

Elucidation of Mechanisms and Selectivities of Metal-Catalyzed Reactions using Quantum Chemical Methodology

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Stefano Santoro,[†] Marcin Kalek,[‡] Genping Huang,[§] and Fahmi Himo^{*,||}

[†]Department of Chemistry, Biology and Biotechnology, University of Perugia, Via Elce di Sotto 8, 06123 Perugia, Italy

[‡]Centre of New Technologies, University of Warsaw, Banacha 2c, 02-097 Warsaw, Poland

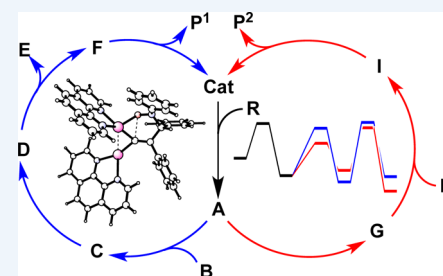
[§]Department of Chemistry, School of Science, Tianjin University, Tianjin 300072, P. R. China

^{||}Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden

CONSPECTUS: Quantum chemical techniques today are indispensable for the detailed mechanistic understanding of catalytic reactions. The development of modern density functional theory approaches combined with the enormous growth in computer power have made it possible to treat quite large systems at a reasonable level of accuracy. Accordingly, quantum chemistry has been applied extensively to a wide variety of catalytic systems. A huge number of problems have been solved successfully, and vast amounts of chemical insights have been gained. In this Account, we summarize some of our recent work in this field. A number of examples concerned with transition metal-catalyzed reactions are selected, with emphasis on reactions with various kinds of selectivities. The discussed cases are (1) copper-catalyzed C–H bond amidation of indoles, (2) iridium-catalyzed C(sp³)–H borylation of chlorosilanes, (3) vanadium-catalyzed Meyer–Schuster rearrangement and its combination with aldol- and Mannich-type additions, (4) palladium-catalyzed propargylic substitution with phosphorus nucleophiles, (5) rhodium-catalyzed 1:2 coupling of aldehydes and allenes, and finally (6) copper-catalyzed coupling of nitrones and alkynes to produce β -lactams (Kinugasa reaction).

First, the methodology adopted in these studies is presented briefly. The electronic structure method in the great majority of these kinds of mechanistic investigations has for the last two decades been based on density functional theory. In the cases discussed here, mainly the B3LYP functional has been employed in conjunction with Grimme’s empirical dispersion correction, which has been shown to improve the calculated energies significantly. The effect of the surrounding solvent is described by implicit solvation techniques, and the thermochemical corrections are included using the rigid-rotor harmonic oscillator approximation.

The reviewed examples are chosen to illustrate the usefulness and versatility of the adopted methodology in solving complex problems and proposing new detailed reaction mechanisms that rationalize the experimental findings. For each of the considered reactions, a consistent mechanism is presented, the experimentally observed selectivities are reproduced, and their sources are identified. Reproducing selectivities requires high accuracy in computing relative transition state energies. As demonstrated by the results summarized in this Account, this accuracy is possible with the use of the presented methodology, benefiting of course from a large extent of cancellation of systematic errors. It is argued that as the employed models become larger, the number of rotamers and isomers that have to be considered for every stationary point increases and a careful assessment of their energies is therefore necessary in order to ensure that the lowest energy conformation is located. This issue constitutes a bottleneck of the investigation in some cases and is particularly important when analyzing selectivities, since small energy differences need to be reproduced.



1. INTRODUCTION

It goes without saying that quantum chemistry today is an essential tool in many disciplines of chemistry. This is particularly the case for organic and organometallic chemistry, wherein the impact has been profound over the years, from the early developments of qualitative concepts for chemical bonding and reactivity using semiempirical methods, to today’s increasingly accurate results obtained with density functional theory (DFT) methodologies.

Continuous developments of the electronic structure methods as well as technical and algorithmic improvements, coupled with the exponential growth in computational power, have made it possible to treat ever larger systems, with ever higher accuracy. Consequently, an enormous number of applications have been published over the years, solving a

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huge number of outstanding problems and gaining vast amounts of chemical insight.

Recent reviews,¹ as well as the various contributions constituting the current special issue of *Accounts of Chemical Research*, summarize very well the state-of-the-art in this field, demonstrating the great levels of depth and breadth of the problems that can be tackled. The calculations are very commonly used to rationalize experimental findings and suggest additional experiments to verify mechanistic proposals, and it is in fact quite usual today to publish joint experimental/theoretical articles in which various aspects of the reaction mechanisms are addressed with the different complementary techniques, thereby developing a better understanding of the question at hand. Quantum chemical calculations are also increasingly frequently used as a predictive tool and in the design of new catalytic systems.²

In this Account, we will discuss a number of illustrative examples from our recent work in this field, with emphasis on how the calculations have been able to unravel new reaction mechanisms and also elucidate the sources of various selectivities of metal-catalyzed reactions. The discussions of the experimental backgrounds of these reactions are kept to a minimum in the interest of space; extended discussions can be found in the original articles. First, however, the computational methodology adopted in these applications will be outlined and commented briefly.

2. COMPUTATIONAL METHODOLOGY

Mechanistic studies of catalytic reactions require the calculation of detailed free energy profiles, including the energies of all transition states and intermediates, at a sufficient level of accuracy. The electronic structure methods used in these kinds of studies have since the 1990s almost exclusively been based on DFT. In our investigations, we employ the widely popular hybrid B3LYP functional,³ which offers a reasonable balance between speed and accuracy. In some of the applications, we also use the more recent M06 functional.⁴ A limitation of B3LYP, and indeed most other functionals, is their inability to describe the attractive dispersion interactions properly. In the studies discussed here, the widely used empirical dispersion correction developed by Grimme⁵ has been added, as it has been shown to improve the results considerably for many different applications. In some of the cases discussed here, it has been critical for the correct reproduction of the selectivity in question.

The geometries are typically optimized with a medium-sized basis set (usually with effective core potentials on the metals), and more accurate energies are then obtained using single-point calculations with a considerably larger basis set. The effects of solvent are usually modeled using implicit solvation techniques, which are fast and have over the years been improved to provide reasonable accuracy. In the cases discussed here, the commonly used CPCM⁶ and SMD⁷ methods have been employed. Free energy corrections are very commonly taken into account using the rigid-rotor harmonic oscillator model, which is also done in the studies presented here.

The selectivity of a reaction is determined by identifying the selectivity-determining transition states from the full energy profiles for the various alternative reaction pathways. The energy differences are then converted to product ratios by classical transition state theory. Thus, the study of selectivities requires typically reproduction of small energy differences, on the order of 1–2 kcal/mol on relative TS energies, something

that usually can be achieved with the computational protocol outlined above. Of course, in this case the accuracy benefits to a large extent from cancellation of systematic errors between quite similar structures.

It is important to point out here that although the methodology is very common and has been employed by many groups for many different applications, it is of course not without problems, and experience has shown that one always has to be cautious and prepared to question it.⁸ Every element of the methodology can be improved, and there are indeed techniques that can achieve higher accuracy.

