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Perspective

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Computational Organic Chemistry: Bridging Theory and Experiment in Establishing the Mechanisms of Chemical Reactions

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ABSTRACT: Understanding the mechanisms of chemical reactions, especially catalysis, has been an important and active area of computational organic chemistry, and close collaborations between experimentalists and theorists represent a growing trend. This Perspective provides examples of such productive collaborations. The understanding of various reaction mechanisms and the insight gained from these studies are emphasized. The applications of various experimental techniques in elucidation of reaction details as well as the development of various computational techniques to meet the demand of emerging synthetic methods, e.g., C−H activation, organocatalysis, and single electron transfer, are presented along with some conventional developments of mechanistic aspects. Examples of applications are selected to demonstrate the advantages and limitations of these techniques. Some challenges in the mechanistic studies and predictions of reactions are also analyzed.

INTRODUCTION

The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble.

Although this statement made by Paul A. M. Dirac in the 1920s is still valid after almost a century,[1] theoretical and computational chemistry has seen major developments since the late 1960s.[2] Calculations have evolved from pencil-and-paper solutions of the Schrödinger equation for the single electron in H_2^+ to supercomputer simulations of enzymatic reactions. This evolution has occurred because computational chemists have learned how to obtain increasingly accurate approximate solutions to the Schrödinger equation by taking advantage of the incredible progress in the speed and capacities of computers. Approximately every decade, one Nobel Prize has been awarded to a theoretical contribution. Now computational chemistry has become involved in nearly every area of chemistry[3] and has become an essential tool, just like common laboratory techniques such as nuclear magnetic resonance (NMR) spectroscopy, infrared (IR) spectroscopy, and mass spectrometry (MS). It has been used in a very broad range of chemistry and has played increasingly important roles in chemistry, materials, and the life sciences.[4] In organic chemistry, computational chemistry is especially important for understanding the structures and properties of compounds and for elucidating mechanisms of chemical reactions, and this, in turn, helps in the design of new reactions and catalysts.[5] Today, a large proportion of chemistry publications contain some computations.

Computational chemistry is well suited to the mechanistic studies of chemical reactions. It can provide detailed potential energy surfaces (PESs) of various possible reaction pathways and the geometrical and electronic properties of reactants, products, intermediates, and transition-state structures, enabling comparisons with various experimental observations such as kinetics, reaction intermediates, isotope effects, and stereochemistry.

The wide applications of computational chemistry are facilitated by significant advances in convenient computational packages,[6−9] especially the popular and long-standing Gaussian series of programs initially developed by Pople and colleagues,[6] and the development of density functional theory (DFT)-based computational methods, originally developed by Kohn (with a lower computational costs and reasonable accuracy, compared to post-Hartree−Fock methods).[10] Pople and Kohn were recognized by the award of the Nobel Prize in Chemistry in 1998.[11] Their contributions significantly promote the practice of computational chemistry. Currently, computations are carried out not only by theoretical and computational groups but also by experimental groups for comparison with their experimental observations.

The scope of this Perspective is limited to the mechanistic understanding of chemical reactions.[12] In particular, we emphasize the importance of collaboration between experimental and computational chemists. A brief survey on the current trends in research is presented with examples. Next, recent developments and applications of experimental techniques and computational methodologies in the studies of organic and organometallic reactions, especially catalysis, are described. Of the large number of examples in the literature, only selected cases with some generality are presented in detail; more examples can be found in recent excellent review articles.[13,14] Remaining challenges in computational organic chemistry aimed at predicting chemistry are also briefly presented.

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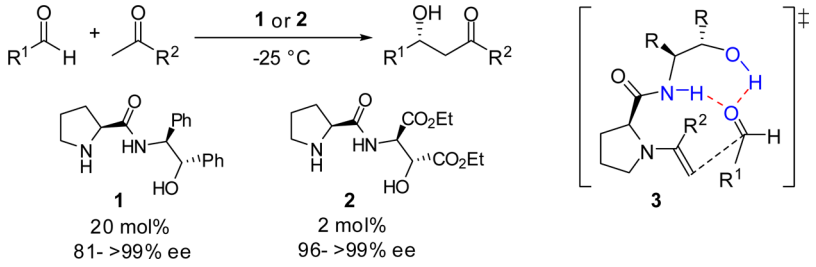
Scheme 1. Prolinamide-Catalyzed Asymmetric Aldol Reaction



SYNERGY BETWEEN COMPUTATIONS AND EXPERIMENTS

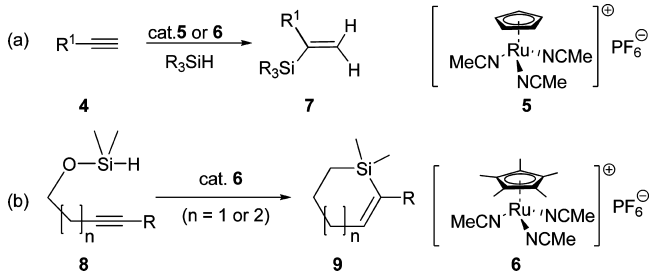
Recent decades have witnessed the increasing connection between computational and experimental chemistry to solve a wide array of organic problems. The synergistic interplay between computations and experiments has been helpful in determining structures and understanding reaction mechanisms. Many of outstanding collaborations between theory and experiment have been extensively reviewed.[15,16]

Our Experience. We begin with two examples from our personal experience to demonstrate this fruitful interplay. Both of the examples began with interesting and new experimental findings, and computational chemistry was then employed to understand the unusual phenomenon at hand. New experiments were subsequently conducted to verify the explanation or hypothesis arising from the calculations. Based on the developed rationale, new catalysts were designed or new chemistry was predicted.

Organocatalysis with Double Hydrogen Bonds. The discovery of the proline-catalyzed direct aldol reaction[17] was a landmark in development of the chemistry of organocatalysis.[18] A valuable extension of proline catalysis is the recognition of prolinamide derivatives as more efficient and practical catalysts (Scheme 1).[19] It was found that prolinamides with a terminal hydroxyl group were more active than those lacking this group. The observed enantioselectivity is highly affected by the substitution pattern of the hydroxyl amide side chain, with compound **1** derived from (1*S*,2*S*)-1,2-diphenylaminoethanol giving the best enantioselectivity. With the aid of computational chemistry calculations, Wu and co-workers found that both the amide and hydroxyl groups form hydrogen bonds with the aldehyde, and the presence of double hydrogen bonds prominently stabilizes the transition structure **3** and reduces the activation barrier.[19] The conformational preference of the seven-membered doubly hydrogen-bonded ring significantly affects the diastereo- and enantioselectivity.[19] On the basis of this model, it could be hypothesized that more active catalysts might be developed by increasing the acidities of the amide and hydroxyl groups. Indeed, Gong et al. found that compound **2**, with two electron-withdrawing ester groups, gave higher reactivity with a reduced amount of the catalyst and excellent diastereo- and enantioselectivities for a broader range of substrates.[20] This double-hydrogen-bond strategy has been widely applied in subsequent design of organocatalysts.[21]

Hydrofunctionalization Catalyzed by Ruthenium Complexes. Hydrosilylation of alkynes catalyzed by transition metal catalysts is one of the most efficient methods to prepare versatile vinylsilanes. While various catalysts can catalyze the reaction, normally *anti*-Markovnikov regiochemistry and predominantly *syn*-addition stereochemistry are observed.[22] These features can be rationalized by the Chalk–Harrod or modified Chalk–Harrod mechanisms.[22,23] However, using cationic Ru(II) complexes as catalysts, Trost and co-worker observed surprising Markovnikov regioselectivity and exclusive *anti*-addition stereochemistry for hydrosilylation of terminal and internal acetylenes (Scheme 2a).[24] They also found that

Scheme 2. Ru-Catalyzed (a) Intermolecular and (b) Intramolecular Hydrosilylation



intramolecular hydrosilylation gives exclusively *endo*-regiochemistry, in contrary to the *exo*-regiochemistry observed with the other catalysts (Scheme 2b). These observations could not be rationalized by known mechanisms and called for a new reaction mechanism.

We were contacted by Trost for a theoretical investigation of the reaction mechanism, and our computational studies revealed the novel mechanism shown in Scheme 3.[25] Several key features of this mechanism are as follows: (1) Due to the significant instability of the Ru(IV) species, oxidative addition of the H–Si bond does not occur. (2) In the subsequent oxidative hydrometalation step through transition state (TS) **11**, the transferring hydrogen behaves as a proton because of the electron-deficient Ru center. This electronic feature partially promotes the observed Markovnikov regiochemistry. (3) The expected Ru(IV)–vinyl species **15** was found not to be a stable intermediate, and instead, the uncommon ruthenacyclopropene intermediate **12** was formed directly. The rotation of the vinyl double bond occurs in such a way that the transferring hydrogen and the silyl group become above and below the ruthenacyclopropene plane. (4) The vinylsilane is formed by reductive silyl migration through TS **13**. (5) The rate-determining step is the oxidative hydrometalation, and thus the stereochemistry is determined by the formation of **12**. This mechanism also explains the observed *endo* regiochemistry for the intramolecular hydrosilylation, because *exo* regiochemistry would require the initial oxidative addition step.

