

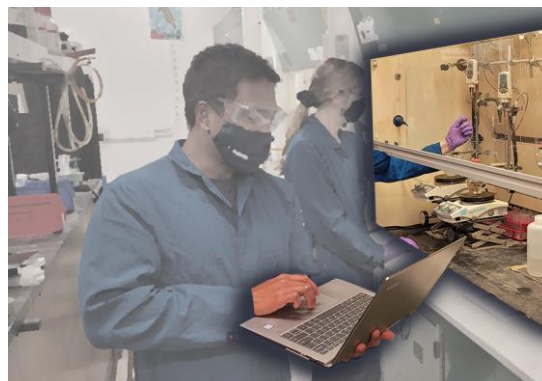
Melding of Experiment and Theory Illuminates Mechanisms of Metal-Catalyzed Rearrangements: Computational Approaches and Caveats

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Dedicated to the memory of Prof. Marilyn Olmstead, a world-class leader in crystallography and extraordinary teacher and mentor.



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Abstract This review summarizes approaches and caveats in computational modeling of transition-metal catalyzed sigmatropic rearrangements involving carbene transfer. We highlight contemporary examples of combined synthetic and theoretical investigations that showcase the synergy achievable by integrating experiment and theory.

Key words rearrangements, Rh-catalysts, carbene transfer, onium ylides, DFT

Introduction

Sigmatropic rearrangements have long been used to facilitate synthetic campaigns toward challenging targets.¹ While, historically, [3,3]-sigmatropic rearrangements have received the most attention, [1,2]- and [2,3]-sigmatropic rearrangements of onium ylides generated via carbene transfer reactions have garnered considerable attention, since they allow for formation of carbon-carbon and/or carbon-

heteroatom bonds that can be otherwise difficult to construct. Efforts to achieve these couplings stereoselectively with transition-metal catalysts have enabled reliable and effective methods to introduce new stereogenic centers in complex target molecules.^{2,3} The most commonly used transition-metal catalysts for these reactions are rhodium and copper-based catalysts,^{4,5} but catalysts based on other metals, such as gold,^{6,7} ruthenium,^{8–11} cobalt,^{12,13} palladium,^{14–16} silver,¹⁷ nickel,¹⁸ and iron^{19–26}, also have been developed for these purposes. In 1981, Doyle and coworkers²⁷ brought new life to the field of transition-metal catalyzed [2,3]-sigmatropic rearrangements, building on past work by Kirmse and Kapps,²⁸ by demonstrating utility for organic synthesis (Figure 1).^{29–36}

Herein, we examine approaches, both theoretical and experimental, for probing the mechanisms of such reactions and feeding the resulting mechanistic knowledge into the reaction design process. Though metal-free carbenes also can form ylides *via* photochemical carbene transfer,³⁷ this approach has been reviewed elsewhere.³⁸

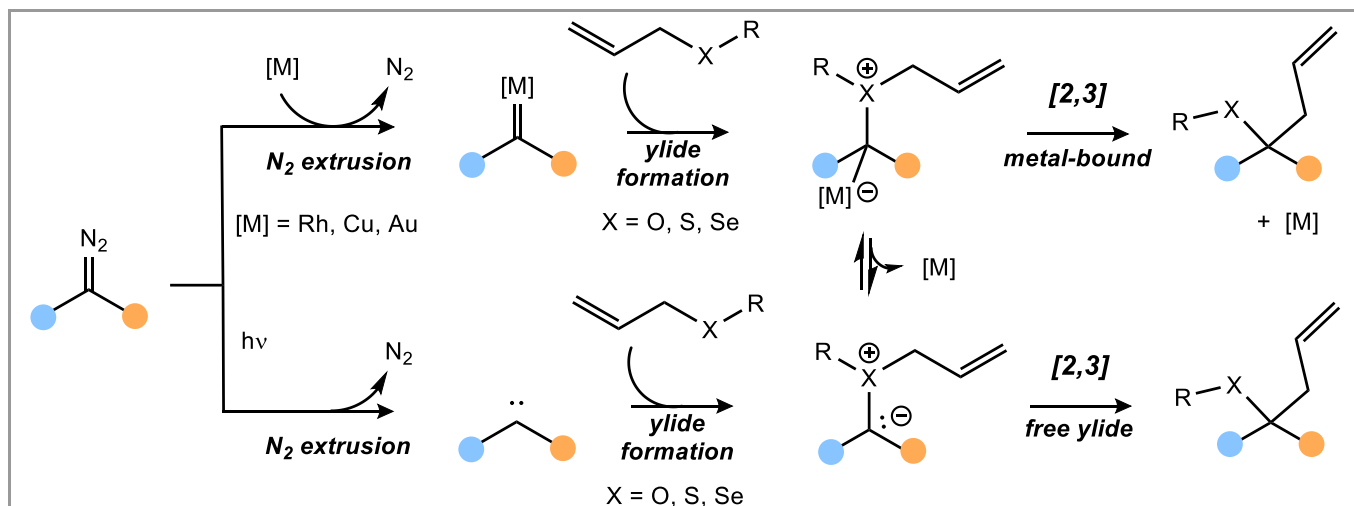


Figure 1. Ylide [2,3]-sigmatropic rearrangements via carbene transfer.

Many mechanistic aspects of metal-promoted rearrangements are not well-understood. For instance, though these reactions often are employed in a stereoselective manner, the origin of enantioselectivity is not always apparent.^{3,39} In addition, it is sometimes unclear which steps in the path to products actually involve a covalently bound metal.^{3,40,41} Freeing such details from the shadows presents an opportunity for discovery.

Experiment and theory provide approaches to studying mechanisms that are often carried out separately or in parallel.⁴² However, as we will discuss later, there are benefits from their intertwining.⁴³ Experimental studies frequently involve control experiments without metals present, competition experiments, and kinetic profiling. Computational studies generally involve applying quantum chemical calculations to glean structural and energetic information about relevant reaction intermediates and transition-state structures (TSSs). In some cases, this information is augmented by analyses of noncovalent interactions and dynamic effects.^{44–49}

The goals of this review are to summarize state-of-the-art computational methods, provide caveats for their application, and highlight studies in which these were combined with laboratory experiments to provide greater insights. We begin with (1) general comments on mechanistic models. We then provide (2) a survey of general approaches and caveats, which includes discussion of density functional theory (DFT) methods, basis sets, conformational analysis, and solvation models. Then, (3) we discuss examples in the literature where experiment and theory both supplied mechanistic details about sigmatropic rearrangements involving metal carbenes. Finally, (4) we conclude with an outlook on the current state of the field, asking what questions remain unanswered and how theory and experiment can be merged more seamlessly.