One very important issue that must be mentioned here is that as the size of the employed models increases, the problem with the conformational search becomes more severe. A large number of isomers and rotamers have to be calculated explicitly for every stationary point in order to make sure that the lowest energy conformation is located. In some cases, the conformational search can be very extensive and can constitute the bottleneck of the investigation. In the applications discussed in this Account, the conformational search was performed manually. That is, for every stationary point, a number of reasonable isomers and rotamers were identified systematically, their geometries were optimized, and their energies were evaluated and compared. The conformational issue is particularly important in the study of selectivity, where small energy differences must be reproduced. For example, in a recent study on the stereoselectivity of the tetrapeptide-catalyzed kinetic resolution of *trans*-2-*N*-acetamidocyclohexanol, a large number of structures of the critical TS were optimized in order to reproduce the experimental results and to identify the factors that govern the selectivity.⁹ In this case, the energy span for the optimized geometries was found to be up to 10 kcal/mol, which shows that a less careful treatment of this issue can have severe consequences and lead to the wrong chemical conclusions.

3. Cu-CATALYZED C–H BOND AMIDATION OF INDOLES

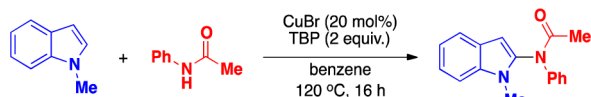
C–H functionalization reactions have received an enormous amount of attention in recent years, and great advancements have been made in terms of their synthetic utility. A major challenge faced in the pursuit of efficient methodologies is the control of the selectivity of the process. C–H bonds are ubiquitous in organic molecules, and thus it is necessary to devise strategies to enhance the catalyst selectivity.

We have used DFT calculations to investigate the reaction mechanisms and the origins of selectivities of two different C–H functionalization reactions, namely, the Cu-catalyzed amidation of indoles (described in this section) and the Ir-catalyzed borylation of chlorosilanes (next section).

Several methodologies have been reported for the selective C–H functionalization of the indole ring, with the preferential reactivity being usually either at the C2 or C3 positions. Typically, a higher reactivity at C2 is explained by the higher acidity of this position, while a preferential reaction at C3 is rationalized by the higher nucleophilicity of this position. However, the reasons for a certain catalyst resulting in a particular selectivity are often unclear, and the possibility of different mechanisms being operative is always an option. In 2010, Li and co-workers reported a copper-catalyzed oxidative amidation of 1-methylindoles.¹⁰ The reaction made use of *tert*-butyl peroxide (TBP) as oxidant and selectively afforded the products of C2-functionalization (Scheme 1). The mechanism

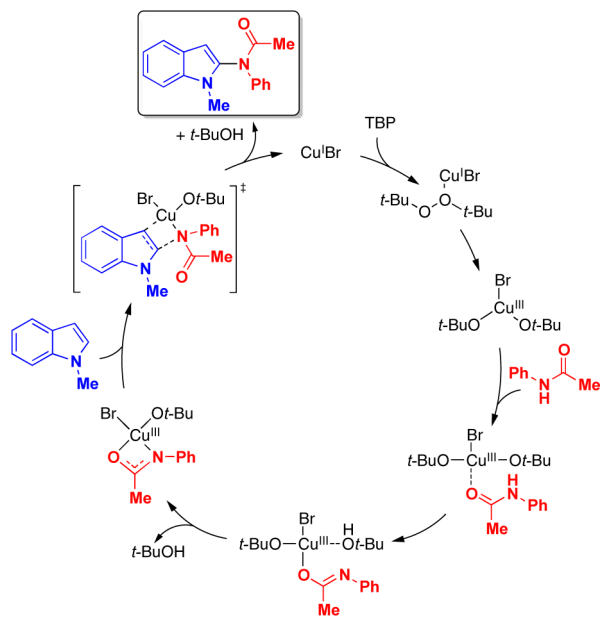
of this reaction and the origins of the observed selectivity were not clear, which motivated a detailed computational investigation.¹¹

Scheme 1. Copper-Catalyzed Regioselective Amidation of Indoles



The catalytic cycle that we proposed on the basis of the calculations is shown in Scheme 2. First, it was found that

Scheme 2. Mechanism of Copper-Catalyzed Regioselective Amidation of Indoles Obtained from the Calculations



copper(I) bromide can be oxidized with a feasible barrier to a Cu(III) species by TBP, in line with the mechanistic hypothesis proposed by Li and co-workers. The subsequent amide coordination and deprotonation, with one of the *tert*-butoxide ligand acting as a base, and *t*-BuOH release occur practically without a barrier. Next, the critical indole amidation step takes place. We located the transition states for this step occurring through the well-established concerted-metalation deprotonation (CMD) mechanism¹² on both C2 and C3 positions (Figure 1). It turns out that in both cases the CMD occurs concertedly with the reductive elimination (CMD-RE). The energy barriers associated with these TSs are reasonable (20.6 and 15.7 kcal/mol for C2 and C3 positions, respectively), but they result in the exclusive amidation at the C3 position, in contrast to the experimental results. Looking for alternative mechanisms that could account for the observed regioselectivity, we found that the amidation can occur through a new kind of mechanism termed four-center reductive elimination (4CRE), with the metal coordinating either C2 or C3 and the amide group attacking the adjacent position (Figure 1). These TSs also have reasonable barriers and, very importantly, the barrier for the reaction occurring on C2 through a 4CRE is lower than that for a CMD on C3 (13.7 vs 15.7 kcal/mol). Thus, the observed regioselectivity can be explained on the

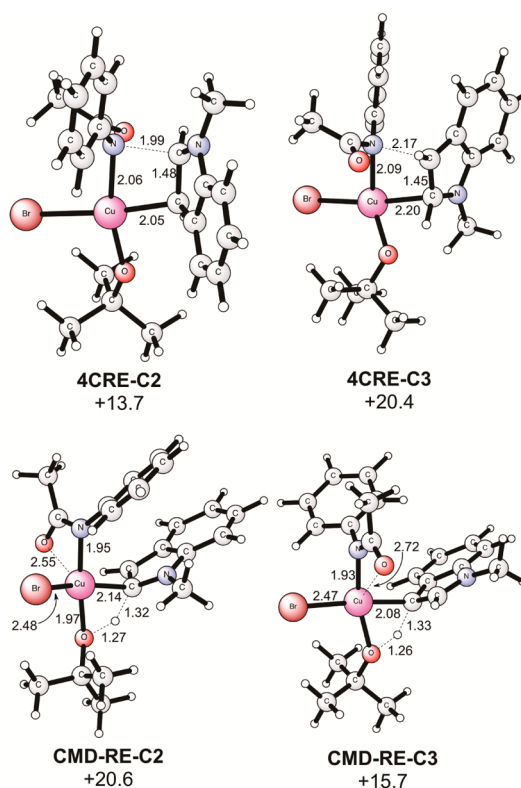


Figure 1. Optimized transition states of copper-catalyzed regioselective amidation of indoles. Energies relative to the common reactants are indicated in kcal/mol.