This novel mechanism is consistent with the results of several recent experiments. In 2013, the first crystal structure of a ruthenacyclopropene complex was obtained, and a reversible silyl migration to the α-carbene was also observed.[26] Sun and Wu recently developed ligand-controlled regio- and stereo-

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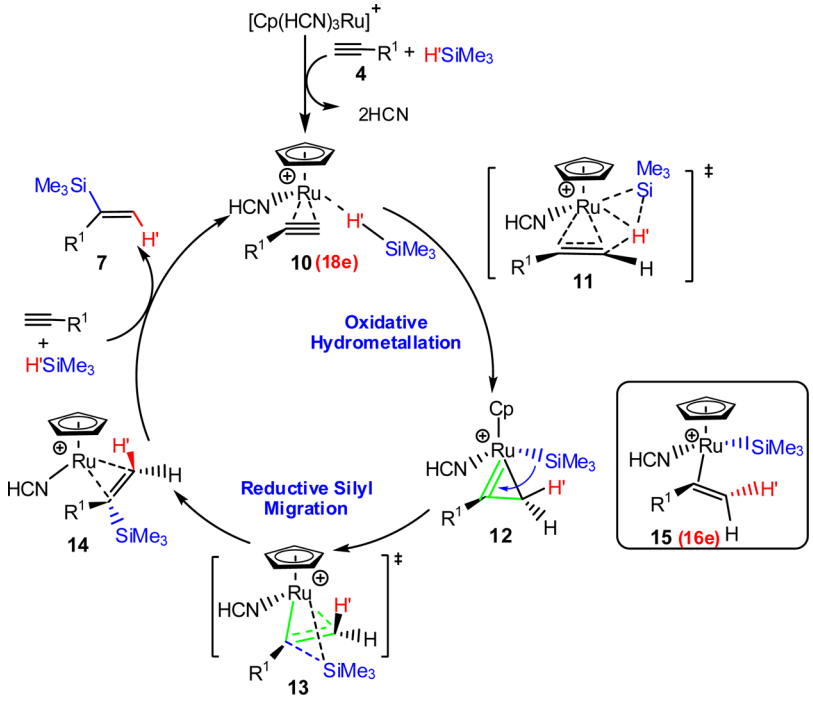
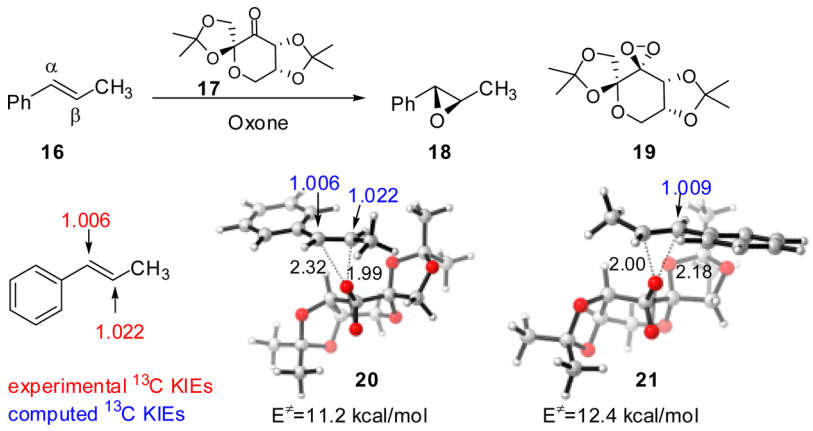
Scheme 3. Wu−Trost Mechanism for Ru-Catalyzed Hydrosilylation of Alkynes and the New Alkyne Insertion Pathway



Scheme 4. Experimental and Computed ^{13}C KIEs for the Epoxidation of *trans*-β-Methylstyrene Catalyzed by a Chiral Ketone Catalyst



divergent hydrosilylation of internal alkynes, in which steric repulsion between the bulky substituent on the alkyne and the ligand plays a key role.[27] Our calculations predicted that **5** and **6** not only catalyze the hydrosilylation but also catalyze hydrogenation, hydrostannation, and hydrogermylation reactions with the same general mechanism.[28] These reactions were recently realized, all with *anti*-addition stereochemistry.[29] In some cases, the final step in Scheme 3 could become the rate-determining step, and thus, the regio- and stereo-chemistry could be altered.[27]

Complementarity of Information from Experiment and Theory. Prediction prior to experiment is an ultimate goal for computational organic chemistry. Computations are more successful in structural predictions. A classical example is the discussion of carbene chemistry in 1970s, which demonstrates how calculations predict and correct misinterpretations of experiments. Landmark works have been well summarized in Goddard and Schaefer's reviews.[30,31] A recent example of structural prediction that was confirmed by subsequent experiment is from the Borden group.[32] However, it still takes time for computations to reach the status of routinely predicting a reaction and its mechanism. In studies of the mechanism of a chemical reaction, especially a catalytic reaction, many possible reaction pathways should be explored. The information elucidated by experimental techniques is critical to the proposal of reasonable models and possible reaction pathways for computational study. Although computation alone sometimes can provide crucial understanding, experimental findings are also vital to derive the reaction mechanism. Therefore, it is desirable to combine experimental and theoretical tools to investigate reaction mechanisms. Many experimental techniques, such as determination of reaction kinetics and linear free energy relationships, isotope labeling, and capture of unstable intermediates using various spectroscopic techniques, are widely applied to mechanistic studies of chemical reactions.[33] In this section, several recent examples

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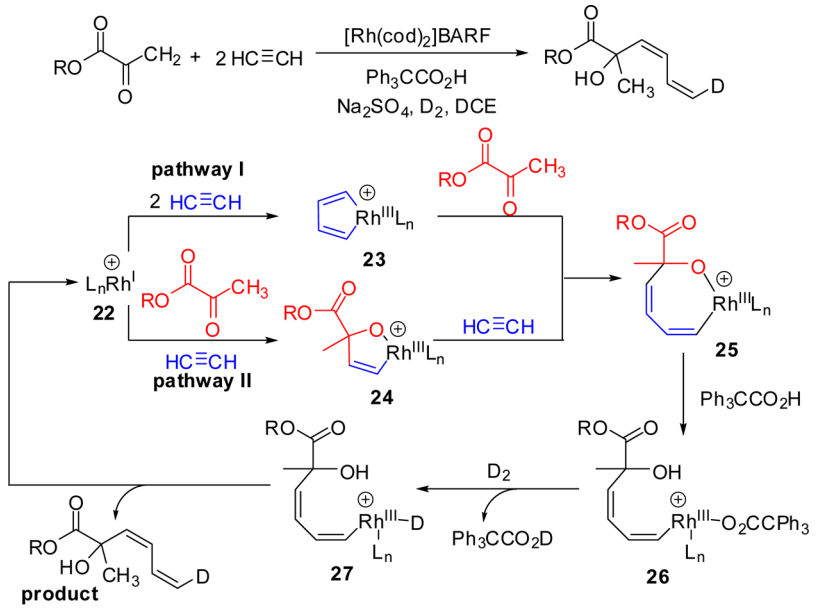
Scheme 5. Plausible Reaction Pathways I and II[a]



[a]Both pathways are consistent with the results of deuterium labeling for the hydrogen-mediated coupling reaction of acetylene to carbonyl compounds. MS and calculations support pathway I.

combining computational studies with kinetic isotope effects (KIEs), MS, and *in situ* IR are presented.

Combine Calculations with Kinetic Isotope Effect. KIE experiments[34] have been broadly applied to mechanistic investigations. As a result of technical developments, KIEs can now be determined more accurately, and calculations can provide more reliable values.[35] The comparison between computed and experimental KIE values provides essential information with which to support or disprove the proposed mechanism(s).[36] One example is the mechanistic study of the Shi epoxidation[37] by Singleton.[38] The chiral epoxide **18** was generated through potassium peroxymonosulfate (oxone) as a stoichiometric oxidant to catalyze oxidation of alkene **16** (Scheme 4). In this reaction, the proposed active oxidant is the dioxirane, **19**, which possesses many possible conformations. The possible involvement of many conformations for **19** as well as many possible orientations for the incoming alkene **16** is great challenge for a computational study. A large conformational space with about 66 transition structures was postulated for this enantioselective reaction.[38] A total of 18 epoxidation transition structures lying within an about 8 kcal/mol range were located, and it would have been difficult to determine the best TS and to decide from the similar computed energies which TS is operative. The experimentally measured ^{13}C KIE, however, indicated a significantly asynchronous C−O bond formation in the epoxidation TS (Scheme 4). The calculated KIE values of all located TSs were compared with the experimental values, and this served to exclude most (15) of the calculated TSs. The computed KIE values for the lowest-energy TS **20** are in excellent agreement with the experimental KIEs (Scheme 4), but the computed C_α KIE for TS **21**, which has energy comparable to that of **20**, is much larger than the experimental value.

The application of deuterium KIE to mechanistic studies has become quite common in C−H activation and functionalization reactions.[39] Deuterium KIE is usually used to assess whether or not the C−H activation step is the rate-determining step. This provides a direct connection with computations, since the rate-determining step is well defined as the step with the highest activation barrier on the calculated PES. Many mechanistic studies which connect computations with deuterium KIE experiments in C−H activation reactions have been reviewed.[40]

Combine Calculations with Mass Spectrometry. For transition-metal-catalyzed reactions, identification of the intermediates can be extremely helpful for understanding the catalytic mechanism. Electrospray ionization mass spectrometry (ESI-MS) provides a relatively simple method to trap and identify reactive intermediates,[41] and computational chemistry provides structures for the corresponding intermediates at atomic details. Therefore, combination of MS and computational chemistry is rapidly becoming the technique of choice for mechanistic investigations and high-throughput screening of homogeneous catalysts.[42]

As an example, based on the results of deuterium labeling, two possible pathways (pathways I and II, Scheme 5) were proposed for the hydrogen-mediated coupling reaction of acetylenes to carbonyl compounds.[43a] Pathway I involves oxidative dimerization of acetylenes, which leads to a cationic rhodacyclopentadiene (**23**), carbonyl insertion into **23** to form **25**, and Brønsted acid-assisted hydrogenolysis through intermediates **26** and **27**. Pathway II differs from pathway I in the sequence of the first two steps: the oxidative coupling between the acetylene and carbonyl to form intermediate **24** is, in this case, followed by the insertion of a second acetylene to form **25**. The ESI-MS experiment detected intermediates **22**, **23**, **25**, and **26**, but the ion corresponding to species **24** was not observed. During a subsequent collision-induced dissociation (CID) experiment, the species **25** was found to dissociate to an ion corresponding to intermediate **23**, suggesting a retro-carbonyl insertion process. Thus, the ESI-MS provided experimental evidence for pathway I, but not for pathway II. Computations revealed a more detailed mechanism. The

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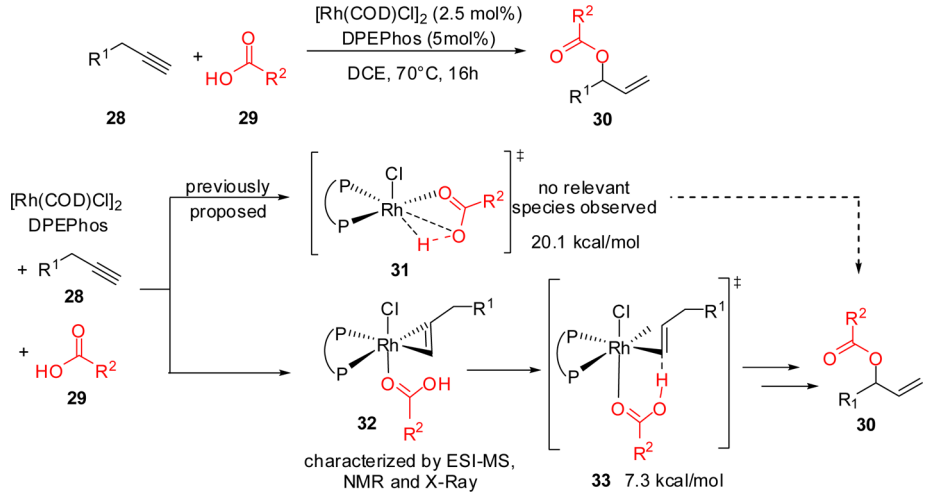
Scheme 6. Proposed Mechanism for Rh-Catalyzed Coupling of Terminal Alkynes with Carboxylic Acids



hydrogenolysis process was calculated to be the rate-determining step, and acetylene−carbonyl oxidative coupling was also calculated to have an activation barrier higher by about 7 kcal/mol than that for the coupling of two acetylenes. Computational studies also revealed that Ph_3CCO_2H acts as a Brønsted acid, assisting Rh−O bond cleavage, and as a ligand, mediating H−H bond cleavage.