1. Mechanistic Models

A reaction mechanism is a *model* that describes how reactants are transformed to products (expressed in an arrow-pushing scheme, a potential energy surface (PES) picture, a collection of molecular dynamics trajectories, etc.).⁵⁰ A *plausible* reaction mechanism is one with which all sets of valid experimental and

computational evidence are consistent. Of course, the *validity* of pieces of evidence can be debated. However, if one discounts a piece of evidence in presenting a mechanistic model, the argument for doing so should be clearly stated. In that a mechanism is a model, it *cannot* be proven.^{51–54} Rather, the best one can do is sift through the multitude of possible mechanistic models that fit the available data, clearly define criteria for ranking them (or not), and propose future tests (experimental or computational) that can lead to model refinement.⁵⁵ After interrogating and refuting hypotheses, one often generates enough confidence in a mechanism to consider it ‘valid’ or ‘accepted,’ which it remains until demonstrated otherwise, a notion stemming from, but not exactly aligned with, the ideas described by the philosopher Karl Popper.^{56,57} But one must not become too invested in an accepted model, for it could be invalidated by future tests. As Richard Feynman famously stated, “...you must not fool yourself and you are the easiest person to fool.”⁵⁸ In the words of astronomer John Gribbin, “the best that can be said is that it [the model] has passed all the tests applied so far.”^{59,60} Of course, a mechanism need not be proven to be useful.⁶¹

Here we focus on computational studies that provide evidence in support of or against a given reaction mechanism. Modeling mechanisms of complex reactions by quantum chemical calculations is now commonplace;^{42,62,63} however, we are aware of (and agree with) the notion from philosophers of science that explanations of organic phenomena, as described by organic theory, simply cannot be reducible (in the philosophical sense) to quantum mechanics alone.⁶⁴

The first step of the modeling process in this context generally involves the application of computational methods to assess the energetic viability of an arrow-pushing mechanism (hypothesized based on existing experimental evidence) by computing relevant structures (reactants, intermediates, products, and the TSSs connecting them) on a PES. The postulated mechanism is consistent with the calculations if computed barriers are low enough that the associated rate would be fast enough under the experimental conditions (based on the Eyring equation), in need of revision if computed barriers are much too high, or in need of a deeper dive if computed barriers are borderline, i.e., at the high end or just beyond the

range of barriers that are reasonable. This process is iterated until a mechanism is found for which all computed barriers are reasonable and that can account for any side products.⁶⁵ A ‘good’ computed energy profile,⁶⁶ therefore, aims to provide a productive and portable model⁶¹ that (i) predicts a reaction mechanism that aligns with laboratory observations, (ii) provides otherwise elusive insight, and (iii) allows new hypotheses to be generated that can be tested in subsequent experiments.⁶⁷ As Plata and Singleton have noted, the “primordial currency of information provided by computational studies consists of the geometries and energies of intermediates and transition states along the mechanism.”⁶⁸ Thus, rigorously scrutinizing theory’s performance against experiment is crucial.⁶⁹ For more in-depth discussion of models in chemistry and what makes a good energy profile, we recommend the work of Eisenstein and coworkers.⁶⁶

2. Theoretical Approaches and Caveats

We discuss some general principles for applying computational chemistry to metal-promoted sigmatropic shifts below, but for thorough tutorials on the nuances involved in modeling organometallic reactions, including nontrivial mistakes, misconceptions, and misinterpretations, we recommend the work of Baik, Peverati, Lan and coworkers.^{70–72}

Recommended computational tools

With the advent of high-performance computing hardware and development of user-friendly quantum chemistry software, the relationship between computation and experiment has strengthened.^{73,74} Density functional theory (DFT) is currently the standard method of choice for interrogating the mechanisms on which we focus here. Unlike wavefunction theory (WFT) methods, which can be much more computationally demanding, DFT approaches solving electronic structure problems in terms of the electron density rather than the wavefunction (although wavefunction-based algorithms are generally used).^{75,76} The choice of DFT methods is generally a practical one; systems of the size (number of electrons) of interest here generally cannot be modeled in a reasonable amount of time with currently-available post-Hartree-Fock WFT methods.^{39–45} Much has been written on what recipe of functional and basis set is best to achieve “chemical accuracy” (<1 kcal mol⁻¹) for particular types of organometallic reactions, and we recommend several recent reviews for a more in-depth discussion on this topic.^{63,71,81,82} We provide several examples below that highlight the importance of (a) knowing which functionals and basis sets have been validated for particular metals (here, mainly Rh, Cu, and Au) undergoing particular types of reactions (e.g., closed shell versus open shell processes), (b) which functionals and basis sets are affordable but sufficient for addressing conformational complexity and variability of ligand arrangements, and (c) which models of solvation, both implicit and explicit, are appropriate for answering the mechanistic questions at hand.

Choice of functional and basis set

Choosing a reasonable functional and basis set (i.e., level of theory) for any mechanistic study can be a daunting task, especially when there is a ‘zoo’ of functionals from which to choose and the size of basis sets can be crucial to achieving accuracy.^{83,84} Choosing a level of theory then becomes a balancing act between achieving the accuracy required for the particular question at hand and the associated computational cost. One challenge in choosing a level of theory for organometallic reactions is the lack of experimentally-determined rates and concomitant Gibbs free energy barriers, which enable the benchmarking required to accurately deduce an appropriate level of theory.⁶⁶

What combination of functional and basis set do we recommend for metal-promoted [2,3]-sigmatropic shifts? The short, admittedly unsatisfying, answer is *it depends*.⁶³ The chosen level of theory is system-dependent and we recommend that new practitioners consult the review by Schoenebeck and coworkers for more in-depth discussion.⁶³

Nevertheless, we do recommend a few starting points for reactions promoted by dirhodium tetracarboxylates, which constitute the bulk of the reactions described here. Some DFT methods we and others^{62,63,66,73} have found useful include ω B97X-D,⁸⁵ B3LYP-D3, B3LYP,⁸⁶ MN15,⁸⁷ PW6B95-D3,⁸⁸ and M06.⁸⁹ It is now common to use density functionals with a dispersion correction (e.g., DFT-D3 such as B3LYP-D3)⁹⁰ to account for medium- and long-range London dispersion (LD) forces—LD is the attractive term in the van der Waals equation and has been shown to be critical in many reactions, but ‘unduly underestimated’.^{45,91} Indeed, some groups have exploited LD interactions to fine-tune the design of new heterobimetallic paddlewheel complexes, showcasing the importance of LD as a design element in the development (and computational modeling) of new catalysts.^{92,93}

For basis sets to use when optimizing geometries, we have had success using double- ζ basis sets like Ahlrich’s def2 basis sets (e.g., def2-SVP⁹⁴) or a double- ζ Pople basis set for non-metals (e.g., 6-31+G(d,p)) plus an effective core potential (ECP) for the transition metals (e.g., SDD⁹⁵ or LANL2DZ⁹⁶—we note that LANL2DZ lacks polarization functions but can be added on for certain atoms⁹⁷). Energies can then be reevaluated through single-point calculations with a larger basis set, such as def2-TZVPP or 6-311+G(d,p) (with SDD for the transition metal). Single-point calculations are those in which the nuclear configuration is kept fixed, but the electronic wavefunction is reevaluated to obtain energies. These types of calculations are used to accurately compute the electronic energy of the system with a larger, more flexible basis set. Generally, coupled cluster methods like CCSD(T) are preferable for SP calculations when the system of interest is small enough (e.g., organic molecules), but for the reactions of interest here, such high-level WFT-based methods are not currently feasible. Moreover, some have advised using single-reference post-HF methods with caution when applied to bond breaking and forming transformations involving transition metals.⁹⁸ It is worth noting that a much more cost-effective alternative, domain-based local pair natural orbital CCSD(T) (DLPNO-CCSD(T)), has been shown to yield results that have accuracy close to CCSD(T) at a much lower computational cost.⁹⁹