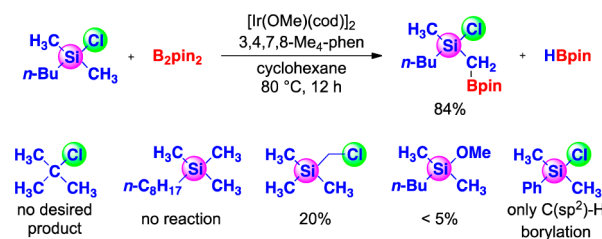
basis of the lower barrier found for the 4CRE mechanism compared with the CMD. The 4CRE mechanism favors the C2 functionalization because of a stabilizing interaction between electrophilic Cu(III) and the nucleophilic C3 position of indole. The 4CRE mechanism is similar to the Heck-like mechanism obtained by Wu and co-workers in their mechanistic study of the *meta*-selective copper-catalyzed arylation of anilides.¹³

Finally, an important technical detail in our study was that the dispersion correction was found to be necessary in order to reproduce the experimental regioselectivity.¹¹

4. Ir-CATALYZED C(sp³)-H BORYLATION OF CHLOROSILANES

In another detailed mechanistic and selectivity study of a C-H activation reaction, we considered the iridium-catalyzed C(sp³)-H borylation of chlorosilanes reported recently by Suginome and co-workers (Scheme 3).¹⁴ The reaction was found to occur exclusively at the primary methyl C-H bond,

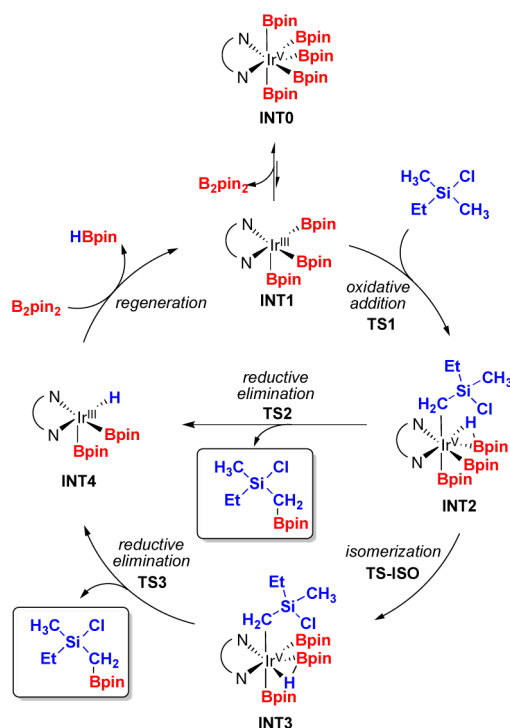
Scheme 3. Ir-Catalyzed C(sp³)-H Borylation of Chlorosilanes



without a secondary borylation product being generated. When $C(sp^2)$ -H bonds are present in the substrate, only $C(sp^2)$ -H borylation was observed in the reaction. Importantly, it was found that the presence of the chlorosilyl group is crucial for the reaction to take place. Upon replacement of the silicon by a carbon or change of the chlorine substituent to a methyl group, no borylation product was observed.¹⁵ Replacement of the chlorine substituent by other moieties, such as chloromethyl or methoxy groups, led to a significant decrease in yields. It was proposed that the chlorosilyl group plays a role as a directing group to coordinate the substrate with either the iridium or one of the boron atoms in the active species [(3,4,7,8-Me₄-phen)Ir(Bpin)₃], which can promote the C-H oxidative addition step.¹⁴

The mechanism of the Ir-catalyzed $C(sp^2)$ -H borylation is well-established, involving Ir(III)/Ir(V) intermediates and consisting of three steps: C-H oxidative addition, C-B reductive elimination, and regeneration of active catalyst.¹⁶ In order to elucidate the detailed mechanism of the $C(sp^3)$ -H borylation of chlorosilanes, and in particular the role of the chlorosilyl group, we performed DFT calculations using both the B3LYP and M06 functionals.¹⁷ The catalytic cycle obtained on the basis of the calculations is shown in Scheme 4.

Scheme 4. Reaction Mechanism Suggested for the Ir-Catalyzed $C(sp^3)$ -H Borylation of Chlorosilanes



The calculations showed first, consistent with previous investigations,¹⁶ that the seven-coordinate 18-electron Ir(V)-intermediate **INT0**, formed by the reaction of [(3,4,7,8-Me₄-phen)Ir(Bpin)₃] (**INT1**), the commonly accepted active catalytic species, with another B₂pin₂ molecule, is the lowest lying intermediate of the overall cycle and constitutes thus the resting state of the catalyst. For the $C(sp^3)$ -H oxidative addition, the proposed directing role of the chlorine could not be observed in the calculations. This step was found to proceed through a transition state without any direct interaction

between the chlorine and the iridium or the boron (**TS1**, Figure 2). Regarding the subsequent C-B reductive elimination, the two employed functionals gave slightly different conclusions. B3LYP-D3 suggested that an isomerization step from **INT2** to **INT3**, involving a change of the hydride position, is required prior to the C-B reductive elimination, with the former step being rate-determining. M06, on the other hand, yielded that the direct C-B reductive elimination is favored. A definitive conclusion could not be drawn regarding this issue on the basis of the calculations. Interestingly, Hartwig and co-workers reported very recently an Ir-catalyzed benzylic $C(sp^3)$ -H borylation of methylenes, where they found that the scenario with the isomerization/C-B reductive elimination is more favored on the basis of both experimental and computational results.¹⁸

Both functionals reproduced quite well the observed experimental trends in the relative reactivity of the different substrates. The bond dissociation energies (BDEs) of the C-H bonds of the substrates and the Ir-C bonds of the Ir(V) hydride intermediates **INT2**, resulting from the C-H oxidative addition step, were calculated in order to rationalize the role of the chlorosilyl group. The results showed that the C-H BDEs are not sensitive to the substituents, while a good correlation between the barriers and the calculated Ir-C BDEs of the Ir(V) hydride intermediates was found. The accelerating role of the chlorosilyl group could thus be attributed to its strong α -carbanion stabilizing property, stemming from a combination of the silicon α -effect and the high electronegativity of the chlorine substituent.

The origin of the preferential borylation of primary over secondary $C(sp^3)$ -H was also considered and discussed in our calculations, and it was concluded that steric effects (repulsion between the alkyl group and the Ir/ligand moiety) are responsible for the experimentally observed selectivity. We found furthermore that the difference between $C(sp^2)$ -H and $C(sp^3)$ -H borylation is mainly due to the different reactivities of the intermediates resulting from the C-H oxidative addition. Distortion/interaction analysis of C-B reductive elimination transition states showed that such a reactivity difference originates from a higher interaction energy in the $C(sp^2)$ -B reductive elimination compared with the $C(sp^3)$ -B counterpart, stemming mainly from the presence of a Ph-B π^* orbital that can enhance the back-bonding interaction with the d orbital of iridium.