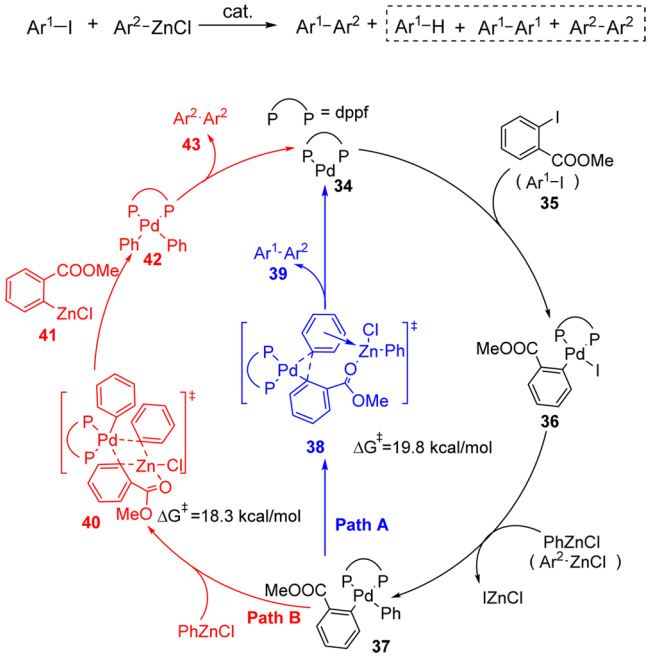
Breit and co-workers investigated the Rh-catalyzed coupling of terminal alkynes with carboxylic acids.[43b] This reaction was originally proposed to involve oxidative addition of rhodium into the OH bond of benzoic acid (Scheme 6). However, no Rh complex bearing either a hydride or benzoate was detected by MS. Instead, a charged complex (**32**) was captured by MS and was also identified by X-ray and NMR techniques. A further CID experiment with **32** generated product **30**. DFT calculations revealed a protonation process with TS **33** that is much more favorable than TS **31**. The protonation process is followed by *β*-hydride elimination, leading to an allene complex which affords the final product **30**. This work demonstrates the importance of using various techniques.

The development of online monitoring MS[44] allows chemical reactions to be tracked in real time and provides a powerful tool for investigation of solution-phase organic reaction mechanisms. Novel ionization methods, e.g., desorption electrospray ionization,[45] offer a simple, general, and efficient way to intercept reactive species. These developments of MS techniques significantly propel mechanistic studies.

Combine Calculations with in Situ Infrared Spectroscopy. Studying the kinetics of a reaction is a powerful tool for mechanistic understanding of chemical reactions. *In situ* IR spectroscopy[46] can be used to monitor the reaction progress because of the technique's sensitivity toward broad functional groups and their concentrations. The measured spectra are often interpreted with the aid of computational chemistry. Therefore, in recent years, it has been applied increasingly to understand the mechanisms of catalytic reactions in combination with calculations. An example is transmetalation in the Negishi coupling reaction.[47]

Transition-metal-catalyzed cross-coupling reactions have become extremely useful in organic syntheses.[46,48] Catalytic coupling of aryl halides and arylmetal species has been studied extensively. The formation of homocoupling and dehalogenation byproducts can be a serious limitation in synthesis and an obstacle to larger industrial-scale development. Based on experiments and computations, the mechanism for the Negishi coupling between methyl 2-iodobenzoate (**35**) and phenylzinc chloride is shown in Scheme 7.[49] Oxidative addition of **35** to

Scheme 7. Mechanism of Negishi Coupling between Methyl 2-Iodobenzoate and Phenylzinc Chloride[a]



[a]The second transmetalation (path B) is crucial for the formation of the homocoupling sideproduct.

Pd(0) followed by transmetalation with phenylzinc chloride leads to the formation of intermediate **37**, which is normally expected to undergo reductive elimination through path A to form the cross-coupling product **39**. A key observation from *in situ* IR spectra is the formation of intermediate **41**, which appears to be derived from a second transmetalation (path B). A kinetic study indicates that the rate of the formation of **41** is nearly equal to the rate of disappearance of the substrate **35**. Computations give more details for the competition between the reductive elimination (path A) and the second trans-

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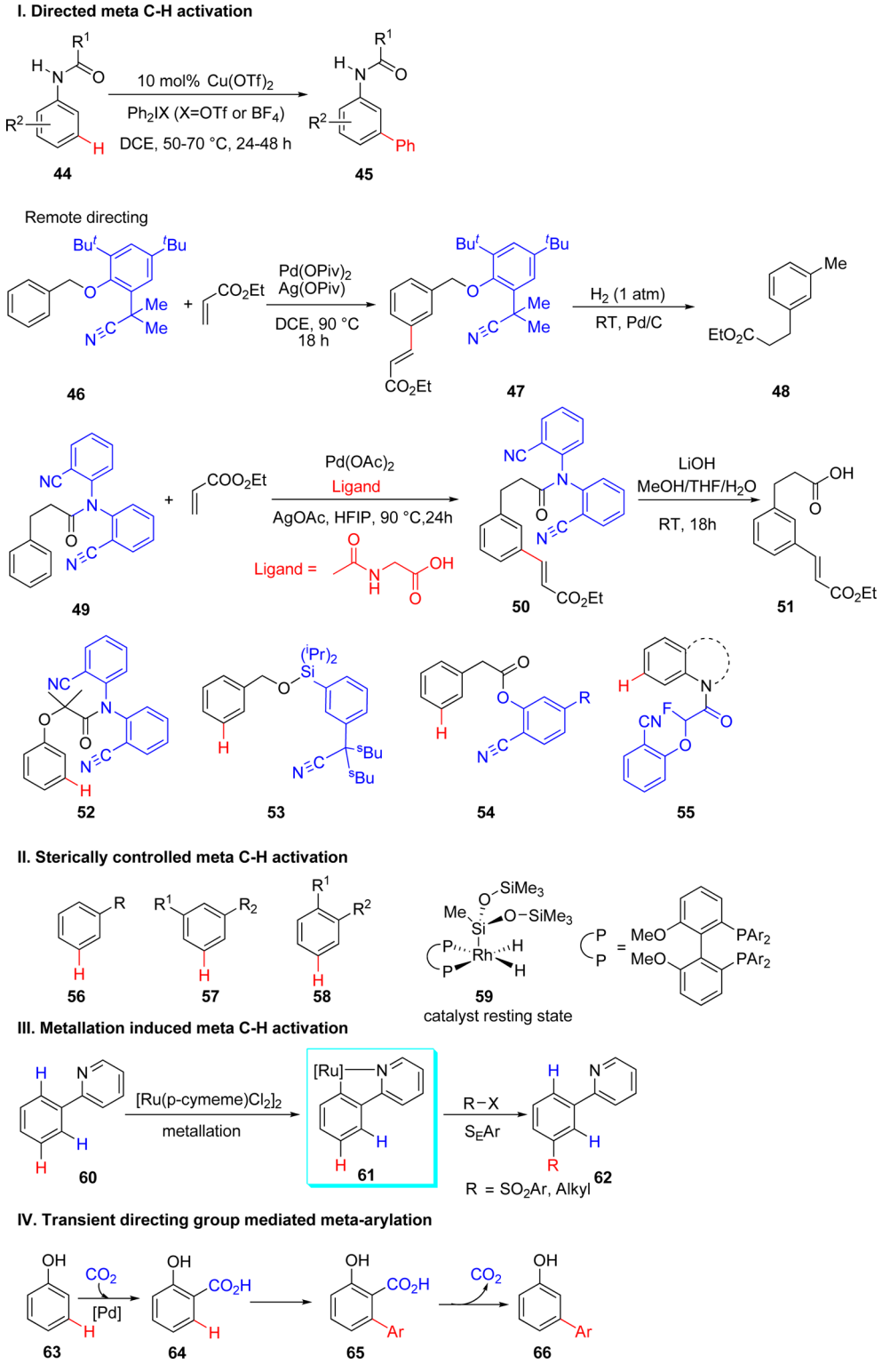
Scheme 8. Successful Strategies for *Meta*-Selective C−H Bond Activation



metalation (path B). The calculated barrier for the second transmetalation is 18.3 kcal/mol via TS **40**, which is 1.5 kcal/mol lower than that for the reductive elimination via TS **38**. Further calculations indicate that an *ortho*-substituent in Ar^1I favors the second transmetalation reaction, while an *ortho*-substituent in Ar^2ZnCl significantly disfavors the second transmetalation. This suggests a strategy to avoid the homocoupling and dehalogenation side products: use a less sterically crowded Ar^1I to react with an *ortho*-substituted Ar^2ZnCl. This strategy has been experimentally proven to work for the simplest case using mono-*ortho*-substituents.[49]

NEW COMPUTATIONAL INSIGHTS INTO *META*-SELECTIVE C−H BOND ACTIVATION

C−H bond activation or functionalization is one of the most active topics in organic synthesis,[50] and significant progress has

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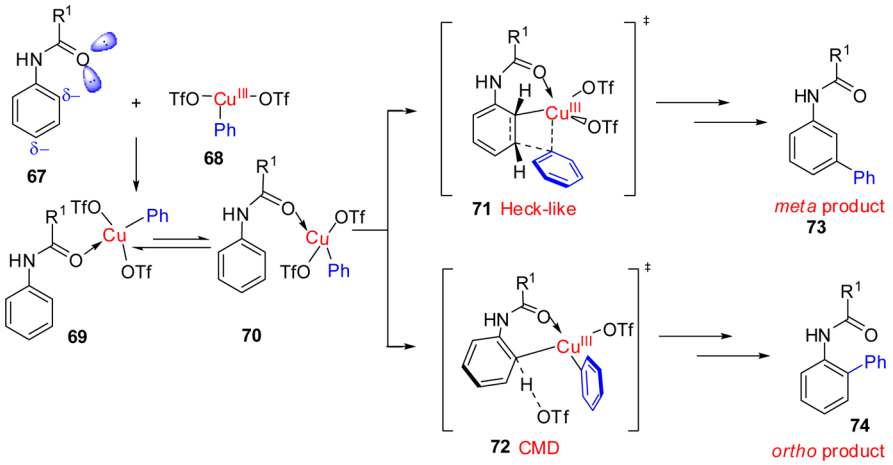
Scheme 9. Proposed Mechanism for *Meta*-Selective C−H Bond Activation by Copper Catalysts



been achieved in the past decade. Computational studies also play an important role in rationalizing the mechanisms, and comprehensive reviews on computational contributions have been published.[51] Controlling regioselectivity in C−H activation is essential to the development of efficient functionalization processes. The approach of chelating-group-directed *ortho*-C−H activation is well established,[52] but *meta*-selective C−H activation is much more difficult to achieve. However, considerable progress has been made recently (Scheme 8).

