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ISBN

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Publication Date

2026-06-25

Peer reviewed|Thesis/dissertation

Understanding Unusual Chemical Stability, Reactivity, and Selectivity
Through Quantum Mechanical Modeling

By
WILLIAM DESNOO
DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in the

CHEMISTRY

of the

UNIVERSITY OF CALIFORNIA
DAVIS

Approved:

Dean J. Tantillo, Chair

Lee-Ping Wang

Jeffrey Neaton

Committee in Charge

2026

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Dedicated to my family, my wife, mother, father and sister.

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Abstract

This dissertation is a collection of computational investigations into unique and unusual chemistry of organic and organometallic reactions. The goal of most studies described herein is to understand how and why molecules react, and ideally leverage that understanding to guide rational design of future chemistry.

Chapter 1 serves as an introduction to physical organic chemistry, describing fundamental theoretical concepts like approximations, quantum chemistry, transition state theory, and catalysis.

Chapter 2 explores a computational tool used to quantitatively and qualitatively investigate pericyclic reactions, a unique class of reactions characterized by aromaticity in the transition state.¹ Here we employ nucleus-independent chemical shifts^{2,3} and normalized multicenter bond orders⁴ to characterize the degree of cyclic delocalization for a series of

reactions. We include well-established pericyclic reactions and pseudopericyclic reactions as positive and negative controls, respectively. Having validated our method, we apply it to edge cases that potentially violate the Woodward-Hoffmann orbital symmetry rules⁵, where the pericyclic nature of the reaction is unclear. This study ultimately changes the understanding of some unique exceptions, while providing an additional tool to physical chemists to probe these fascinating reactions.

Chapter 3 explores an organometallic palladium catalyst that couples two allyl fragments together.⁶ Our original aim of this project was to examine a proposed pericyclic transmetalation step in the reaction, but the project evolved to include several additional unexpected pericyclic, and selectivity/rate determining outer-sphere reductive elimination steps. This project challenges the traditional assumptions made regarding palladium catalysis, while proposing alternative pathways that are more kinetically feasible than what had been originally proposed.

Chapter 4 explores an organocatalyst that catalyzes an incredibly difficult enantioselective Wagner-Meerwein 1,2 shift of a purely aliphatic substrate.⁷ To impart selectivity on an unactivated and unbiased substrate is a daunting task, as no functional groups enable strong interactions with the chiral catalyst. Our mechanistic investigation identifies the key selectivity determining step that differs from the rate determining step, and propose non-classical hydrogen bonds and sterically confined cavity give rise to the exceptional enantioselectivity.

Chapter 5 details the design of a σ -allyl cation, a hypercoordinate carbocation that had been proposed in 1980 but has never been experimentally determined.⁸ Even theoretically, the only plausible proposed minimum⁹ has been shown to undergo rapid degradation due to quantum tunneling, even at incredibly low temperatures of 10 K.¹⁰ Our study leverages a

counterintuitively designed framework to kinetically stabilize σ -allyl cations by using boron substituents, perhaps the most thermodynamically destabilizing substituent for an electron deficient carbocation. Our results show that rational design of unique chemical systems can require unorthodox approaches, and hope to spur on the synthesis of a historically elusive species.

Acknowledgements

I am grateful for the overwhelming support I've received from my friends, family, peers, and mentors. I would not be where I am today without their support. In particular, I'd like to express my gratitude for my PI, Dean Tantillo, who has provided me many opportunities to grow as a scientist, a writer, an educator, a mentee, and a mentor. He has changed how I approach chemistry, teaching, and thinking in general. He has set me up for success by providing me the opportunity to do research on fascinating projects in organic, organometallic, and unusual bonding chemistry that inspires my own creative approach in chemical modeling. Dean's support goes beyond just me, and extends to all research group members and students he interacts with.

I would like to acknowledge the other members of my dissertation committee, Jeffrey Neaton, who was an equally kind and supportive mentor as Dean and provided me a stepping stone to where I am today. And Lee-Ping Wang who has taught me fundamentals of physical chemistry and similarly is an incredibly kind and brilliant scientist.

I'd like to thank all my peers and colleagues including Alexander Smith, Eric Taw, and

Yusuf Shaidu from the Neaton group; Wang-Yeuk Kong, Croix Laconsay, Yusef Ahmed, Yumeng Cao, and Audrey Lin from the Tantillo group. I'd also like to thank my undergraduate mentors and professors, Daniela Kohen and Matthew Whited for helping me get started on my current academic trajectory. I'd like to thank all my many collaborators including Jeffrey Long, Zackariah Nairoukh, Jeffrey Rudolf, Santanu Panda, Benjamin List, Jared Shaw, and Daniel Whitehead. We express gratitude toward Renana Poranne and her research group for guidance in creating and interpreting current density plots.