5. INTERMEDIATE TRAPPING IN V-CATALYZED MEYER-SCHUSTER REARRANGEMENT

A very interesting class of metal-catalyzed reactions for which quantum-chemical calculations may be very insightful for explaining the selectivity are processes involving the so-called intermediate interception strategy. In this approach, the mechanistic pathway is diverted from its ordinary tracks by trapping of a catalytic intermediate intermolecularly with an added reagent or intramolecularly with a functional group introduced into the substrate. By utilizing unique chemical reactivities of the transient species, such reactions often enable entry to otherwise not readily accessible structural motifs. However, there exists an inherent challenge associated with the intermediate interception. Namely, in order for this strategy to be successful, the trapping step must take place more efficiently compared with the pathway followed normally by the catalytic reaction. We have investigated computationally two related processes developed by the group of Trost consisting of

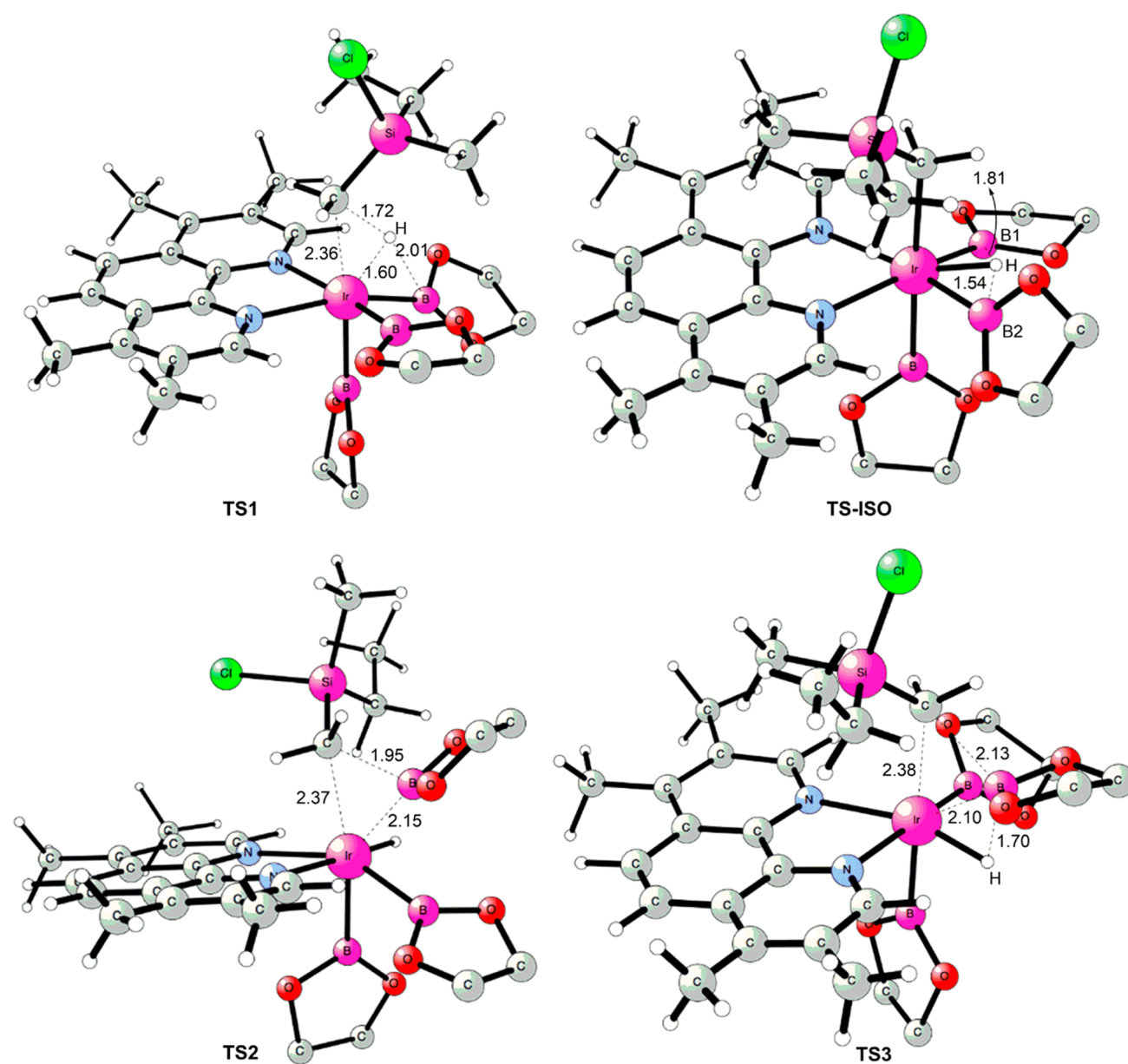
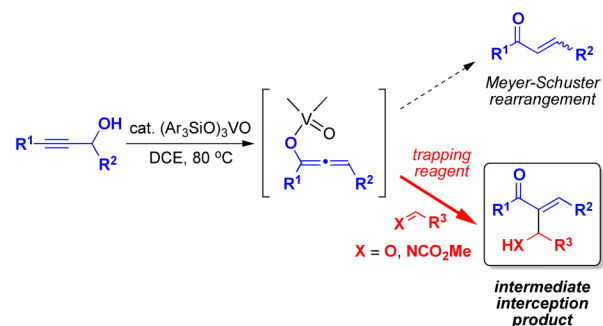


Figure 2. Optimized structures of selected transition states for the mechanism of Ir-catalyzed C(sp³)-H borylation of chlorosilanes.

vanadium-catalyzed Meyer–Schuster rearrangement combined with aldol- and Mannich-type additions, which at their core employ the interception of a catalytic vanadium enolate species (Scheme 5).¹⁹

The calculations were able to shed light on a number of aspects of the reaction mechanism that previously lacked proper understanding (Figure 3).²⁰ The resting state of the catalyst was identified as an off-cycle tris(triarylsilyl) orthovanadate, while the active form was found to be a mixed vanadate ester incorporating only a single propargylic alcohol reactant moiety. The study of the 1,3-migration step posed a particular challenge due to the difficulties with calculating the barrier for a dissociative ionic pathway. Considering the nonpolar nature of the reaction solvent, the barrier was estimated by the energy of the associated ion-pair, which was found to be somewhat lower than the alternative concerted transition state. This is corroborated by the experimentally observed loss of stereochemical information from an enantioenriched chiral substrate.^{19b} Importantly, the

Scheme 5. Interception of Vanadium Enolate Intermediate with Aldehyde or Imine Leading to Combined Meyer–Schuster Rearrangement–Aldol/Mannich Reaction



initial ligand substitution and the subsequent 1,3-shift were found to constitute the largest span on the free energy profile, determining the overall rate of the reaction. This result is in