The first strategy is to use directing groups. An important contribution to the field of *meta*-selective aromatic C−H functionalization came from Gaunt and co-workers, who developed *meta*-selective arylations of anilides and α-aryl carbonyl compounds by a Cu(II) catalyst and diaryliodonium salt.[53] These transformations proceed under mild conditions and form unexpected *meta*-arylated products for a broad scope of substrates.

Another way to direct the catalyst to the vicinity of a *meta*-C−H bond is to link the substrate by a longer linkage, but this raises difficulties associated with the assembly of a conformationally rigid cyclic pretransition state. On the other hand, selectively accessing a *meta*-C−H bond instead of *ortho*/*para*-C−H bonds brings another challenge. An impressive breakthrough was reported by the Yu group,[54a] who developed a series of end-on templates which enable remote *meta*-selective C−H activation. These nitrile-containing templates successfully override electronic and steric effects and direct the activation of remote *meta*-C−H bonds of electron-rich monosubstituted arenes.[54a] The templates can be easily removed after C−H functionalization, and this provides a possible general strategy for *meta*-selective C−H activation. After this pioneering work, a variety of templates[54] were designed and successfully applied to *meta*-C−H activation (Scheme 8-I). The substrate scope was extended beyond arenes to heterocycles,[54d,e] and many types of C−H functionalization, including olefination, acetoxylation, arylation, and methylation, have been realized, suggesting a promising future for the template strategy.

A different strategy to achieve *meta* selectivity is to take advantage of steric effects,[55] which guide reactions to proceed at the less hindered position (Scheme 8-II). The steric control has been successfully applied in Ir-catalyzed[55a−d] or Pd-catalyzed[55e] C−H functionalization to obtain *meta* selectivity in monosubstituted, 1,3-disubstituted, and symmetrically 1,2-disubstituted arenes. Recently, Hartwig and co-worker reported a remarkable breakthrough in Rh (**59**)-catalyzed selective C−H silylation of unsymmetrically 1,2-disubstituted arenes.[55f] The reaction sensitively discriminates between the steric differences of remote substituents and selectively takes place at the position *meta* to the smaller substituent. So far, this strategy has been unsuccessful for monosubstituted arenes.

The Frost group developed the Ru-catalyzed *meta*-selective sulfonation of 2-phenylpyridines (Scheme 8-III).[56] They proposed that the formation of a Ru−C_{aryl} bond induces a strong *para*-directing effect, which guides the sulfonation reaction to occur selectively in the position *meta* to the chelating group. A similar strategy was employed by Ackermann for *meta*-selective C−H alkylation with secondary alkyl halides (Scheme 8-III).[57] In a recently published work from the Larrosa group, carbon dioxide was used as a transient directing group which assists the Pd-catalyzed arylation to selectively proceed at the position *meta* to the phenol hydroxyl group as shown in Scheme 8-IV.[58]

The mechanism of the Cu-catalyzed *meta*-selective C−H bond activation has been studied both by experiment and calculations,[59] and a kinetic study clearly indicated that both Cu(OTf) and $Cu(OTf)_2$ catalyze the reaction (Scheme 9). Interestingly, the former catalyzes the reaction faster than the latter, suggesting that Cu(II) has to undergo an inductive period to form Cu(I), which is the active form. Cu(OTf) reacts with Ph_2IOTf to generate a Ph_2CuOTf intermediate (**68**) that coordinates favorably with the carbonyl oxygen of the substrate (**69** and **70**). There are two pathways. In the Heck-like pathway, the phenyl group attacks the *meta* position as an electrophile (**71**), and after deprotonation, it leads to the formation of the *meta* product, **73**. The second pathway is classical concerted metalation−deprotonation (CMD) pathway (**72**), which leads to the formation of the *ortho* product, **74**. The Heck-like TS is found to be generally lower in energy than the CMD TS. Cu(III) is highly electron-deficient, leaving a partial positive charge on the phenyl group of the amide substrate which becomes a good electrophile. For many other metals, such as Pd, this is not the case. This mechanism explains why a bulky *t*-Bu group on R^1 increases reactivity; it destabilizes the *trans* form of the coordination complex **69**.

In the case of **46**, a theoretical study indicates that a monomeric $Pd(OAc)_2$ is not the active catalyst because it not only leads to a high activation energy but also gives a significant

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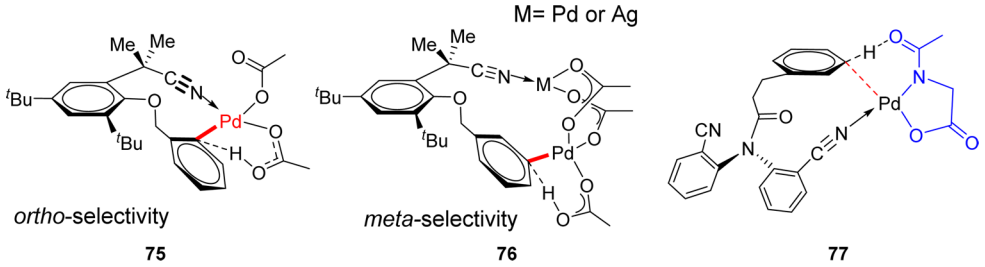
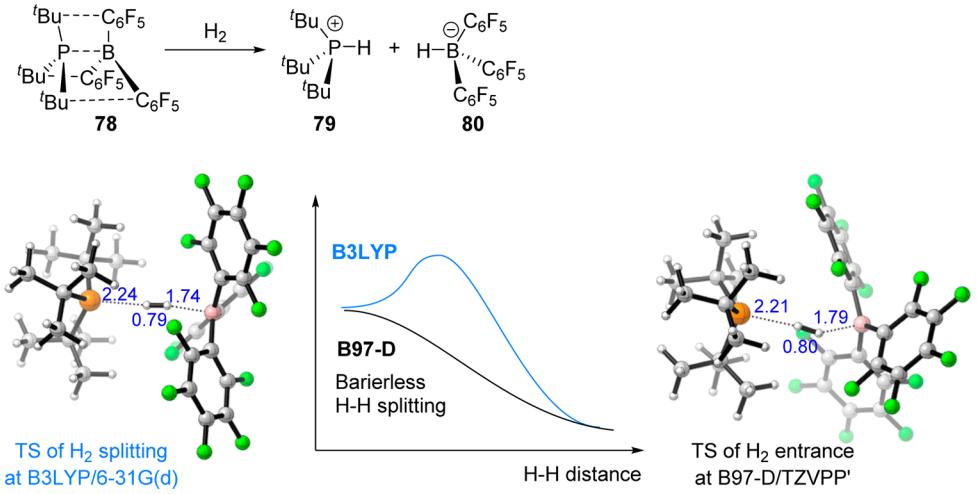
Scheme 10. Models for the *Meta*-Selective C−H Activation of 46 and 49 by Remote Directed Pd(II) Catalyst



Scheme 11. Transition Structure of H_2 Splitting Optimized at B3LYP/6-31G(d) (Left) and Transition Structure of H_2 Entrance Optimized at B97-D/TZVPP′



preference to *ortho*-C−H bond activation (**75**, Scheme 10),[60] which does not agree with the experiment. As the rate-determining C−H bond activation occurs via a CMD TS, the short-chain template allows only a 10-membered-ring TS for the *ortho*-C−H bond activation. *Meta* and *para* TSs, with 11- and 12-membered rings, respectively, are significantly destabilized by ring strain.[60] Calculations indicate that a dimeric $Pd_2(OAc)_4$ may be the active catalyst for the C−H bond activation because it not only has a lower activation energy but also reproduces the experimentally observed *meta*-C−H bond activation (**76**, Scheme 10). The dimeric catalyst allows the reaction to occur at the *meta* carbon. It is interesting that a hetero catalyst, $(AcO)_2Pd$−Ag(OAc) (**76**), may be the most effective catalyst. Experimentally, extra Ag(I) salt (2.5 equiv) is needed to produce a high yield. A Pd−Ag heterodimer was reported by Hor and co-workers, and Ag had a high affinity for the nitrile group.[61] Such a heterodimeric model was proposed for Pd-catalyzed amination of *N*-arylbenzamide.[62]

For the reaction of **49**, a mono-N-protected amino acid is found to be critical for the *meta*-C−H bond activation. Theoretical calculations and MS experiments led to the development of the following model:[63] the amino acid coordinates with Pd(II) in a bidentate mode; a mono-N-protected amino acid increases catalytic activity because its bidentate coordination stabilizes monomeric Pd(II) catalyst, and in addition, the N-protecting carbonyl group serves as an internal base to deprotonate the C−H bond (**77**, Scheme 10). This model is also able to reproduce the experimentally observed enantioselectivity of a variety of pro-chiral substrates.[64]

USE OF DFT-D AND QM/MM IN INVESTIGATING ORGANOCATALYSIS

DFT Including Dispersion Effect. In the past two decades, the use of DFT has become more popular.[65−68] B3LYP became the most used functional of DFT,[69,70] even a standard method. With increasing number of applications of B3LYP, more and more limitations of the functional have been reported.[71] One of the main issues is the erroneous description of the long-range dispersion interaction. This is critical in the binding processes involved in many reactions. Currently, there are two popular solutions to this problem: incorporation of a semiclassical dispersion correction into the current functions and development of new functions parametrized to include dispersion effects. DFT including dispersion (DFT-D) by Grimme[72] and M06 series by the Truhlar group[73] are two representative examples of the former and the latter, respectively.