Several caveats are in order regarding basis sets. First, basis set superposition error (BSSE) is attributed to an overestimation of the strengths of intermolecular interactions and thus overestimation of the binding energy between two fragments when small basis sets are used. This can lead, for example, to problems in predicting metal-ligand or metal-substrate binding energies. Second, basis set incompleteness error (BSIE) results from all fragments not having large enough basis sets composed of appropriate types of basis functions, i.e., not providing results near the complete basis set (CBS) limit.⁹⁵ We recommend the tutorial review by Morgante and Peverati, and references therein, for a deeper dive into the sources of these errors and ways to remedy them.⁷⁰ In short, however, larger basis sets are usually better, although that is not guaranteed for DFT calculations. It is also generally better to include diffuse basis functions (important for anions and systems with long-range non-covalent interactions) and/or polarization basis functions—which give molecular orbitals the potential for a larger spatial “spread” from the nuclei and increased “flexibility”, respectively—when quantitative agreement with experiment is necessary and doing so is cost-effective.^{101,102} However, one should be cautious in adding these to smaller basis sets (e.g., double- ζ basis sets).¹⁰¹ Third, an ‘ultrafine’ integration grid, (e.g., (99,590) grid at minimum), is recommended, as smaller grids may introduce considerable errors in computed free energies.¹⁰³ This grid size is the default grid in commonly used software,¹⁰⁴ but it is prudent to check for one’s software of choice. These caveats being mentioned, we would like to re-emphasize that the choice of theoretical method should be rooted in studies (previously reported or carried out during a mechanistic study) in which computational methods are benchmarked against experimental data or, if such data does not exist, against results from higher level theoretical methods.⁷⁴

Some metal-carbene reactions may require consideration of electronic states beyond closed shell singlet states—i.e., all electrons paired—in which case, open shell electronic structure calculations become (radically) important.^{105,106} DFT methods, however, can still be useful if results are viewed with appropriate caution, e.g., consideration of whether reactivity comes from separate electronic states (DFT is likely okay) or relevant electronic states have multireference character (DFT is not okay).^{98,105,107–109} A collaborative experimental and theoretical study of Rh-catalyzed oxonium ylide formation/[2,3]-rearrangement is a good case in point: Davies and coworkers discovered in their computations that an intermediate directly following the [2,3]-rearrangement transition state revealed other electronic states (closed-, open-shell singlet and triplet states) all within energies close to each other.³³ In other words, it gets electronically complicated after ylide formation and the [2,3]-rearrangement occurs, and as the authors point out, requires multideterminant calculations for a full picture of the energetic landscape. Without employing these methods, however, they came up with a simplified model, which revealed that these states cross near the intermediate region on the PES, which indicates that the [2,3]-rearrangement is more “reactant-like” and spared any radical character. These computational results helped rationalized some of their experimental results.

For the radical-inclined, we recommend the element Fe. Systems involving Fe are infamously challenging to model given the complexity introduced by different spin states. Though this has for many years encouraged theoreticians to avoid Fe, some have admirably taken the plunge.^{110,111} Take, for example, the importance of open-shell species in iron-containing systems, which has been crucial in studies of iron porphyrin (heme) carbenes, a source of lively debate. Here, DFT methods are still the method of choice.^{112,113} For advice on properly modeling such systems, we direct the reader to recent reviews.^{113–115}

Conformations and ligand binding modes

One significant challenge to overcome in modeling most reactions is ensuring that the conformational space available on the hyperdimensional potential energy surface ($3N-6$ dimensions for non-linear systems, N = number of atoms) is appropriately sampled. For example, Zimmerman and coworkers investigated the effects of conformational flexibility on reaction rates for reductive elimination of representative nickel bisphosphine catalysts (Figure 2).¹¹⁶ They found that the barriers for reductive eliminations varied significantly between conformations, providing an important caveat for those working in this field. Low-cost computational methods, such as Grimme’s CREST, have proven effective for rapid conformational searching.¹¹⁷ In organometallic chemistry, complexity arises not only from ligands being large and “floppy” but also from ligand-metal binding modes sometimes not being static. In addition, it is important to determine whether multiple conformations of TSSs are close enough in energy to contribute to predicted rates, i.e., TSS conformations within 2-3 kcal/mol of the lowest energy TSS conformation should be accounted for by Boltzmann averaging. For example, the groups of Takacs and Liu—in a joint experimental and theoretical effort—demonstrated the critical role of conformationally flexible TADDOL-derived phosphite ligands on reactivity and selectivity in Rh-catalyzed asymmetric hydroboration, highlighting the importance of conformational issues for catalyst/ligand design.¹¹⁸

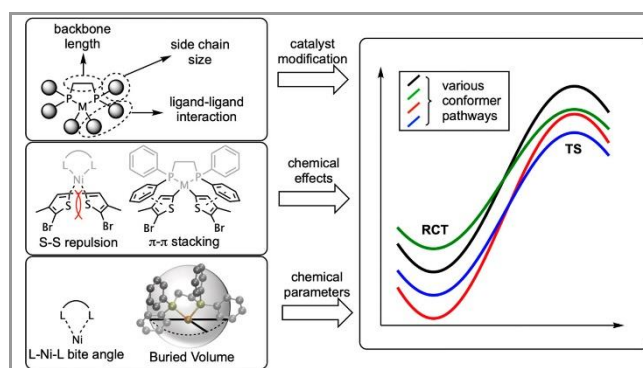


Figure 2. Various effects on catalyst ligands that can influence conformer space and the energetically preferred mechanistic pathway. Adapted with permission from Vitek, A. K.; Zimmerman, P. M.; Jugovic, T. M. E. *ACS Catal.* **2020**, *10*, 7136–7145. Copyright 2020 American Chemical Society.

A representative example relevant to metal-promoted [2,3]-sigmatropic shifts involves the use of chiral dirhodium tetracarboxylate paddlewheel (and related) catalysts. In general, chiral ligands in this field are quite large, so ligand conformations can become important.^{119–121} For instance, ligand

blocking groups around the metal dimer catalyst core can adopt either up (α) or down (β) configurations leading to multiple arrangements (Figure 3) that should be considered.¹²⁰ And the ligands in each of these arrangements may be able to adopt several different conformations. Similar issues have been described for 4-fold symmetric iron complexes used for CO₂ and O₂ reduction.^{122,123}

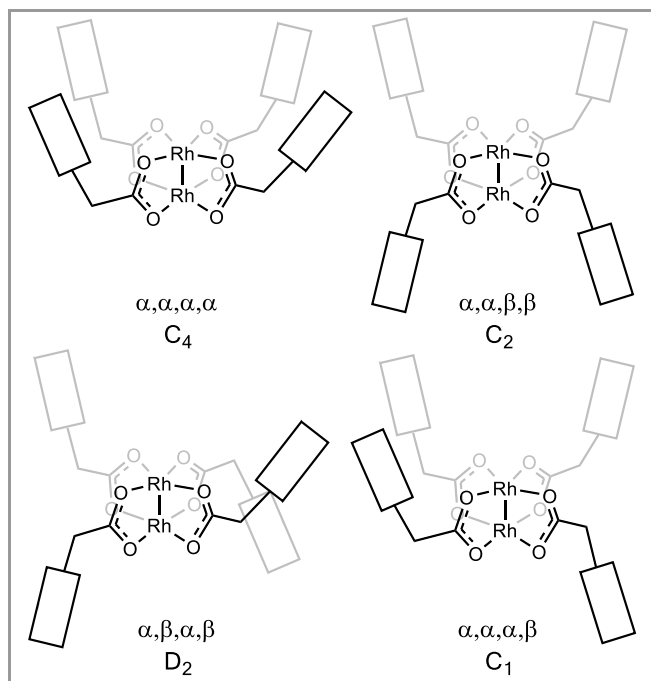


Figure 3. Different possible ligand arrangements for chiral dirhodium(II)

catalysts and their associated point groups (assuming chiral ligands).