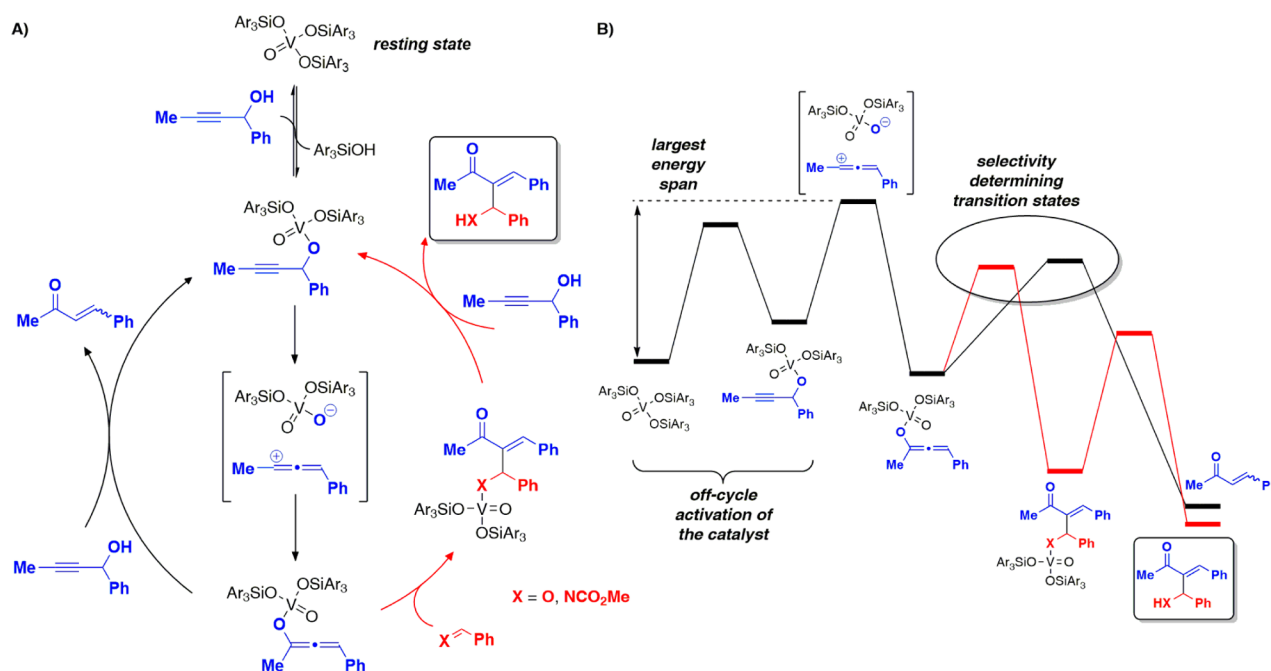


Figure 3. (A) Computationally established mechanism of the reaction from Scheme 5 and (B) the corresponding free energy profile.

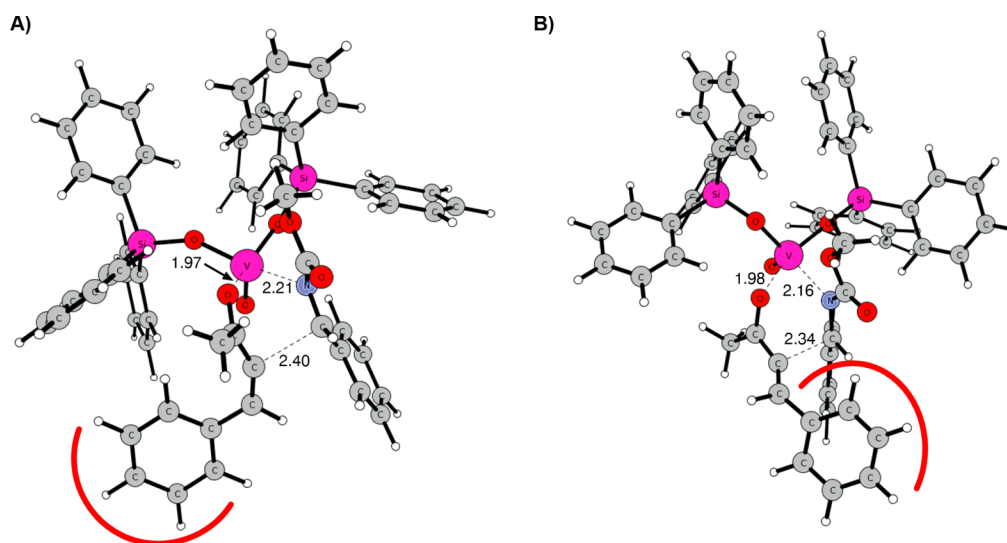


Figure 4. Optimized structures of the transition states for the trapping of vanadium enolate with an imine, leading to (A) (Z)-configured and (B) (E)-configured Mannich products.

contrast with the previous suggestion that the product release that takes place later in the catalytic cycle is rate-determining.¹⁹ The calculations also provided an explanation for the preferential formation of the (Z)-isomers of the products, which were found to originate from the steric interactions blocking one face of the enolate from the approach of aldehyde or imine (Figure 4).

Next, we examined the selectivity of the reactions with respect to following the two competing branches of the catalytic cycle. It was established that both steps diverging from the common vanadium enolate intermediate are irreversible; hence the relative energy of the corresponding transition states determines the final product ratio. The calculated values showed that for both the aldol and Mannich versions of the reaction, the trapping by the added electrophile is barely energetically favored over the normal Meyer–Schuster

rearrangement pathway. These findings agree very well with the experiments, which required the use of an excess of the propargylic alcohol and its slow addition to the reaction mixture in order to secure high yields of the desired products. Namely, the former compensates for the inevitable partial conversion of propargylic alcohol into ketone, while the latter maintains a low concentration of the alcohol in the reaction mixture, slowing the undesired intermolecular transesterification/tautomerization pathway.

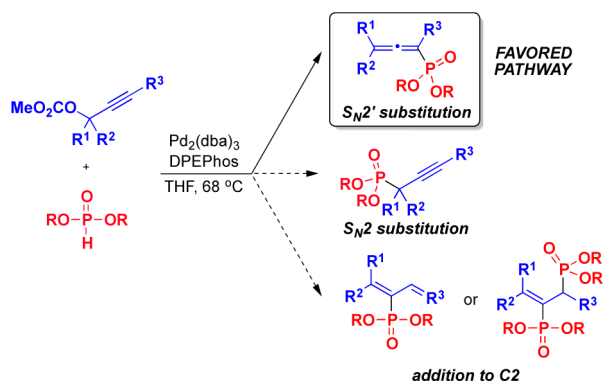
6. Pd-CATALYZED PROPARGYLIC SUBSTITUTION WITH PHOSPHORUS NUCLEOPHILES

We have investigated the mechanisms and selectivities of two metal-catalyzed processes involving allene-containing compounds. In the first, the Pd-catalyzed propargylic substitution with phosphorus nucleophiles described in this section, the

allenes are products of the reaction, while in the second, the Rh-catalyzed 1:2 coupling of aldehydes and allenes (next section), they play the role of substrates.

One of the most general methods providing access to a variety of allenes is the palladium-catalyzed S_N2' propargylic substitution.^{21,22} Its applicability is, however, limited to the use of hard organometallic nucleophiles, for example, organozinc reagents. Heteroatom (N- and O-centered) as well as soft carbon nucleophiles follow alternative pathways in the reaction with propargylic substrates, leading to nonallenic compounds.²² A notable exception are H-phosphonates, which afford P-substituted allenes in good selectivity (Scheme 6).²³ The

Scheme 6. Possible Pathways in the Palladium-Catalyzed Reaction between Propargylic Carbonates and H-Phosphonate Diesters



palladium-catalyzed S_N2' propargylic substitution with the phosphorus nucleophiles features several additional advantages from the synthetic point of view, such as a full control of the stereochemistry and mild reaction conditions allowing for the synthesis of complex P-allenes of interest to biological and pharmaceutical chemistry.