In an emerging area, frustrated Lewis pairs (FLPs) demonstrate their potential as a new catalyst for organic synthesis,[74] e.g., metal-free catalytic hydrogenation.[75] Using sterically encumbered Lewis acid and Lewis base to prevent formation of a stable classical adduct (e.g., **78**), reactive FLPs can split H_2 by an unconventional mechanism. Pápai located a heterolytic H_2 cleavage TS (Scheme 11) with B3LYP/6-31G(d) and proposed a model in which H_2 is split at the preorganized active centers.[76] However, with two-dimensional PESs calculated in B97-D/TZVPP′, which includes dispersion, no TS along the minimum energy path of increasing the H−H bond could be found.[77] The results with MP2/CBS and SCS-MP2/CBS methods are consistent with the B97-D result. Therefore, Grimme and Erker doubted that the H_2 splitting TS from B3LYP is likely to be artifactual due to the lack of

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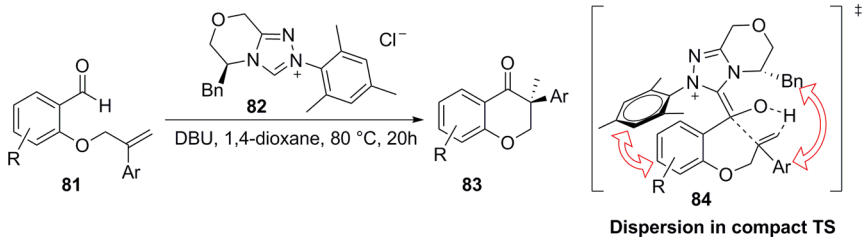
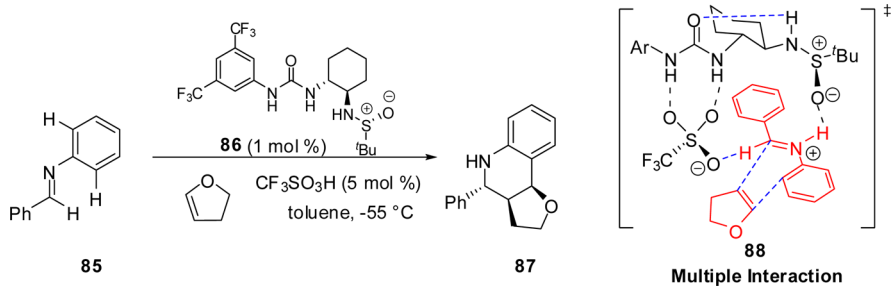
Scheme 12. Proposed Dispersion Interactions as a Key Role in the Stereochemistry of NHC-Catalyzed Hydroacylation of Alkenes



Scheme 13. Enantioselective Povarov Reaction Catalyzed by a Cooperative Network of a Chiral Urea and a Brønsted Acid



dispersion interaction between the large substituents. With B97-D, the entrance of H_2 into the FLP center was proposed to be the rate-determining step, followed by the barrierless splitting of H_2.

Similarly, DFT-D was applied to a study of a highly stereoselective N-heterocyclic carbene (NHC)-catalyzed hydroacylation of alkenes.[78] As shown in Scheme 12, a new all-carbon quaternary stereocenter is formed via a six-membered-ring TS (**84**), which is the stereoselectivity-determining step. The dispersion-corrected functionals B2PLYP-D and BP86-D correctly describe the dispersion effect in such a compact TS and successfully explain the observed high stereoselectivity. These cases demonstrated the importance of dispersion interactions and also raised a caution against excluding large substituents in some model calculations.

Cooperative catalysis is a new concept in which more than one catalyst is used in a synergistic fashion. A combination of catalysts may increase the reaction rate by speeding up different elementary steps or improve the selectivity by suppressing side reactions. Jacobsen applied this strategy to design a network of non-covalent interaction to cooperatively catalyze an enantioselective Povarov reaction (Scheme 13).[79] The computational difficulty lay in balancing multiple interactions, e.g., electrostatic interactions, hydrogen bonds, and $\pi-\pi$ interactions, which may promote or suppress competing pathways to yield the desired product, **87**. M05-2X was used to investigate the catalytic system. The energetic estimation of different bindings, e.g., hydrogen bonds and the salt bridge, helped in the design of the chiral environment. TS **88** also explained the origin of the enantioselectivity.

This impressive case demonstrated that more prominent experimentalists are beginning to exploit computational chemistry.[79,80] However, this case also raises the challenge to calculate the multiple interactions equally well in cooperative catalysis. Since the development of many functionals was based on different training data sets in the past decade, different functionals may be good at describing a certain type of systems, such as main groups or transition metals.[81] However, for the emerging applications of cooperative catalysis, dual catalysis, or other tandem catalysis in a single pot,[82] a universal or general functional is needed to describe the multiple interactions, including electrostatic interaction, coordinative interaction, and hydrogen-bonding.

In terms of transition metals, Norrby reported the advantage of B3LYP-D and M06 in describing the complexation of $Pd(PPh_3)_4$.[83] Since dispersion was not accounted for, the B3LYP method underestimated the binding energy and predicted $Pd(PPh_3)_2$ as the most stable species. The error of the calculated binding energy by the B3LYP method is >30 kcal/mol compared to the experiment. This finding might raise a serious caution for the calculations on Pd chemistry.[84] Dispersion is not only critical for the binding of late transition metal complexes, we also found that the M06 method performed well in describing the binding enthalpies in d^0 W complex. By benchmarking with measured values, M06 was found to be superior to B3LYP and BP86.[85]

Hybrid Methods: QM/MM and ONIOM. The computational costs for quantum mechanics (QM) methods with increasing size of the systems are poorly scaled; therefore, it is impracticable or impossible to reliably study large systems by QM methods. There are two common strategies to study reactions involving environments or large substituents: truncation of the systems and hybrid or multiscale methods. Instead of unrealistic simplified model systems, one can generally divide large molecules into two regions, in which the chemically important region is treated by an expensive and accurate QM method and the remaining environment region is approximated by efficient but low-level methods. Molecular mechanics (MM) methods are usually used as the low-level method in hybrid QM/MM and ONIOM(QM:MM) methods, whereas a lower-level QM method can be applied in ONIOM(QM:QM) methods.[86]

$$E_{\mathrm{QM/MM}} = E_{\mathrm{QM}} + E_{\mathrm{MM}} + E_{\mathrm{QM-MM}}$$

$$E_{\mathrm{ONIOM2(high:low)}} = E_{\mathrm{high,model}} + E_{\mathrm{low,real}} - E_{\mathrm{low,model}}$$

Goodman and co-worker applied the ONIOM approach to investigate chiral phosphoric acid-catalyzed hydrogenation of

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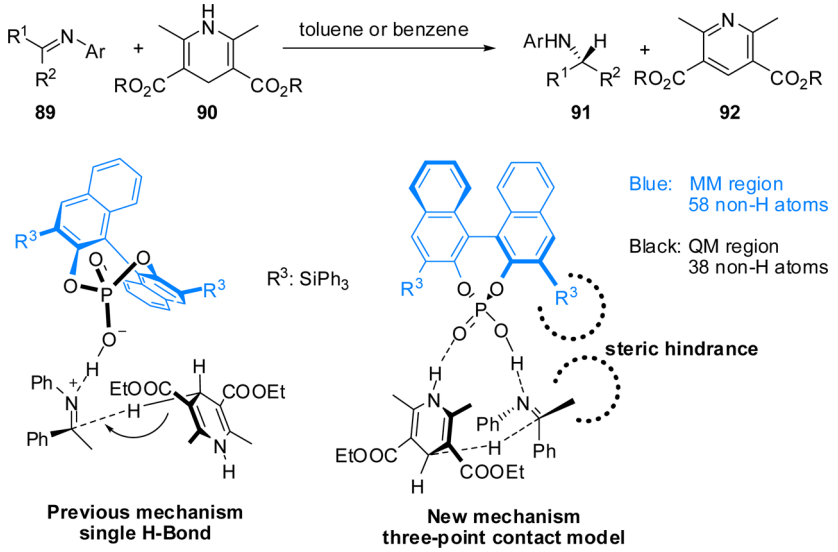
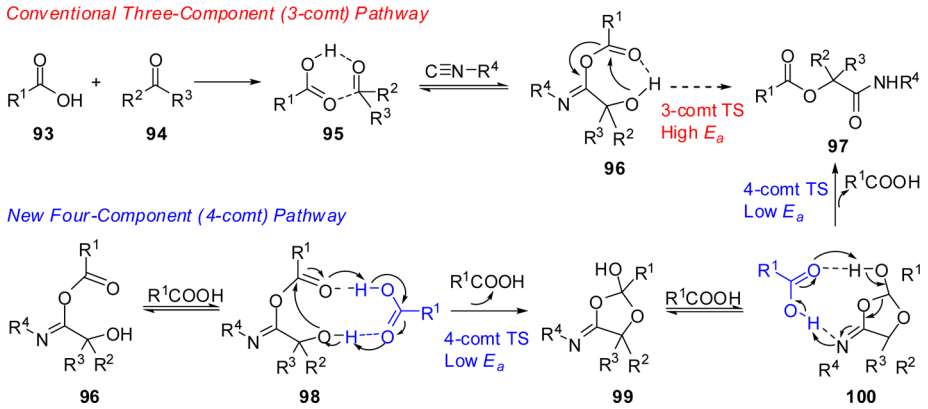
Scheme 14. Transition States Located with ONIOM (B3LYP/6-31G(d):UFF) for the Reaction between 89 and 90 Catalyzed by a BINOL-Phosphoric Acid



Scheme 15. Mechanism of the Passerini Reaction[a]



[a]The conventional three-component pathway is shown in red (above), while the new four-component pathway is shown in blue (below).

imine **89** by Hantzsch esters **90**.[87] Geometry optimization with ONIOM(B3LYP/6-31G(d):UFF) followed by single-point calculations (MPWB1K/6-31G(d,p) in toluene with polarizable continuum model (PCM)) was performed. An efficient ONIOM method enabled the modeling with the real MacMillan catalyst containing bulky $SiPh_3$ as the substituent on BINOL-phosphoric acid,[88] and a new mechanism explaining the enantioselectivity with a "three-point contact model" was proposed (Scheme 14). Differing from a previous mechanism involving a single-hydrogen-bond imine−Brønsted acid complex, the new model includes an additional hydrogen bond between the NH of the Hantzsch ester and the phosphate oxygen stabilizing the TS. With the third "contact", i.e., the steric hindrance involving R^3, the TS is confined to an orientation leading to the observed product **91**.

