 76]. In 1959, allylic palladium was prepared by Smidt and Hafner, which was the beginning of π-allyl metal chemistry [77]. The same year, Shaw and Ruddick reported an elementary reaction of oxidative addition [78]. In 1974, Wilkinson reported another elementary reaction of β-hydride elimination [79]. Those works led to a series of following mechanistic studies for organometallic reactions. In 1972, Heck and Nolley reported a palladium-catalyzed coupling reaction between aryl halides and olefins, which was named Heck reaction [80]. Meanwhile, a series of palladium-catalyzed cross-coupling reaction, including Kumada coupling with Grignard reagent [81], Suzuki coupling with aryl borane [82], Negishi coupling with organo zinc [83], Stille coupling with aryl tin [84], and Sonogashira coupling with alkynyl copper [85], were reported. Those reactions made transition metal-catalyzed cross-coupling reactions one of the most important ways to construct new C—C covalent bonds in synthetic chemistry. Therefore, R. F. Heck, E. Negishi, and A. Suzuki won the 2010 Nobel prize in chemistry. Also in 1971, W. S. Knowles applied chiral bisphosphine ligands as ligand in rhodium-catalyzed hydrogenation reactions, which had opened up a whole new field of asymmetric catalysis with transition metals [86]. W. S. Knowles shared 2001 Nobel prize in chemistry with K. B. Sharples and R. Noyori, who promoted the research upsurge of asymmetric catalysis. Moreover, Chauvin, Grubbs, and Schrock won the 2005 Nobel prize in recognition of their outstanding contributions in transition metal-mediated metathesis of olefins.

Based on the advances of methodology study and ligand design, transition metal catalysis has become one of the important means for synthetic chemists to construct more complex new substances in this century. The current pursuit is to selectively construct multiple covalent bonds in one reaction synchronously by transition metal catalysis. To achieve this goal, transition metal catalyst has been employed to selectively activate some inert covalent bonds. The most famous example – transition metal-mediated C—H bond activation – became the focus of chemists. This process could afford a carbon–metal bond directly, which could be used as a powerful nucleophile in further transformations. In modern organometallic chemistry, multistep elementary reactions in series have been extensively studied, which could afford a battery of new covalent bonds through one catalytic cycle. Synthetic efficiency in organometallic chemistry has become the focus of attention. Hereon, transition metal catalysis with higher turnover numbers was pursued to further improve the economy and environmental protection. Current research on transition metal catalysis is also devoted to improving the accuracy of synthesis, aiming at achieving specific functional group transformation in the exact location. To achieve these goals, the design of transition metal catalysis becomes more complex, and the requirements for suitable ligands are higher. It is necessary to design the corresponding ligands manually according to aspects of structure, electronic properties, steric effect, and coordination ability. These auxiliary designs also make the catalytic cycle with transition metal lengthier; meanwhile, the possibility of side reactions increases. Therefore, mechanistic studies for transition metal catalysis became more and more important, which were helpful for design of new catalysis, enhanced efficiency, increased selectivity, improved turnover number, and accurate synthesis.

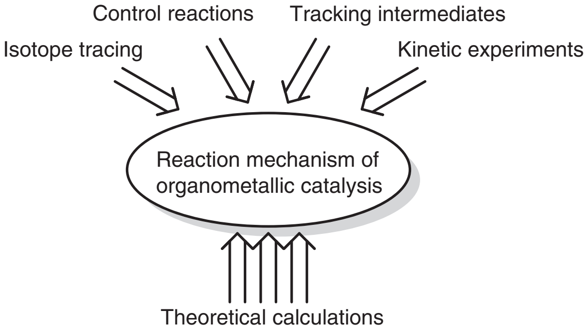
1.2 Using Computational Tool to Study the Organometallic Chemistry Mechanism

Transition metal catalysis is one of the most powerful tools for the construction of new organic materials, whose development trend is more efficient as well as more complex. Therefore, studying the mechanism of organometallic catalysis has become even more essential, and has proved to be the basis for the design of new ligands, catalysts, and reactions.