In order to understand the intriguing selectivity observed in the reaction shown in Scheme 6, we performed a thorough computational investigation of the possible pathways and established a plausible catalytic cycle (Scheme 7).²⁴ It was

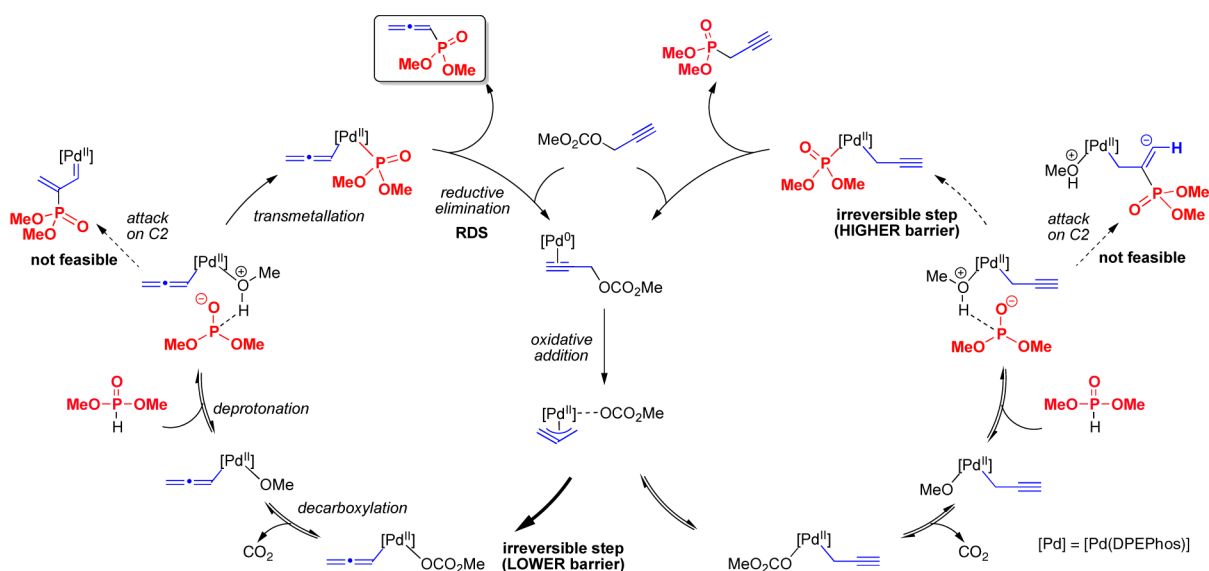
found that the reaction takes place via consecutive oxidative addition, decarboxylation, H-phosphonate deprotonation, transmetalation (ligand exchange), and finally reductive elimination. The last step was identified as being rate-determining for the overall transformation, although it is not involved in deciding the selectivity of the reaction.

The key difference in the behavior of H-phosphonates compared with other nucleophiles originates from the lack of free electron pairs on phosphorus in the incipient reagent, implying the necessity for deprotonation prior to any bond-forming event. According to the calculations, the abstraction of proton is feasible exclusively by a palladium-bound methoxide, forming a phosphite anion, whose dissociation into the solution is strongly energetically disfavored. Thus, the generated nucleophilic species can only attack on the central carbon of either η^1 -allenyl or η^1 -propargyl moiety in the parent complexes (but not η^3 -propargyl, present in an intermediate earlier in the cycle) or participate in the transmetalation (Figure 5). The energies calculated for the corresponding transition states clearly point to the latter alternative as the favored pathway, leading eventually to the experimentally observed product. The calculations provided also an explanation for the preferential formation of allenyl- over propargylphosphonates. Interestingly, the first irreversible steps determining this selectivity were found to be different in the two branches of the catalytic cycle (see Scheme 7), highlighting the importance of a complete computational analysis of the full mechanism.

7. Rh-CATALYZED 1:2 COUPLING OF ALDEHYDES AND ALLENES

Murakami and co-workers reported recently the novel rhodium-catalyzed coupling of aldehydes and allenes shown in Scheme 8.²⁵ It was found that instead of 1:1 coupling (hydroacylation), 1:2 coupling products formed from one molecule of aldehyde and two molecules of allene. A very intriguing feature of this reaction is its remarkable regioselectivity. In principle, there exists a large number of possible different isomers of 1:2 coupling products. However, when [RhCl(dppe)] is used as a catalyst, compound A was obtained as the major product, accompanied by two minor isomers, B

Scheme 7. Computationally Established Mechanism of the Reaction from Scheme 6



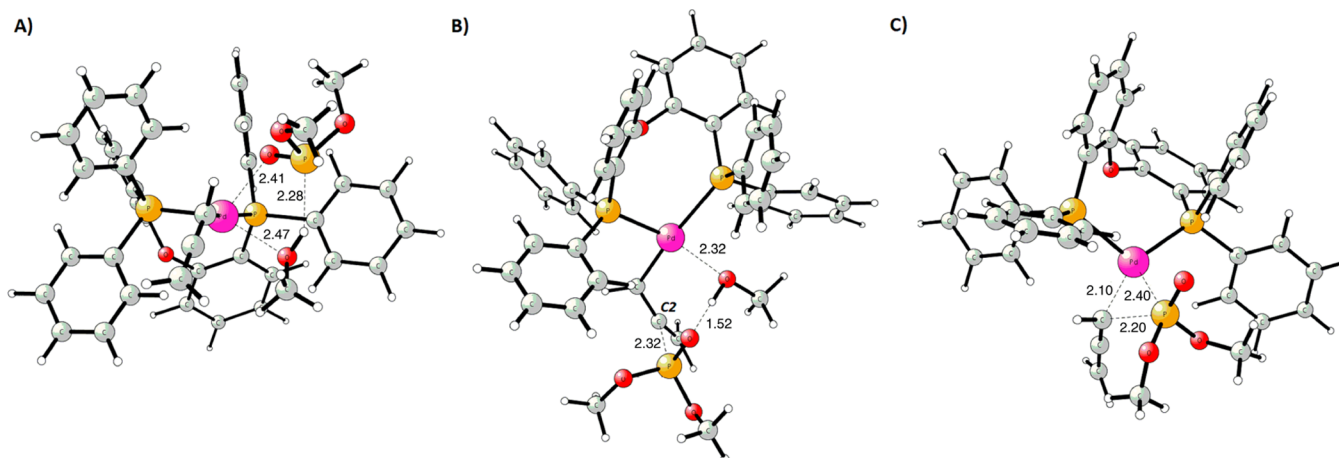
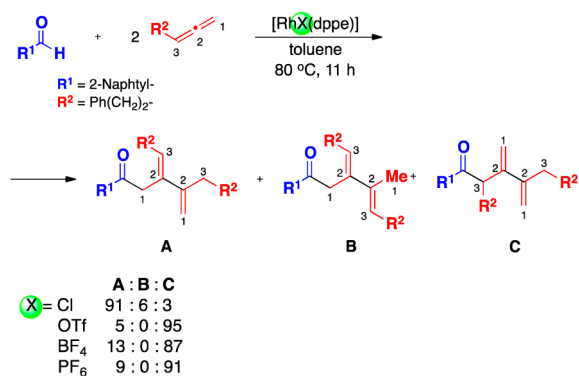


Figure 5. Optimized structures of selected transition states from the allenyl branch of the mechanism shown in Scheme 7: (A) transmetalation, (B) attack on carbon C2, and (C) reductive elimination.