USE OF AN AUTOMATED PATHWAY SEARCH IN UNDERSTANDING MULTICOMPONENT REACTIONS

Multicomponent reactions (MCRs) are those reactions in which three or more reactants are brought together in a single reaction vessel to form a new product containing portions of all the components. Recently, MCRs have attracted attention in organic syntheses due to their high atom-, step-, and energy-economic properties.[89] However, it is difficult to study the mechanisms of MCRs, as there can be many possible pathways among the reactants. Locating TSs is one of the principal tasks, and to locate a TS, a proper initial guess is needed. Moreover, the failure of the system to follow important paths may lead to serious errors and meaningless results.

Recently, Maeda and Morokuma developed an automated reaction pathway search method which does not rely on any initial guess and thus may be a reliable means of path determination.[90,91] The simple idea is just pressing the reactants to each other by a constant force to reach reactive sites, approximate TS structures, and, eventually, products. Hence, this method has been called an artificial force-induced reaction (AFIR). This procedure can be performed very efficiently just by minimizing a function called the AFIR function. It should be noted that the approximate TS and product geometries can easily be reoptimized to the corresponding true TS and product structures by geometry optimization without the artificial force. For similar purposes involving the automatic exploration of a complex reaction system, Liu and co-workers have developed an unbiased PES

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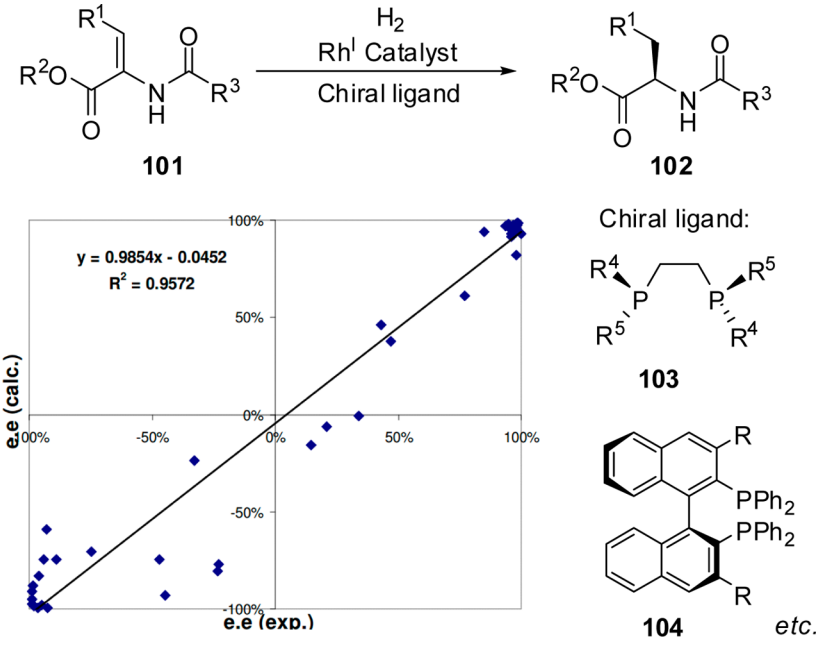
Scheme 16. Correlation Plot for Rh-Catalyzed Hydrogenation of Enamides[a]



[a]Adapted from ref 99. Copyright 2008 American Chemical Society.

searching method named the stochastic surface walking method.[92]

The AFIR approach has been successfully used in the investigation of the reaction pathways of the isocyanides involved in the Passerini reaction,[93,94] an attractive combinatorial reaction in syntheses of natural products and pharmacologically interesting peptides. The conventional mechanism has been proposed as shown in Scheme 15, involving three components. However, Morokuma and co-workers showed that the activation barrier for this three-component pathway is too high to explain the rate of the reaction at room temperature. Using the AFIR method, they found a four-component reaction pathway with one more R^1COOH molecule has a significantly reduced activation barrier (Scheme 15). This suggests that the AFIR method may have broad applications on the mechanistic study and design of MCRs.[95]

PREDICTION OF ENANTIOSELECTIVITY WITH FORCE FIELD

In transition-metal-catalyzed enantioselective reactions, the correct choice of a chiral ligand to achieve high enantioselectivity remains a challenge. Utilizing computational methods to make a fast prediction of the selectivity of different chiral ligands would be very helpful for experimentalists. Because of the large number of chiral ligands and the large conformational space of flexible ligands, the QM method is far too expensive. The MM method allows fast calculations with low cost. However, traditional force fields cannot describe bond making and breaking processes in a TS. In such cases, a transition-state-specific force field (TSFF) is needed.[96] Norrby and co-workers have developed such a method, called the Q2MM method, in which parameters for TSFF were fitted entirely with QM data (Hessian).[97]

The Q2MM method generates reaction-specific force fields and has been successfully used to predict selectivity in many types of reactions, including the very useful hydrogenation reaction (Scheme 16).[98] Wiest and Norrby previously developed a TSFF based on the hydrogenation reaction, and then they utilized this force field to predict the selectivity of a new set of chiral ligands and substrates (Scheme 16).[99] Finally, the experiments were performed with the new ligands and substrates to check the accuracy and reliability of the computational results. It is noteworthy that excellent agreement between the calculated *ee* and experimental *ee* was observed ($R^2 > 0.90$). Thus, the Q2MM method provides a fast and relatively accurate tool for the prediction of selectivity in asymmetric reactions.

In a similar scenario for simulating large-scale systems, Goddard and co-workers developed a reactive force field (ReaxFF) to describe bond-breaking/bond-forming by utilizing relationships between bond distance and bond order and between bond order and bond energy.[100] Although the parameters have been developed only for hydrocarbons with the aim of studying the combustion reactions and decomposition of condensed-phase energetic materials,[101] many applications might be found for transition metal catalysis if such a reaction force field could be developed for organometallic systems.

RADICAL AND SINGLE ELECTRON TRANSFER MECHANISMS

Radicals have attracted a great deal of attention from many fields.[102] There has been long-term interest in biochemistry because radicals are related to many physiological regulation processes and a variety of diseases.[103] Atom-transfer radical polymerization became a research direction in polymer chemistry, first reported by Wang and Matyjaszewski.[104,105] MacMillan introduced the concept of singly occupied molecular orbital (SOMO) activation into organocatalysis.[106] Also, radicals are ubiquitously applied in organic syntheses.[107]

Recently, Houk, Siegel, and co-workers[108] reported a novel selective method of converting arenes to phenols using phthaloyl peroxide (**106**) as an oxidant. The computational study reveals a "reverse-rebound" mechanism in which C−O

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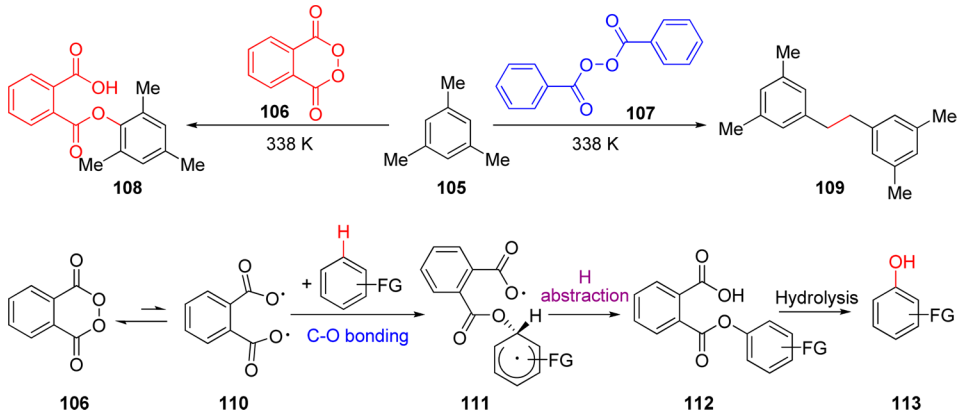
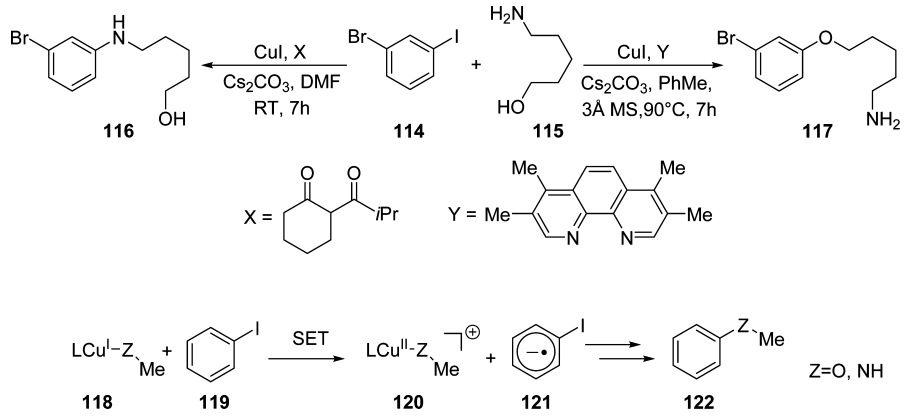
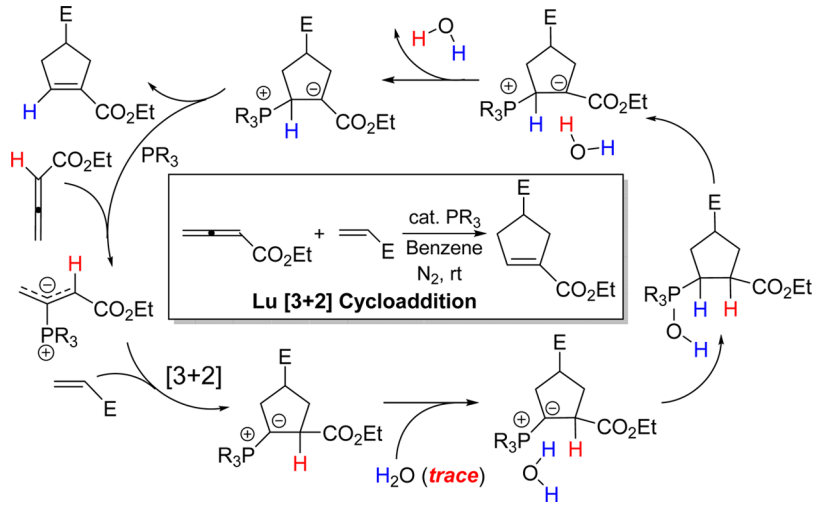
Scheme 17. Proposed Reverse-Rebound Mechanism of Aryl C−H Oxidation



Scheme 18. Ligand-Controlled Cu-Catalyzed Ullmann-Type Reactions



Scheme 19. Water-Assisted Mechanism of Lu's [3+2] Reaction



bond formation occurs first and intramolecular H-abstraction takes place subsequently (Scheme 17). The phthaloyl peroxide (**106**) serves as a diradical source facilitating intramolecular H-transfer (**111**). Due to the lack of an internal radical like **111**, benzoyl peroxide (**107**) prefers to abstract a H from the weaker C−H bond of a methyl group via a normal rebound mechanism.[109] Thus, no phenols were observed. The employment of phthaloyl peroxide leads to excellent selectivity for aromatic C−H bond functionalization and broad functional group compatibility.