One approach to avoiding the problem of conformational complexity is to carry out calculations using small, inflexible ligands, e.g., formate groups, acetate groups or truncated chiral ligands. While this approach is often reasonable, one must be exceedingly cautious when employing it to assure that important substrate–ligand interactions are not missed. For instance, Hamada and Nemoto found changes in product distributions upon simply changing the ligand type in their dirhodium(II) catalysts from Rh₂(NHCO^tBu)₄ to Rh₂(NHCOMe)₄ to Rh₂(OCOMe)₄ in a Rh-catalyzed carbene insertion into C–N bonds (Figure 4).¹²⁴

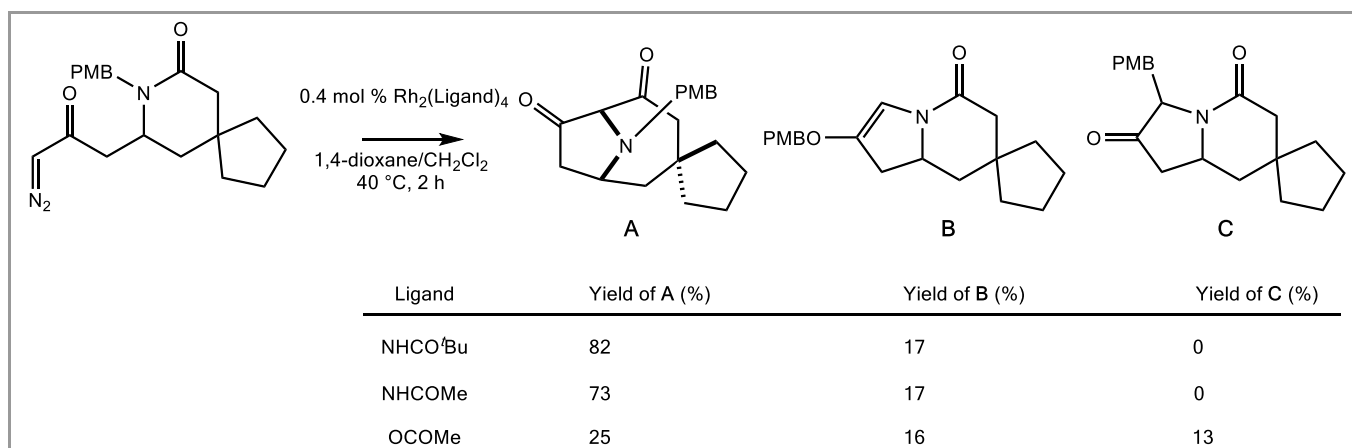


Figure 4. Mechanistic experiment on ligand effects in Rh-catalyzed formal insertion into amide C–N bonds. The yield of A, B, and C are dependent on ligand type. Figure adapted from on Hamada and Nemoto.¹²⁴

Solvation

Accurately modeling the effects of solvent on reactivity has been a longstanding challenge. As we learn more about the ways in which different solvent models can impact computed energies—which inform theoretical predictions/conclusions—the clearer it becomes that treating solvent accurately can make all the difference, especially in cases where the number of components involved is large or interactions with solvent molecules are potentially strong.^{68,125} As Eisenstein and coworkers describe, there are three general approaches to modeling solvent, which vary in computational

cost: (1) implicit (continuum) solvent models, (2) hybrid models of explicit and implicit solvent (sometimes called “hybrid cluster-continuum models” or “microsolvation”), and (3) explicit solvent models.⁶⁶ Indeed, solvent effects can be drastically important in adequately modeling metal-catalyzed rearrangements; for instance, the Koenigs group discovered a dependence of [1,2]- or [2,3]-sigmatropic rearrangement product yields depending on the solvent in Rh-catalyzed rearrangement reactions.¹²⁶ The origin of this solvent-dependence is still unknown.

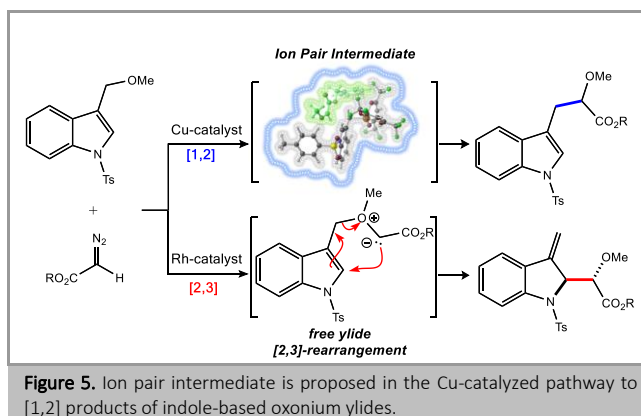
By far, the least computationally intensive approach, and most widely used today, is the implicit approach. In this crude but useful method to model solvent, the solute is placed within a solvent cavity described by a continuum with a fixed dielectric constant. Practitioners have a choice of different implicit solvent models.¹²⁷ Frequently used ones include density-based models (SMD)¹²⁸ and polarizable continuum models (PCM).¹²⁹ As with the choice of level of theory, we caution against haphazardly selecting an implicit solvent model to use. Rather, these solvent models should be applied with the caveat that many were parameterized for particular atomic radii and nonelectrostatic terms. Some solvent models were developed specifically for use with certain functionals and many continuum solvent models are parameterized for reactions occurring at 298 K.^{130,131} In general, we recommend comparing computed reaction barriers against experiment (e.g., rates, activation parameters, selectivity) with various models, but it is prudent to make sure that the results are not highly sensitive to the model chosen – that could be a sign of problems with the mechanism, not just the solvation model. If experimental data is lacking for a given reaction, basing the model selection on past benchmarking studies is the next best thing.^{87,98}

In some cases, including explicit solvent molecules may be critical to reproduce experimental observations.^{50,132} Computing the properties of solutes in a large box of explicit solvent molecules, however, is often not feasible (which is the case for many of the reactions discussed here). In cases where a full statistical treatment of solvent is absolutely necessary, however, such as those in which solvent-solute interactions or solvent reorganization is critical to the mechanism, *ab initio* molecular dynamics (AIMD) methods, in which solvent molecules are treated with quantum chemistry (often semiempirical methods, but ideally with a method as reliable as that used for the solute), can be used.^{132–135}