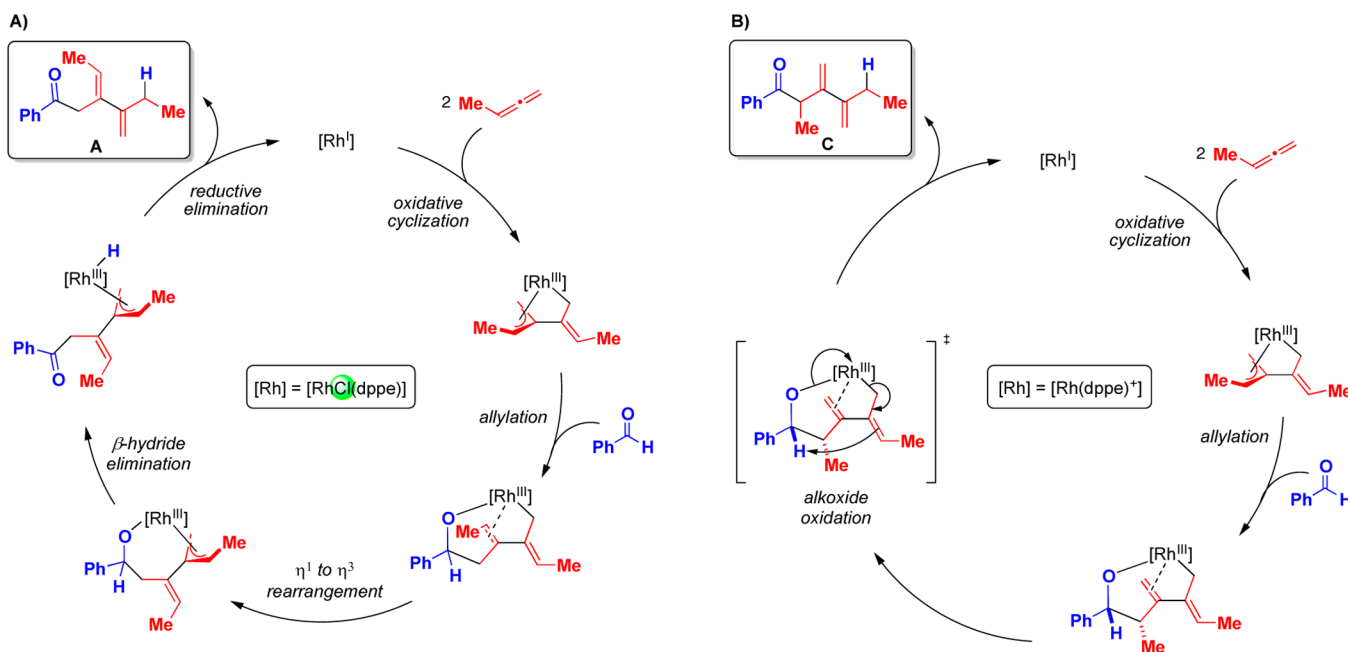
Scheme 8. Rh-Catalyzed 1:2 Coupling of Aldehydes and Allenes



and C, with a ratio of 91:6:3. Interestingly, the counterion of the rhodium catalyst was found to have a profound impact on the selectivity. Namely, upon replacing the chloride by noncoordinating counterions (e.g., TfO⁻, BF₄⁻, or PF₆⁻), only products A and C were formed, and the selectivity switched to compound C becoming the dominant product.

Murakami and co-workers proposed that the reaction is initiated by oxidative cyclization of aldehyde and allene to generate a five-membered oxarhodacyclic intermediate. Subsequent insertion of allene into Rh–C bond followed by β-hydride elimination and C–H reductive elimination would give the final 1:2 coupling products.²⁵ Considering that rhodium complexes have been widely used in hydroacylation and cycloaddition of unsaturated compounds, alternative pathways, such as those initiated by oxidative cyclization of the two allenes or by C–H oxidative addition of aldehyde, are possible.

Scheme 9. Computationally Established Mechanisms for the 1:2 Coupling of Aldehyde and Allenes Catalyzed by (A) [RhCl(dppe)] and (B) [Rh(dppe)]⁺



^aOnly the pathway leading to the major reaction product is shown in each case.

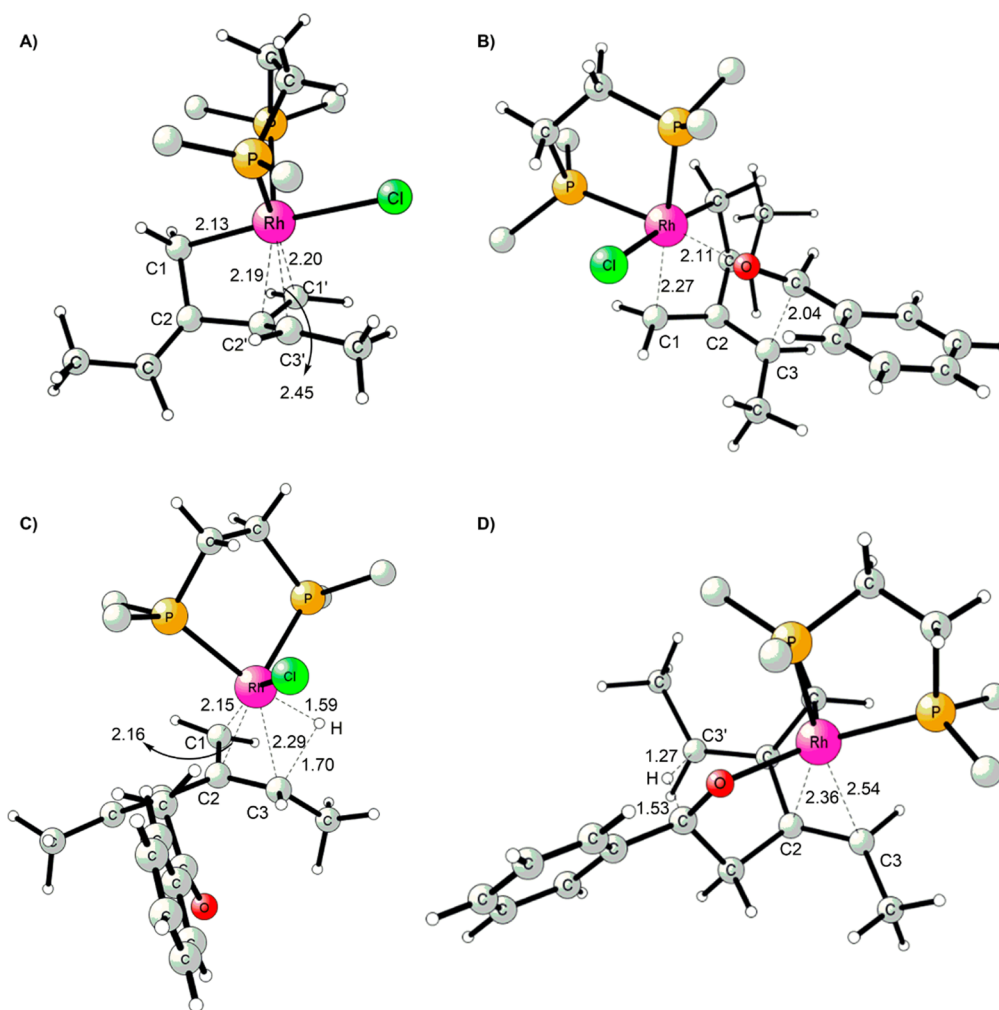


Figure 6. Optimized structures of selected transition states and intermediates involved in the mechanism of 1:2 coupling of aldehyde and allenes: (A) η^3,η^1 -bis(allylic) Rh(III) complex; (B) allylation TS with $[\text{RhCl}(\text{dppe})]$; (C) reductive elimination TS with $[\text{RhCl}(\text{dppe})]$; (D) alkoxide oxidation TS with $[\text{Rh}(\text{dppe})^+]$.