The first-row transition metals (e.g., Fe, Cu) are more abundant, cheaper, and less toxic than noble metal catalysts. Therefore, the development of reactions catalyzed by first-row transition metals has attracted great attention, and much progress has been made.[110] However, the mechanistic understanding of these reactions remains deficient.[111] In contrast to Pd, Pt or other noble metal catalysts usually involve classical two-electron elemental steps (e.g., oxidative addition or reductive elimination), the first-row transition metals often tend to undergo a single electron transfer (SET) process.[112]

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Since a SET process usually involves a change in spin state of the metal center, it presents a challenge to computational studies.[113]

The accuracy of thermochemistry for SET can be improved by computational electrochemistry benchmarking.[114−117] However, the barrier of SET is either roughly estimated from reaction energies of related species involving this process or estimated by using Marcus−Hush and Savéant theories.[118] Houk and Buchwald investigated the mechanism of Cu-catalyzed Ullmann-type reactions (Scheme 18).[119a] A SET mechanism was found to be favorable in reactions promoted by a β-diketone ligand. As shown in Scheme 18, the barriers for SET from Cu^{I} complexes to iodobenzene (**119**) were estimated from reaction free energies which were calculated from the energies of completely separated Cu^{II} species (**120**) and the iodobenzene ionic radical (**121**). Activation free energies for SET were also calculated by Marcus−Hush and Savéant theories and are similar to the reaction free energies. Fu and Liu also used reaction free energies to estimate the barrier for the SET process for the same reaction.[119b]

■ ADDITIVE AND SOLVENT EFFECTS

Development of accurate solvent models is essential for simulation. Various solvent models have been established to account for the solvent effects, and currently the PCM is one of the most widely used implicit solvation methods.[120] In this model, the solvent is treated as a polarizable continuum with a dielectric constant, and the solute is placed in a cavity created within the solvent reaction field.[120] It has been found, however, that in practical applications the effects of solvent are sometimes too complex to be described by the several known physical parameters.

Water often plays extremely important roles in enzyme catalysis.[121] Recently, it has been found to play a catalytic role in many reactions. For example, Lu found that allene derivatives react with activated alkenes catalyzed by a phosphine to effectively build cyclopentene compounds (Scheme 19).[122] Through theoretical calculations and subsequent isotope experiments, Yu and co-workers proposed the involvement of one explicit water molecule in a key 1,2-hydrogen shift step.[123] Thus, the reaction can be significantly accelerated by adding a minimal amount of water. Such a role for water is also found in many reactions, including Morita−Baylis−Hillman and related reactions, asymmetric [3+2] cyclization reactions, and other reactions.[124]

Recently, Sunoj also reported that a solvent molecule, i.e., methanol, plays an important role in organocatalysis and in Pd-catalyzed reactions.[125] In these cases, a protic solvent molecule acts as a proton shuttle for the proton transfer. Ru-catalyzed hydrogenation of ketones was proposed to occur via a concerted asynchronous TS in the gas phase.[126,127] By means of incorporation of an implicit solvent model or an explicit solvent molecule, Ikariya found that Ru-catalyzed hydrogenation of ketones may proceed via a stepwise pathway, in which a metastable ion-pair intermediate is stabilized by solvent.[128]

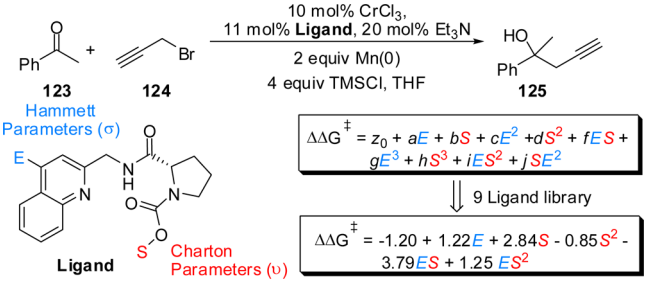
Acevedo and Jorgensen investigated classic Cope elimination reactions in H_2O, THF, and DMF solvents which show different reactivities.[129] Two computational methods were employed to consider explicitly a larger amount of the solvent molecules. One is a QM/MM approach in which hundreds of the explicit solvent molecules outside the reaction system were described by the MM method. The other used a traditional PCM solvent model. Calculations indicate that only the QM/MM approach reproduced the experimentally observed solvent effect well. Using the QM/MM method and adding an appropriate number of ions as explicit solvent, Acevedo, Jorgensen, and Evanseck also successfully studied some important reactions in ionic liquids.[130]

The calculation of reaction entropy in solvent is another challenge. Most QM calculations are done in the gas phase, and solvent effects are usually calculated with implicit solvent models.[120] While reaction entropy in the gas phase can be obtained quite accurately, the calculation of reaction entropy in solvent remains challenging.[131−133] A common and quick approximation for reaction entropy in solution uses the reaction entropy calculated in the gas phase. However, when the number of the reactant molecules is larger than that of the product molecules, the loss of entropy is overestimated and thus the calculated activation free energy are overestimated. Several rough approximations by scaling the entropy term have been applied to account for this effect in different systems.[134−137] At an extreme, Sakaki estimated the entropy by completely neglecting the translational and rotational contributions, taking only the vibrational contribution into account.[137] The development of accurate computational methods for the calculation of reaction entropy for reactions in solvent is urgently needed in the future.[138]

■ CORRELATIONS AND INFORMATICS

A majority of scientific laws are based on finding correlations in a large amount of accumulated observations. Considering the increasing number of publications in chemistry, a means of finding a correlation from the relevant information is an important and urgent issue. Recently, Sigman reported a three-dimensional free energy correlation between well-established electronic and steric parameters (e.g., Hammett values and Charton values, see Scheme 20) and reaction barriers.[139] On

Scheme 20. Three-Dimensional Free Energy Relationships Correlating Steric and Electronic Effects



the basis of a fitted polynomial equation, the enantioselectivity of the given chemical reaction can be predicted. This approach enables the evaluation and optimization of chiral ligands with a small training set of experimental data. Although empirical fitting does not immediately provide a clear physical meaning, it may still be very attractive to apply practically to a broad range of reactions.[140,141]

Another strategy is to find correlations based on the foundation of physical chemistry. For example, the correlation between bond dissociation energy with electronic properties of substituents,[142] the relationship between the Mayr equation and the frontier molecular orbital,[143] and the relationship between radical stability and acidity have been reported.[144]

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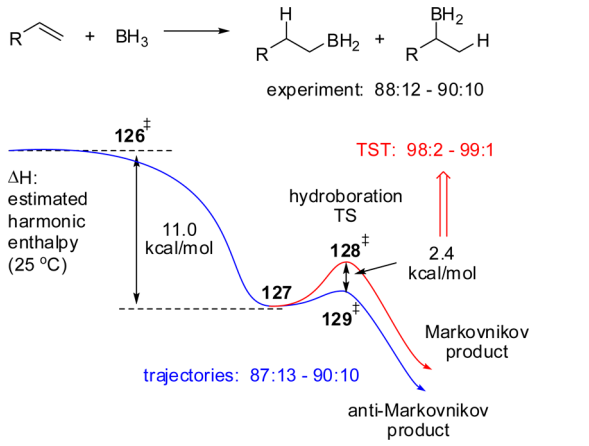
Recently, Garg and Houk developed an effective method to predict the possibility of yielding a heteroaryne and the regioselectivity for the heteroaryne, based on DFT calculations on arene dehydrogenation energies and aryne angle distortion.[145] Similar strategies can also be applied to cyclohexynes and cyclopentynes.[146] These examples demonstrate the feasibility of quantitative prediction based on the qualitative physical chemical concepts, but the difficulty lies in the choice of an approximate parameter to describe a chemical property.[147]

BEYOND TRANSITION STATE THEORY

When a kinetic-controlled reaction can undergo various competing pathways leading to different products, the selectivity is mainly determined by the corresponding calculated free-energy barrier based on transition state theory (TST)[148] or Rice–Ramsperger–Kassel–Marcus (RRKM) theory.[149] However, a few reactions have recently been found difficult to be explained by the classic TST, and consideration of dynamic factors becomes important. In addition, a combined experimental and theoretical study of the photodissociation of formaldehyde revealed a new reaction mechanism completely bypassing the conventional TS: a roaming mechanism.[150]

Oyola and Singleton measured the regioselectivity of hydroboration of propene-d_6 at 21 °C (Scheme 21),[151] which

Scheme 21. Nonstatistical Dynamical Effects in Hydroboration of Propene



is smaller than the regioselectivity computed by several reliable QM methods based on conventional TST. Direct dynamics showed that trajectories starting from a variational transition structure **126**‡ (anti-Markovnikov: 87–90%) can almost reproduce the experimental regioselectivity, whereas trajectories starting from **127** (π-complex), on the other hand, lead to an overestimated regioselectivity (99%). These dynamics simulations suggest that, owing to excess energy gain from the initial complexation step and a very low barrier for the subsequent hydroboration step, the "hot" π-complex has a higher chance to access a higher-energy Markovnikov TS (**128**‡) (nonstatistical dynamical effects), and this reduces regioselectivity. Truhlar and co-workers proposed that the reaction follows a mixture of indirect statistical and direct nonstatistical processes.[152] In addition, Glowacki et al. used a statistical RRKM-master equation model to rationalize the observation by allowing stepwise collisional relaxation of hot intermediates with the solvent.[153]