In lieu of modeling a box of explicit solvent, one might be able to capture explicit solvent effects with the microsolvation approach. In this approach, only a few explicit solvent molecules around the solute are used within an implicit model for the remainder of the solvent.¹²⁵ This approach may be useful in reactions where ionic or zwitterionic species dominate, whose relative energies are not expected to be computed accurately with implicit models.¹²⁵ The microsolvation approach is viewed by some (including us) as a last resort effort when the options for accounting for solvent are otherwise exhausted (or computationally intractable), because many systems are adequately modeled in implicit solvent¹²⁵ and adequately sampling configurations of explicit solvent molecules is a daunting (and frequently neglected) task.^{62,70} Preliminary evidence from our work indicates that including explicit solvent at the presumably vacant axial position of dirhodium complexes can modulate reactivity of dirhodium tetracarboxylates, which aligns with a number of experimental studies that show that axial coordination can influence electronic communication between the two Rh atoms in these complexes.^{136–140} In this case, however, the question to be addressed with microsolvation was well-defined; it was specific to a particular position where solvent could bind. Any electron donor (including reactants) could, in principle, coordinate the vacant, axial coordination site of dirhodium complexes, which may (or may not) have a non-negligible effect on reaction

barriers.¹⁴¹ Considering nuances like these often shed light on particular gray areas of complex mechanisms.

A particularly problematic situation arises when ion pair intermediates occur along a reaction pathway. For instance, in a collaborative experimental and theoretical study with the Tambar group on tandem ylide-formation/rearrangement reactions promoted by Rh and Cu, we proposed a mechanism based on results of DFT calculations (IEFPCM(DCM)-UB3LYP-D3(BJ)/SDD[6-31+G(d,p)]//IEFPCM(DCM)-UB3LYP/LANL2DZ[6-31G(d)]) involving an ion pair intermediate along the pathway to the product (Figure 5).¹⁴² It is known that ion pair intermediates (e.g., in carbocation reactions) can be formed and react before surrounding solvent equilibrates, necessitating explicit solvent modeling to account for dynamics.¹⁴³ In our case, such modeling was not possible, so we resorted to simply proposing a reactivity model consistent with experiments and shored up by structural comparisons. We hope, however, that explicit solvent modeling of the accuracy we would need will become accessible in the future.



3. Synergy of Experiment and Theory – Case Studies

Computational studies on reactions involving transition-metal catalysts have evolved alongside synthetic methodologies, providing useful insight into mechanisms. For instance, a substantial amount of mechanistic insight has been generated by studies involving close collaboration between groups specializing theory and experiment: ranging from C–H^{144–147} and Si–H insertion,^{148,149} cyclopropanation,^{145,150–153} and mapping catalyst space.¹⁵⁴ In this section, we review representative mechanistic studies of metal (mainly Rh and Cu)-catalyzed sigmatropic rearrangement reactions that have benefitted from attention from both experiment and theory camps.

Metal-bound or free ylides?

First, we focus our attention on whether metal catalysts remain bound to substrates for [2,3]-sigmatropic rearrangements catalyzed by Rh(II) and Cu(I) catalysts. Later, we will discuss [1,2]-sigmatropic rearrangements.

Though many experimental groups have developed and are developing methodology for transition-metal promoted [2,3]-sigmatropic rearrangements, and, in doing so, have carried out control experiments that bear on mechanism, computational work has lagged behind.^{38,40,155–157} A key question that emerged

from experiment—that is still not definitively clear for many onium ylides formed by Rh(II) and Cu(I) catalysts by carbene transfer—is whether the metal catalyst remains explicitly bound to its substrate during the [2,3]-rearrangement step. The dearth of theoretical insight into this question was brought to our attention *via* recent appeals for theoretical insight in the work of Koenigs and coworkers and through our collaborative work with the Driver, May, Shaw, and Tambar groups.^{142,158,159} Hock and Koenigs have stated, “it would still be very helpful if these experimental findings could be further supported by DFT calculations to improve our understanding of the subtle differences between these rearrangement reactions.”⁴⁰ We took up this call to action.

What sort of experimental evidence was available for us to use in shaping our study? In control experiments where the metal catalyst is varied and all else is kept that same, if stereo-, chemo-, and regioselectivity are unperturbed, then a plausible explanation is that a free ylide is involved. For instance, whereas Clark and Hansen¹⁵⁵ observed a catalyst-dependence on product ratio in their study of metal-catalyzed ylide [2,3]-rearrangements, which led to the conclusion that metal-bound ylides were involved, studies by the groups of Wang¹⁵⁶ and Koenigs¹⁶⁰ reported catalyst-independence on the product ratio for their ylide rearrangement reactions, suggesting the existence of free ylides.

By delving into such previously-published experimental studies, we set out to (1) confirm that our theoretical approaches could provide results consistent with experiments and (2) determine the physical factors that impact whether metal-catalyst remains bound during the rearrangement step, thereby setting the stage for future reaction design.⁴¹ In the four reactions examined, three with Rh and one with Au, we found that our calculations supported the conclusions from control experiments. Here, we utilized the (U)B3LYP/LANL2DZ[6-31G(d)] level of theory to investigate

the mechanism (single-point calculations with dispersion correction and with other functionals produced qualitatively similar results). From this study we concluded that the steric bulk adjacent to the carbene center played the most significant role in determining whether a metal catalyst dissociated or remained bound to the ylide intermediate.

Almost simultaneously, Dang and coworkers published a related computational study (SMD(DCM)-M06-L/SDD[6-311++G(d,p)]//M06-L/SDD[6-31G(d)]). They found that allylic iodides and sulfides can form ylides in the presence of Cu(I)-bisoxazoline catalysts that can either undergo a metal-bound or free ylide rearrangement (Figure 6).¹⁶¹ In particular, iodonium ylides¹⁶² were shown to have Cu bound during the [2,3]-rearrangement while sulfonium ylides rearranged free of Cu catalyst. By computing systems with different substrates, ligands, and solvents, they ascribed this difference to the (thermodynamic) stability of metal-bound and free ylides, which, they suggest, is mainly controlled by the heteroatoms (I or S).¹⁶¹

In discussing the nature of the oxonium, sulfonium, and selenonium ylides in our study—wherein we found metal-bound oxonium ylides and free sulfonium and selenonium ylides—we made the point that our conclusions “should not be generalized to all similar ylides undergoing [2,3]-rearrangements.”⁴¹ The work by Dang’s group bolsters our observation that the nature of the ylide is system-dependent. Enabled by the work done by experimental (and other computational) groups, we seem to have converged on two key factors that determine whether an ylide intermediate is free or metal-bound: (1) steric bulk directly attached to the carbene carbon⁴¹ and, (2) the electronic nature of the heteroatom directly bound to the carbene carbon.¹⁶¹