1.2.1 Mechanism of Transition Metal Catalysis

Generally, reaction mechanism could be considered to be all elementary reactions used to describe a chemical change passing in a reaction. It is to decompose a complex reaction into several elementary reactions and then combine them according to certain rules, so as to expound the internal relations of complex reactions and the internal relations between total reactions and elementary reactions. The rate of chemical reaction is closely related to the specific pathways through which the reaction takes place.

To study the law of chemical reaction rate and find out the intrinsic causes of various chemical reaction rates, synthetic chemists must explore the reaction mechanism and find out the key to determine the reaction rate, so as to control the chemical reaction rate more effectively. As shown in Scheme 1.4, traditional research methods for reaction mechanism include: (i) determining the important intermediate or decisive step of a reaction by isotope tracing, (ii) determining the effect of different factors (e.g. reaction temperature, solvent, substituent effect, etc.) on reaction rate and selectivity by competitive test, (iii) studying the relationship between the reaction rate and the concentration of reactants and catalysts obtaining by kinetic experiments, and (iv) characterizing and tracking intermediates by instrumental analysis. However, these methods are often macroscopic observation of the average state of many molecules, which cannot watch a process of the transformation for one molecule from a micro-perspective. Fortunately, theoretical calculations based on first principles have become one of the important means to study the reaction mechanism with the development of software and the improvement of hardware computing capability in recent several decades. Through theoretical calculation and simulation, the transformation of one molecule in reaction process can be "watched" more clearly from the microscopic point of view. Actually, theoretical calculation can be considered to be a special kind of microscope, which can see the geometrical structure, electronic structure, spectrum, and dynamic process at atomic level, and is helpful for chemists to understand the real reaction mechanism.



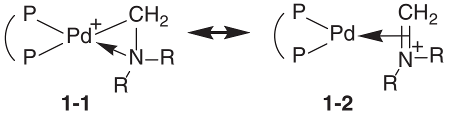
Scheme 1.4 Revealing the reaction mechanism of organometallic catalysis.

The combination of theoretical and experimental techniques could not only greatly improve the efficiency of reaction and yield of product, but also uncover the factors that control the selectivity of product more clearly. The promotion of theoretical study to experimental investigation could be summarized into "3D," i.e. description, design, and direction. Based on the data obtained from experimental technique, detailed description for the mechanism of organometallic catalysis could be fulfilled using theoretical calculations. Based on the results of computations, the mechanisms could be verified by the designed experiment. To put in a nutshell, theoretical calculations could play a critical role in the direction of transition-metal-organic synthesis.

1.2.2 Mechanistic Study of Transition Metal Catalysis by Theoretical Methods

Quantum chemical computation based on first principle provides a powerful tool for the mechanistic study of transition metal catalysis. Since the whole content of this book is to discuss the theoretical calculation-based study for the mechanism of transition metal catalysis, we will give only a few examples to show how to study the reaction mechanism by theoretical calculations.

Generally, mechanism research of transition metal catalysis initially faces a series of studies involving the molecular structure and electronic states. As an example, (Xantphos)Pd(CH_2NBn_2)$^+$ is an important precursor for aminomethylation reactions, the geometric structure of which has been confirmed by X-ray analysis [87]. However, why this complex could be formed and the electronic properties of this complex still remained unclear. As shown in Scheme 1.5, in resonance structure **1-1**, the Pd—C bond is a normal single bond, and Pd—N is a coordination bond. The formal positive charge is localized on palladium, and the formal oxidation state of palladium is +2. Alternatively, the iminium moiety acts as a monodentate ligand coordinated with Pd(0) in resonance structure **1-2**, and the formal positive charge is mainly localized on the iminium moiety. The real structure of this complex would be a mixture of resonance structures **1-1** and **1-2**. On the other hand, the bond orders of Pd—C, Pd—N, and C—N are determined to be 0.322, 0.135, and 0.965, respectively, which indicate that the Pd—C and Pd—N bonds are very weak. More importantly, these data support that the C—N is a double bond and **1-2** is most likely to be the main structure of this complex. Further frontier molecular orbital studies also supported this point.