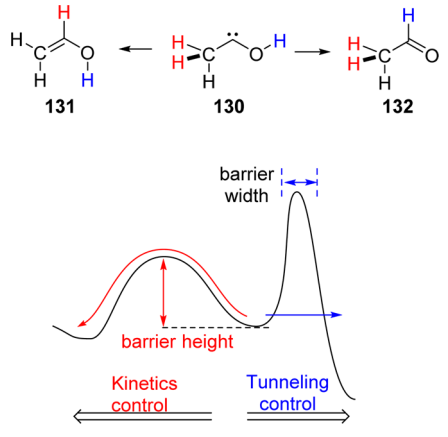
Houk and co-workers investigated the dynamic effect on the mechanisms of eight Diels–Alder reactions by direct dynamics at 298 K.[154] The molecular dynamics (MD) simulations showed that the C–C bonds are mostly formed within around 50–60 fs from TSs, and the time gap between the formation of the two bonds is generally just around 5 fs. Since such a time gap is shorter than the vibrational period, the mechanism of these Diels–Alder reactions is dynamically concerted. When temperature is increased to ~1000 K, the stepwise diradical intermediates were observed in a small amount of the trajectories.

Another recent emerging dynamic effect is bifurcation, in which a single TS can lead to two or more intermediates.[155] Very recently, Tantillo revealed a remarkable and complex reaction network by quasiclassical direct dynamics calculations, showing that the selectivity of biosynthesis is determined by dynamical effects.[156]

Quantum mechanical tunneling plays a key role in reactivity of some organic and enzymatic reactions.[157] Tunneling probability normally increases with lighter mass atoms, a low reaction barrier height and/or a narrow barrier width. Recently, more computational and experimental evidence indicated that heavy-atom tunneling can be involved in some organic reactions with narrow barriers, as the effect of the barrier width on the tunneling probability is more critical.[158,159]

Many NHCs are stable and widely used as catalysts or ligands, whereas oxygen-donor-substituted carbenes are not stable. Recently, Schreiner and co-workers designed an elegant route to investigate hydroxymethylene and methylhydroxycarbene.[160,161] They synthesized and characterized hydroxymethylene at 11 K, but the hydroxymethylene was short-lived and was found to undergo rearrangement to give formaldehyde via hydrogen tunneling through a computed high barrier (29.7 kcal/mol). In addition, they later demonstrated the new concept that quantum tunneling can control selectivity of a 1,2-hydrogen shift from methylhydroxycarbene (CH_3COH, **130**) to give acetaldehyde (**132**) through a computed barrier of 28.0 kcal/mol at 11 K, an example of tunneling-controlled reactivity, (Scheme 22), rather than the classical kinetic-controlled reaction to give vinyl alcohol (**131**) with a computed lower barrier of 22.6 kcal/mol. This 1,2-hydrogen shift is suppressed when CH_3COD is used. Moreover, Borden and co-workers computationally predicted that the ring-expansion reaction rate of noradamantylmethylcarbene to 2-methyl-

Scheme 22. Tunneling-Controlled and Kinetic-Controlled Reactions



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adamantene (kinetic control) is lower than the formation of 3-vinylnoradamantane via hydrogen migration (tunneling control) at cryogenic temperatures.[162]

■ DEVELOPMENT OF ACCURATE QM METHODS

Highly accurate computed activation enthalpies of the Claisen rearrangement of chorismate to prephenate catalyzed by chorismate mutase (13.1 kcal/mol) and hydroxylation of *p*-hydroxybenzoate catalyzed by *p*-hydroxybenzoate hydroxylase (13.3 kcal/mol) were obtained by QM/MM calculations, in which density-fitting local correlation coupled-cluster singles and doubles model (DF-LCCSD(T0)) was used as the most accurate QM method.[163] These computational results are consistent with experimental results (12.7 and 12.0 kcal/mol, respectively), approaching chemical accuracy (error within 1.0 kcal/mol compared to CCSD(T)/CBS limit), while expensive CCSD(T) calculations with a poor scaling ($O(N^7)$) for large systems are avoided. A related domain-based local pair natural orbital local correlation method, DLPNO-CCSD(T), was also developed and used to study the mechanism of the asymmetric hydrogenation of olefins catalyzed by an Ir phosphino-oxazoline complex (containing 88 atoms at most).[164] The Ir^{III}/Ir^{V} couple was concluded to be involved in the catalytic cycle. These two local correlation coupled-cluster methods—combined with explicit correlation methods to speed up convergence to the basis sets limit and density-fitting type approximations to avoid calculations of four-index two-electron repulsion integrals—are promising efficient, highly accurate QM methods with which to study quite large organic and organometallic reactions.

Very recently, accurate and challenging lattice energy calculations of crystalline benzene within sub-kJ/mol accuracy was reported to allow distinguishing different polymorphs by combining several advanced QM methods,[165] such as the CCSDT(Q) method, orbital-specific-virtual, explicitly correlated local correlation OSV-LCCSD(T0)-F12 method, the fragmentation method (many-body expansion up to tetramers), the density matrix renormalization group (DMRG) method, and long-range corrections.[166] The computed best estimate of the lattice energy at 0 K is $-55.90 \pm 0.76 \pm 0.1$ kJ/mol. In this connection, one exact QM method, full configuration interaction quantum Monte Carlo (FCIQMC), was also applied to study properties (e.g., cohesive energy) of a few small molecules in the solid state.[167]

The DMRG method is an efficient method for the description of one-dimensional strongly correlations in many-body systems, and it has been rapidly developed in combination with a few quantum chemistry methods (CASSCF, PT2, and CI).[166b] The DMRG-CASSCF method has been applied to the study of two very challenging systems: a Mn_4CaO_5 cluster in photosystem II and the iron−sulfur cluster.[168] Very recently, Gagliardi and Truhlar developed multiconfiguration pair-density functional theory (MC-PDFT), in which the dynamic correlation part is evaluated by an efficient DFT method and could be applied for larger or more challenging systems.[169]

■ FURTHER CHALLENGES

Although current computation methods allow study of many types of systems, further methodology development is still urgently needed for a broad range of systems. In another frontier, some systematic understanding of fundamental chemical problems is needed for the design of more powerful catalysts and the development of new chemistry. We list some of these below.

Ligand Effect. In designing metal-based catalysts, the reactivity and selectivity are normally fine-tuned by coordinating ligands.[170] Many ligands have been developed, and they have found wide applications in catalysis.[171] Currently, the selection of a ligand for a particular system is still based largely on screening experiments. It would be highly desirable to develop qualitative or semiquantitative, or even quantitative methods to guide the experimental selection of ligands in catalyst design. For example, a systematic understanding of effects of various ligands on the bond energy, coordination energy, redox potential, and oxidative addition/reductive elimination will be extremely valuable.[172] The issue, however, is quite complicated and requires careful experimental and theoretical consideration. Much information may already exist in the literature, and large-scale chemo-informatics investigations may provide fruitful information.

Solvent Effect. The choice of solvent, and sometimes cosolvent, can be crucial to reactivity and selectivity.[173] For example, the use of trifluoroethanol or pentafluoropropanol may have a special effect.[174] Also, as to the reaction on interfaces, water may have very different properties.[175] Understanding the solvent effect on reactivity and selectivity is one of the most challenging issues to the theoretical community. A possible strategy is to develop force fields for various solvents or to apply QM/MM methods to study reactions in solutions. Another way is to develop better physics-based implicit solvent models.[120] Mixed explicit solvent/implicit solvent models have also been used.[176] A key problem relates to configuration of solvent molecules, which requires extensive sampling to get meaningful statistical results, but QM/MM MD is very expensive. One promising approximation is the minimum free energy path developed by Yang and Hu.[177]

Effects of Additives, Bases, and Acids. The use of small amounts of special salts, common bases, or strong acids/weak acids can sometimes have significant effects on reactivity.[178] Currently, there is little understanding of these effects, and the choice among them is based on screening. For example, does the additive form some sort of cluster with the catalyst?[60,62,179] How are the anion of the base and its counterion involved in the TS?[180] How does a strong acid dissociate an anionic ligand?[181] It would be very helpful if we could develop some general understanding of these effects. This area of research provides great opportunities for collaborations between computational and experimental chemists. Recently, for example, Gao and co-workers reported an understanding of the Hofmeister series.[182]

Photoredox Catalysis. Nature uses sunlight as a source of energy to convert CO_2/water to carbohydrates and H_2O to H_2 and O_2.[183] In organic synthesis, the development of photoredox catalysis is becoming one of the most active research areas.[110b,106,184] As mentioned earlier, photoredox catalysts were first used together with organocatalysts with the concept of SOMO reactivity.[185] There is currently little theoretical understanding of this photoredox catalysis, and technically, there is a need for better calculation methods with which to study redox potentials, SET dynamics, and thermodynamics.

***De Novo* Enzymes.** As many organic reactions in different enzymes, development of highly efficient and excellent chemo-, regio-, and stereoselective organic reactions are essential and challenging for chemists. Recently, computational enzyme designs for several organic reactions (e.g., Kemp elimination)

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have been developed by combining experimental and multiscale computational methods.[186] Unfortunately, efficiency of these reactions in these artificial enzymes still needs to be improved, and the types of reactions should be expanded, which partly requires development of accurate and efficient methods to predict complex protein structures.

CONCLUDING REMARKS

Exciting progress has been made in mechanistic understanding of chemical reactions, stereochemistry, and catalysis. This progress has been coupled with the development of various experimental and theoretical techniques as well as close collaborations between experimental and computational chemists. It is expected that this area of research will develop continuously and play an increasingly important role in many frontiers of chemistry. For example, the synthesis of functional polymers needs strict controls of reaction rate and stereochemistry. We conclude this Perspective with quoting the second half of Dirac's statement:[1]

> *It therefore becomes desirable that approximate practical methods of applying quantum mechanics should be developed, which can lead to an explanation of the main features of complex atomic systems without too much computation.*

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Notes

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