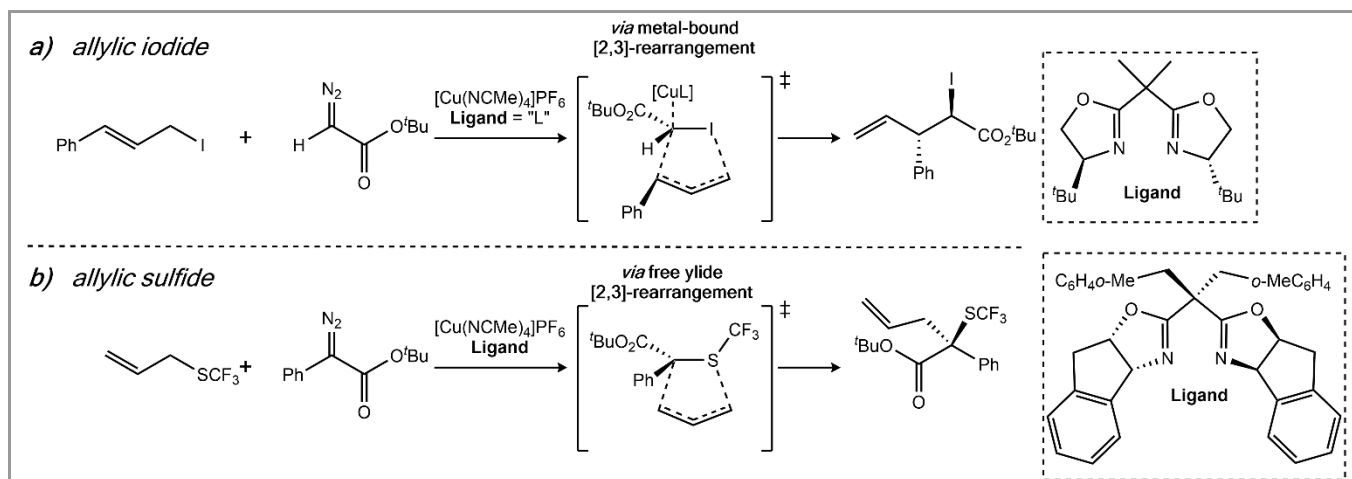


Figure 6. Metal-bound and free ylide [2,3]-sigmatropic rearrangements of iodonium and sulfonium ylides supported by DFT calculations. Existence of a free sulfonium ylide and metal-bound iodonium ylide undergoing the [2,3]-sigmatropic rearrangement has implications for experiment. See Liu, Z.; Jin, X.; Dang, Y. *ACS Catal.* 2021, 11 (2), 691–702.

Metal dissociation before the end of a catalytic cycle may be more general. For instance, Schomaker, Fernández and coworkers reported an aziridinium ylide-formation/[2,3]-rearrangement reaction to form azetidines that appears to involve a free ylide intermediate.^{163,164} As a result of joint

experimental and computational efforts (SMD(DCM)-B3LYP-D3/def2-SVP), the authors revealed not only that a free ylide is energetically favorable over a Rh-bound ylide, but also that the stereospecificity (enantioselectivity and high

diastereoselectivity) of this reaction can be attributed to a concerted [2,3]-sigmatropic rearrangement (Figure 7).¹⁶⁴

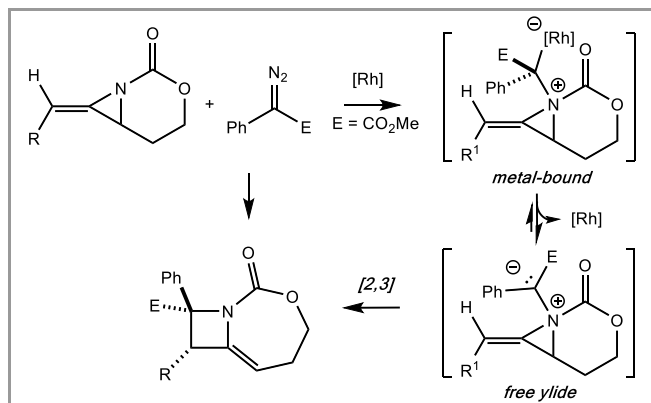


Figure 7. A free aziridinium ylide intermediate is predicted to be operative in a concerted [2,3]-rearrangement to azetidines.

Another recent study by Koenigs and coworkers, in which theory and experiment were combined, led to the conclusion that free ylides are operative in [2,3]-sigmatropic rearrangements of organoselenium compounds with triazoles in the presence of dirhodium catalysts.¹⁴¹

Premature catalyst dissociation might afflict ylides undergoing [1,2]-rearrangements (or Stevens rearrangements for ammonium ylides) as well.^{32,165–167} For instance, in stereoselective C–H insertions with $\text{Rh}_2(\text{R-PTAD})_4$ catalysts, forming six-membered ring tetrahydroisoquinolines with high diastereo- and enantioselectivity, Shaw and coworkers observed no [1,2]-rearrangement side products.¹⁵⁹ In one case, however, they observed a rearrangement product and initiated a collaboration with our group to confirm that this was indeed the case (Figure 8). Our calculations ((U)B3LYP/LANL2DZ[6-31G(d)]) revealed that the Rh-catalyst (modeled as $\text{Rh}_2(\text{OAc})_4$) dissociated before the [1,2]-rearrangement step. Synergy between theory and experiment, again, illuminated mechanistic detail that might not have been revealed otherwise. These results echo past computational studies by our group, in collaboration with Driver and coworkers, on Rh-promoted indole formation from vinyl/azidoarenes that involved competing [1,5]-shifts.¹⁵⁸ For that reaction, our DFT calculations ((U)M06/SDD[6-31+G(d,p)]) led us to conclude that the Rh catalyst was not necessarily involved in the rearrangement step, since computations without Rh bound corresponded to the experimentally observed selectivity while those with Rh bound did not.

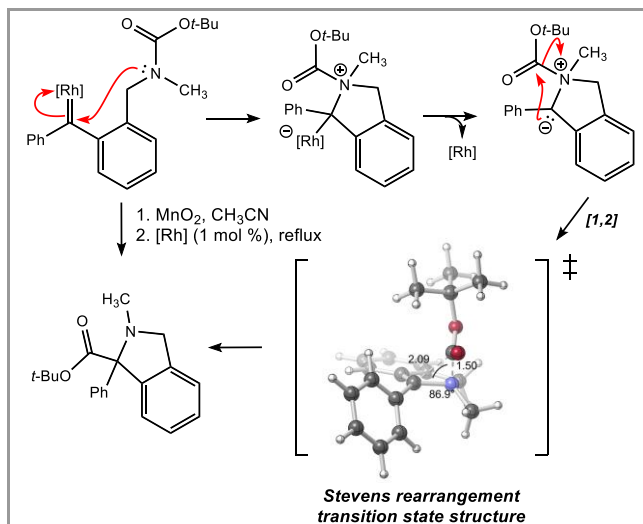


Figure 8. Isoindoline product is formed by ylide-formation/Stevens [1,2]-rearrangement in the presence of Rh catalyst. DFT calculations support a free ylide Stevens [1,2]-rearrangement.

While these computational studies do not cover all types of metal-catalyzed sigmatropic rearrangements, they do point to potentially general principles. And while they vary in the degree of integration between the computational and experimental teams, they show that combining results from both sides can shine light on mechanistic nuances.