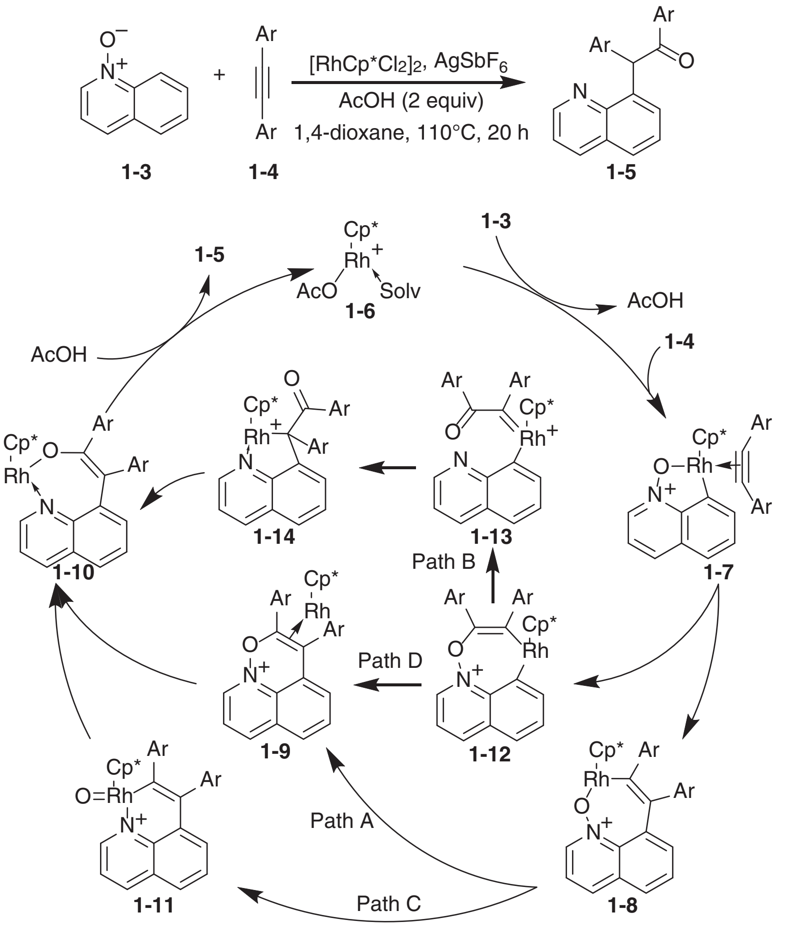


1-1 **1-2**

Scheme 1.5 The resonance structures of (Xantphos)Pd(CH_2NBn_2)$^+$.

To summarize, computational organometallic chemistry focuses on some of the stationary points on potential energy surface for the corresponding reactions, which could be used to compare the possible elementary reactions. The lowest energy reaction pathway could be found by theoretical calculations, which is helpful for chemists to understand the reaction mechanism and design new reactions.

As an example, computational method was used to study the mechanism of rhodium-catalyzed coupling reaction of quinoline *N*-oxide and acetylenes. As shown in Scheme 1.6, four possible pathways were taken into account (i.e. paths A–D) [88]. All these four pathways begin with the coordination of quinoline *N*-oxide to Rh(III) precursor **1-6**, which is followed by an *N*-oxide-directed electrophilic deprotonation by acetate and coordination of acetylene substrate to give rhodacycle **1-7**. The subsequent insertion of the acetylene substrate into the Rh—C bond of intermediate **1-7** gives intermediate **1-8**, which is a common intermediate for