DFT calculations were performed to elucidate the detailed mechanism of this novel reaction and to rationalize the origins of the selectivity.²⁶ Both neutral $[\text{RhCl}(\text{dppe})]$ and cationic $[\text{Rh}(\text{dppe})^+]$ catalytic systems were considered and compared in order to understand the peculiar counterion effect.

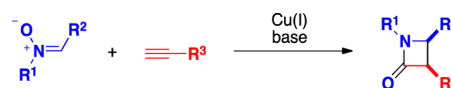
At each step, all possible reactions were considered, and a large number of isomers and rotamers were calculated for each stationary point. The calculations suggested the following reaction mechanism (Scheme 9): (1) The reaction is initiated by oxidative cyclization of two allenes. Interestingly, instead of the expected five-membered rhodacycle intermediate, this step leads to the formation of a η^3,η^1 -bis(allylic) Rh(III) complex (see Figure 6). (2) The second C–C bond forming step to incorporate the aldehyde moiety into the structure was found to take place through an allylation reaction (Figure 6) that has a lower barrier than a migratory insertion into the Rh–C bond. (3) After the allylation step, the calculations showed that the following steps are different depending on the catalyst employed. For $[\text{RhCl}(\text{dppe})]$, η^1 to η^3 rearrangement, β -hydride elimination, and C–H reductive elimination were found to be responsible for the formation of the final products, while in the case of $[\text{Rh}(\text{dppe})^+]$, an alkoxide oxidation step (Figure 6) leads directly to the 1:2 coupling products. Very importantly, this difference in the mechanism explains why

three products are observed for $[\text{RhCl}(\text{dppe})]$ but only two for $[\text{Rh}(\text{dppe})^+]$, and it also reproduces the experimentally observed trends in the product distribution. The calculations showed that the overall selectivity of the reaction is determined by the inherent selectivities of several elementary steps. The Rh–allyl complexes, which can adopt both η^3 and η^1 configurations, are key intermediates present throughout the catalytic cycle and have important implications on the selectivity.

8. Cu-CATALYZED COUPLING OF NITRONES AND ALKYNES

The Cu(I)-catalyzed reaction between a nitron and a terminal alkyne, known as the Kinugasa reaction, allows an easy entry to β -lactams, with perfect atom economy and generally good diastereoselectivity (Scheme 10).²⁷ The reaction was originally disclosed by Kinugasa in 1972 using a stoichiometric amount of

Scheme 10. Kinugasa Reaction: Copper-Catalyzed Synthesis of Lactams



assisted intramolecular nucleophilic attack gives a four-membered ring intermediate, which after copper release and tautomerization evolves to the final product. The copper is thus involved in every step of the reaction, lowering the energy barrier for each of them: First, it acidifies the alkyne making its deprotonation feasible. Second, it allows the cycloaddition to occur in a stepwise fashion, with lower energy barriers compared with a concerted cycloaddition. Finally, copper acts as a Lewis acid on the ketene promoting the final nucleophilic attack.

Alternative pathways involving an initial deprotonation assisted by one copper ion or the cycloaddition occurring on the parent alkyne were also tested and found to be associated with higher energy barriers. It should be considered, however, that the relative energies of the different mechanistic possibilities could be sensitive to the reaction conditions, such as the natures of the copper ligand, the base, and the solvent employed.

In addition to the reaction mechanism, the enantioselectivity was investigated for the case of the bis(zaferrocene) ligand designed by Fu that afforded enantioenriched products in up to 93% enantiomeric excess.³⁰ All the possible pathways studied for the nonenantioselective reaction were also considered with the chiral ligand. It was found that two different mechanisms, namely, the pathway described above involving two copper ions and a mechanism with the initial cycloaddition occurring on the parent alkyne, have quite similar energy barriers and are both able to account for the experimentally observed enantioselectivity. Considering the limitations of the computational methods, it was not possible to rule out either of the two possibilities. In both mechanisms, the preferential formation of one of the two enantiomers was found to depend on steric effects exerted by the bulky zaferrocene groups.

9. CONCLUDING REMARKS

We have in this Account summarized a number of studies performed recently in our group to illustrate how quantum chemical methodology can be used to develop better understanding for complex reaction mechanisms and to elucidate the origins of selectivities of metal-catalyzed catalytic processes. Quantum chemistry is a dynamic research field, with continuous developments of methods and methodologies to study various aspects of chemistry. Enormous progress has been made in the field of mechanistic homogeneous catalysis, and the future promises even greater momentum.

To speculate a bit, it is reasonable to expect that the accuracy of practically every aspect of the methodology mentioned above will witness improvement in the future. For example, more accurate electronic structure methods based on coupled cluster theory are already starting to become affordable and provide thus a viable option for this field. More accurate ways of treating the solvation and the thermal corrections are also being developed.

It is also likely that the growing computer power will allow for automated unbiased searches and conformational sampling for large systems. These developments will make quantum chemistry an even more powerful tool with even greater predictive powers. Like in other fields, some aspects of the methodology will become more of a black-box, while other elaborate aspects will continue to need the expertise of experienced computational chemists.

AUTHOR INFORMATION

Corresponding Author

*E-mail: fahmi.himo@su.se

Notes

The authors declare no competing financial interest.

Biographies

Stefano Santoro was born in Campobasso, Italy, in 1980. He received his Ph.D. degree from the University of Perugia in 2009 (under supervision of Profs. Claudio Santi and Marcello Tiecco). In the period 2010–2014, he was a postdoctoral researcher at Stockholm University with Prof. Fahmi Himo, after which he became an assistant professor at the University of Perugia.

Marcin Kalek was born in Łódź, Poland, in 1983. He obtained his M.Sc. degree from the University of Warsaw in 2005 and his Ph.D. from Stockholm University in 2011 under supervision of Prof. Jacek Stawinski. After completing two postdoctoral fellowships with Prof. Fahmi Himo at Stockholm University (2011–2013) and with Prof. Gregory C. Fu at the California Institute of Technology (2013–2015), he returned to Poland and joined the faculty of the University of Warsaw as an assistant professor in 2016.

Genping Huang was born in Anhui, China, in 1984. He received his Ph.D. (2011) at Qinghai Institute of Salt Lakes, Chinese Academy of Sciences, China, under supervision of Prof. Yahong Li and Prof. Yuanzhi Xia. After his postdoctoral work with Prof. Fahmi Himo at Stockholm University (2011–2014), he joined the faculty at Tianjin University, China, as an associate professor of chemistry.

Fahmi Himo was born in 1973 in Hassake, Syria. He graduated from Stockholm University in 2000 under supervision of Profs. Leif Eriksson and Per Siegbahn. He then spent two years as a Wenner-Gren postdoctoral fellow with Prof. Louis Noodleman at the Scripps Research Institute (2000–2002) and three years as a Wenner-Gren Fellow at the Royal Institute of Technology in Stockholm (2002–2005). He worked then as an assistant professor at the same place (2005–2009) before moving to his current position as a professor at Stockholm University.

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