Conformations and ligand binding modes of paddlewheel complexes

As mentioned above, ligand binding modes and conformations in chiral dirhodium tetracarboxylate complexes can have important effects on reactivity and selectivity. In a study that reported the crystal structure and computed structure of one such paddlewheel complex, $\text{Rh}_2(\text{S-PTTL})_4$, Fox and co-workers described the so-called “chiral crown” conformation ($\alpha,\alpha,\alpha,\alpha$) (Figure 9). They found that $\text{Rh}_2(\text{S-PTTL})_4$ crystallized in this arrangement, consistent with the computed lowest-energy form found by DFT calculations (OLYP/TZP).¹⁶⁸ By elucidating the preferred structure of this complex, they were able to pin specific structural features to chemo-, enantio-, and diastereoselectivity of intermolecular cyclopropanation reactions involving $\text{Rh}_2(\text{S-PTTL})_4$. A similar chiral crown conformation was discovered for $\text{Rh}_2(\text{S-NTTL})_4$.¹⁶⁹ Subsequent X-ray crystallography and computational studies demonstrated that these chiral crown forms are more general for *tert*-leucine-derived dirhodium paddlewheel complexes,¹⁷⁰ results with implications for the use of these (and potentially other related catalysts) in other reactions, such as [2,3]-sigmatropic shifts.

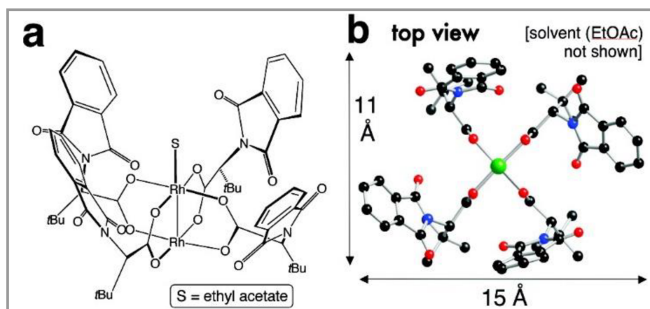


Figure 9. Chiral crown conformation of $\text{Rh}_2(\text{S-PTTL})_4$. Adapted with permission from DeAngelis, A.; Dmitrenko, O.; Yap, G. P. A.; Fox, J. M. J. Am. Chem. Soc. 2009, 131 (21), 7230–7231. Copyright 2009 American Chemical Society.

No metal, just light

One study by the groups of Koenigs and Xu further highlights the synergy between theory and experiment: their study revealed interesting diastereoselectivity differences between oxetane and thietane starting materials (Figure 10).¹⁷¹ Presumably, after extrusion of nitrogen and carbene formation, a free ylide is generated, which undergoes [1,2]-rearrangement. The origin of observed differences in diastereoselectivity was investigated by DFT calculations (SMD(CHCl_3)-(U)B3LYP/6-

311+G(d,p)//SMD(CHCl_3)-(U)B3LYP/6-31G(d)), which revealed a diradical pathway for both oxetane and thietane derived ylides. The differences in diastereoselectivity were not attributed to divergent reaction mechanisms, but differences in critical C-O and C-S bond lengths in TSSs (Figure 11). One wonders, in the thietane ylides, if this type of reactivity could be controlled by chiral metal catalysts and enable asymmetric reactions using them.

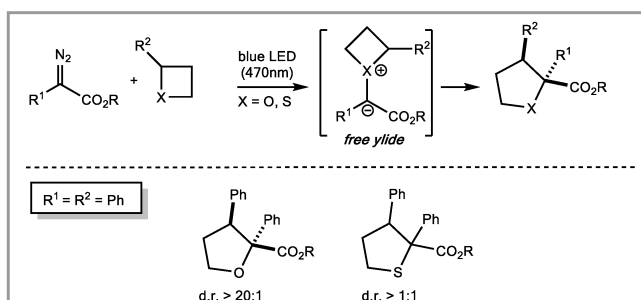


Figure 10. Erosion of diastereoselectivity in sulfonium ylides compared to oxonium ylides.

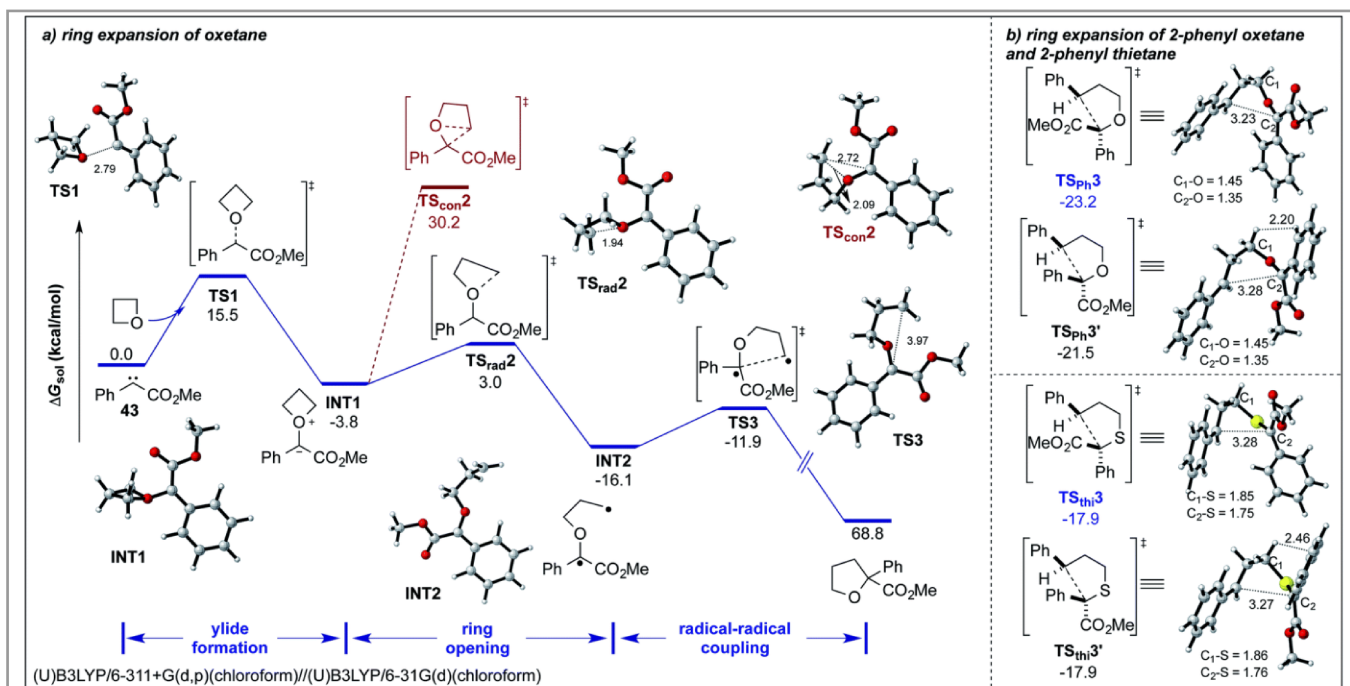


Figure 11. Energy surface for oxetane ring expansion by photochemical carbene transfer. Density functional theory calculations reveal diradical mechanistic pathway to ring expansion product. Adapted with permission from the Royal Society of Chemistry, Copyright 2019. S. Jana, Z. Yang, C. Pei, X. Xu and Rene M. Koenigs, Chem. Sci., 2019, 10, 10129. DOI: 10.1039/C9SC04069B. Published by The Royal Society of Chemistry.