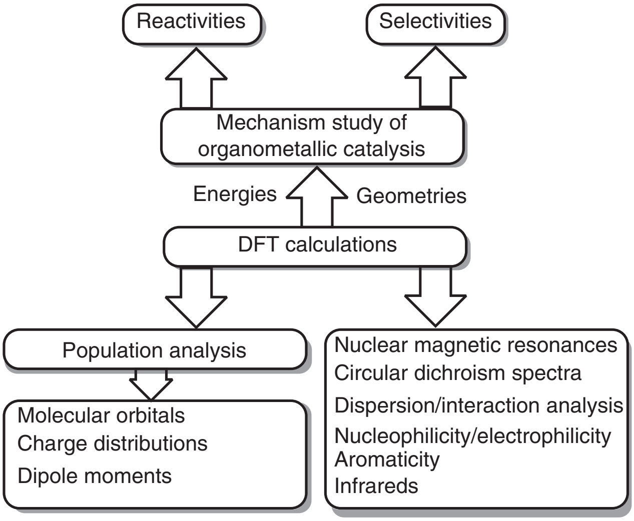


Scheme 1.6 Mechanism of rhodium-catalyzed coupling reaction of quinoline *N*-oxide and acetylenes. Source: From Li et al. [88].

both paths A and C. In path A, complex **1-8** is proposed to undergo a reductive elimination reaction to form a new C—O bond in π-coordinated complex **1-9**. The N—O bond in complex **1-9** would then oxidatively add back to Rh(I) to generate Rh(III) enolate intermediate **1-10**. Protonolysis of intermediate **1-10** by acetic acid would release one molecule of product **1-5** and regenerate complex **1-6**. Product **1-5** could also be generated by the protonation of intermediate **1-14**, which is an isomer of intermediate **1-10**. In path C, the migration of the oxygen atom from complex **1-8** would lead to the formation of Rh(V)–oxo intermediate **1-11**. A subsequent oxygen insertion into Rh—C(vinyl) bond may give rise to intermediate **1-10**, which is the common intermediate in path A. Alternatively, the insertion of the acetylene substrate into the Rh—O bond of intermediate **1-7** would give rise to a common intermediate **1-12**, which could proceed along path B or path D. For path B, cleavage of the N—O bond would lead to the formation of α-oxo carbenoid species **1-13**, which could undergo carbene insertion to give intermediate **1-14**.

This intermediate is either protonated directly or isomerizes to intermediate **1-10**, followed by protonolysis to afford product **1-5** together with the regeneration of active catalyst **1-6**. Intermediate **1-12** could also undergo reductive elimination through path D to give complex **1-10**. All four of these different pathways have been evaluated in the current study by using theoretical calculations. The computational results revealed that path A is the most favorable process for this reaction.

In fact, quantum chemical calculations have become one of the conventional methods to study the mechanism of transition metal catalysis (Scheme 1.7). The basis function of computational organometallic chemistry is to calculate the geometries and energies of stationary points, including local minimums and transition states, so as to construct potential energy surface for the catalytic cycle and explore the reaction mechanism. Information of molecular orbital, charge distribution, dipole moment, and so on can be achieved by computational population analysis, which is propitious to study factors of reactivity and selectivity. More useful information, including infrared, nuclear magnetic resonance, circular dichroism spectra, dispersion interactions, nucleophilicity/electrophilicity, and aromaticity, also can be achieved by theoretical calculations for organometallic chemistry.



Scheme 1.7 Mechanism study of organometallic catalysis by density functional theory (DFT) calculations.

Over recent several decades, massive experimental and theoretical investigations were reported about organometallic catalysis. In those works, theoretical studies have proved to be indispensable routine technique for modern synthetic organic chemistry. Consequently, we herein provide a book to summarize and generalize the theoretical advances regarding organometallic catalysis. In Chapter 2, we summarize the popular computational methods, which are of benefit for the mechanism study of organometallic catalysis. We discuss the theoretical studies of elementary reactions in Chapter 3. Detailed processes for all the familiar elementary reactions in organometallic catalysis discovered by theoretical calculations are summarized in this chapter. Based on those two chapters, the second part of this book is organized by the type of transition metals, which are used as catalyst in organic reactions.

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