How to 'Cope' with nonstatistical dynamic effects

Similar to ylide-formation/[2,3]-rearrangements, C-H activation/Cope rearrangements ([3,3]-sigmatropic shifts)^{172,173} can be promoted by dirhodium catalysts.¹⁷⁴ Davies and coworkers, for example, reported a joint experimental and theoretical study in which the mechanisms of these cascade processes were interrogated (Figure 12).¹⁷⁵ Results from DFT calculations (B3LYP/6-311+G(2d,2p)[Rh-RSC+4f]/B3LYP/6-31G(d)[Rh-RSC+4f]) support a pathway involving a concerted, yet highly asynchronous, hydride-transfer/C-C bond-forming process in which a post-transition state bifurcation (PTSB) is

involved. Reactions that contain PTSBs involve a single (ambimodal) transition-state structure on the potential energy surface that leads to two products without intervening minima—a fork in the pathway downhill in energy toward the products.^{49,176–178} Here, the ambimodal transition-state structure corresponded to the hydride-transfer process and the two products were related by a Cope rearrangement.

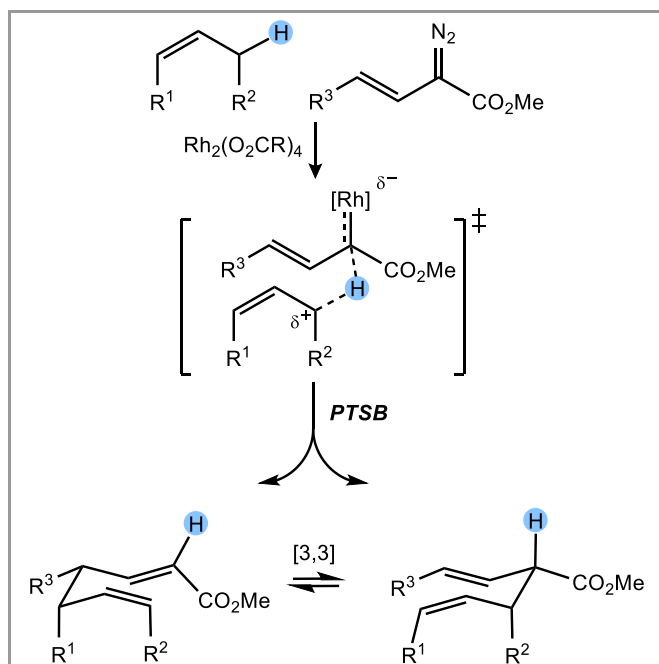


Figure 12. Post-transition state bifurcation is suggested in C-H activation/Cope rearrangement reaction by Davies and coworkers. If a PTSB exists, then nonstatistical dynamic effects determine product selectivity.

To predict product ratios for reactions with PTSBs, one generally needs to carry out AIMD simulations. Our group did this for a related $\text{Rh}_2(\text{OAc})_4$ -promoted reaction involving a transition state for hydride transfer to a Rh-carbene that we found (using B3LYP/LANL2DZ[6-31G(d)] calculations) to be connected to both β -lactone and ketene/ketone products – the former arising from net C–H insertion and the latter from fragmentation (Figure 13).¹⁷⁹ Using AIMD simulations, we predicted that fragmentation should be preferred over the desired C–H insertion process, consistent with experimental results reported by Lee.¹⁸⁰ This study demonstrated that computational exploration of a reaction mechanism can lead to the proposal that unwanted side products might arise from PTSBs.^{165,179,181} Still, much has yet to be learned. Recent strides have been made in constructing bifurcating energy surfaces,¹⁸² predicting major products of PTSBs without elaborate simulations,^{183,184} and mapping reaction pathways in phase space.¹⁸⁵

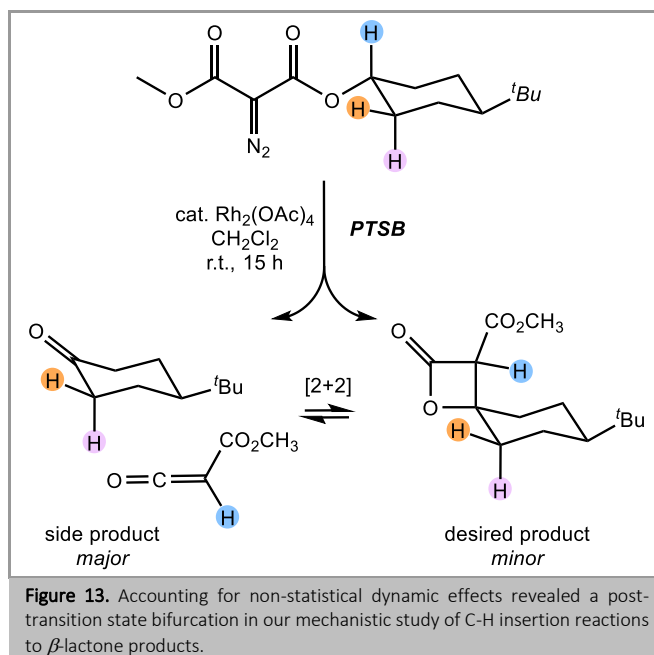


Figure 13. Accounting for non-statistical dynamic effects revealed a post-transition state bifurcation in our mechanistic study of C–H insertion reactions to β -lactone products.

4. Outlook

Electronic structure calculations are now ubiquitous in mechanistic chemistry due to significant leaps in modern computational power and reductions in barriers to entry for learning quantum chemistry software.^{186,187} In this review, we have merely touched the tip of the iceberg when it comes to applied computational approaches for solving complex mechanistic problems. For example, some are utilizing statistical tools to generate catalyst maps for dirhodium(II)¹⁵⁴ (and other) complexes to aid catalyst selection/design.^{188,189} Others are harnessing the power of machine learning methods for accelerated reaction discovery and chemical space exploration.^{190–192} Nonetheless, we hope that we have given readers a snapshot of the utility of computational approaches through tales of transition-metal catalyzed sigmatropic rearrangements. We also hope that the caveats we describe are taken to heart. Both theory and experiment bring powerful insight to the table in designing reactions. The future of both fields seems bright, but the future when theory and experiment work together seems even brighter.

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Biosketches

 A portrait of Croix J. Laconsay, a young man with short dark hair, smiling. He is wearing a grey sweater over a blue collared shirt. Behind him is a large periodic table of elements.	Croix J. Laconsay was raised in Kaneohe, Hawaii, USA. He obtained a B.S. in Chemistry from Marist College and then moved to Jerusalem to work with Prof. Sason Shaik for a year on a Fulbright scholarship. He moved to UC Davis in 2017, where he is now a Ph.D. student under the guidance of Prof. Dean J. Tantillo. His current research interests include solving mechanistic problems involving metal-carbene chemistry, heterolytic fragmentations, and reactions in the presence of external electric fields.
 A portrait of Dean J. Tantillo, a man with glasses and a beard, smiling. He is wearing a dark t-shirt and is holding a small, white, ball-and-stick molecular model. In the background, there is a computer monitor and some laboratory equipment.	Dean J. Tantillo was born and raised in Quincy, Massachusetts, USA. He received an A.B. degree in Chemistry in 1995 from Harvard and a Ph.D. in 2000 from UCLA (with Ken Houk) and then moved to Cornell where he did postdoctoral research with Roald Hoffmann. Dean joined the faculty at UC Davis in 2003. Research in Dean's group involves, among other things, developing mechanistic models for organic, biosynthetic and organometallic reactions.