It goes without saying, but of course I'd like to thank my entire family: My mother, for her unfaltering and unconditional love; my father, for his kindness curiosity and a figure to aspire to; my sister, for character-building sibling love; all my cousins, aunts, and uncles who were also my closest friends growing up; and my grandparents who have supported the entire family. I'd like to thank my dog, Jasper, for getting me outside, engaged in the neighborhood community, and being an infinite source of love and joy. I'd like to extend a special appreciation to my wife, and my best friend, Teagan. You have been my closest supporter in this last decade of my life. I truly could not imagine a life without you.

I'd like to acknowledge all the journals that have provided permission to reproduce my publications in my dissertation. This includes the American chemical society, The Journal of Organic Chemistry, Wiley Angewadte Chem— International Edition, and Springer Nature. I would like to acknowledge my peers who have shared their experience, knowledge, and companionship.

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- (1) Jaramillo, D. E.; Jaffe, A.; Snyder, B. E.; Smith, A.; Taw, E.; Rohde, R. C.; Dods, M. N.; **DeSnoo, W.**; Meihaus, K. R.; Harris, T. D. Metal–Organic Frameworks as O₂-Selective Adsorbents for Air Separations. *Chemical Science* **2022**, 13 (35), 10216–10237.
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- (3) Cao, Y.; Kong, W.; **DeSnoo, W.**; Tantillo, D. J. Metallocarbenes as Substituents in 8-Electron Electrocyclizations. *Eur. J. Org. Chem.* **2024**, 27 (7), e202301183. <https://doi.org/10.1002/ejoc.202301183>.
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- (7) **DeSnoo, W.**; Tantillo, D. J. PeriRxn, a Tool for Assessing Pericyclicity through Nucleus-Independent Chemical Shifts and Normalized Multicenter Bond Orders. *J. Org. Chem.* **2025**, 90 (32), 11469–11477. <https://doi.org/10.1021/acs.joc.5c00919>.

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1.0 — Introduction

1.1 Quantum Chemistry — What and Why?

Computational chemistry has emerged as a powerful tool to understand and predict chemical reactivity. Through combined advances in hardware, software, and algorithms, computational chemistry has grown in efficiency and accuracy leading to increased practical usage in academia and industry.

Quantum chemistry is a subsection of computational chemistry, focusing on quantum mechanical modeling of electronic wavefunctions to achieve physically derived and accurate models of chemical bonding and interactions. Understanding quantum chemistry requires a familiarity with fundamental physical approximations and equations, while applying it requires intuition specific to the chemistry of interest (organic, inorganic, catalysis, characterization). Herein we will overview the fundamental background of the physics and chemistry to understand and apply quantum chemistry to complex systems.

Theoretical physicists are famous for using approximations to model complex systems. A humorous example is the spherical cow metaphor, where a model cow is simplified as a sphere. A sphere captures the mass, density and volume of the cow but clearly fails to capture important details that make a cow a farm animal. This approximation may be effective for total biomass of cows but is clearly an oversimplified model for a farmer. In quantum mechanical modeling, the appropriate choice of approximation depends entirely on which properties of the system you need to capture.

1.2 The Schrödinger Equation

The classical representation of particles is an inadequate approximation of quantum systems. Although it can capture how ideal gases behave, it cannot capture chemical reactivity effectively. This is because small particles in quantum mechanical systems cannot be described by classical Newtonian physics. Instead, the quantum state of a system is conveniently and fully described by the wave function Ψ . Any observable quantity can be derived by operating on the Ψ with the appropriate operator. For example, the energy of a system is determined by applying the Hamiltonian operator to the wave function. This form is famously known as the time-independent Schrödinger equation and is remarkably simple yet powerful.

$$\hat{H}\Psi = E\Psi$$

The Hamiltonian operator ($\hat{H}$) acts upon the wavefunction (Ψ) and E is the total energy of the system. As the total energy of a system is the sum of kinetic energy and potential energy, we will expand the Hamiltonian as a sum of kinetic and potential energy operators.

$$\hat{H} = \hat{T} + \hat{V}$$

Where $\hat{T}$ is the kinetic energy operator and $\hat{V}$ is the potential energy operator. The Newtonian kinetic energy equation and using the equation for momentum yields the expression for kinetic energy as a function of momentum.

$$KE = \frac{1}{2}mv^2$$

$$p = mv$$

$$KE = \frac{p^2}{2m}$$

This expression holds true for quantum mechanics, however we need to replace the momentum variable with the quantum mechanical momentum operator.

$$\hat{p} = -i\hbar\nabla$$

Where $\hbar$ is Planck's constant, and ∇ is the del operator. Substituting this expression into 1.5 yields our final expression for the kinetic energy operator.

$$\hat{T} = -\frac{\hbar^2}{2m}\nabla^2$$

Having derived the kinetic energy operator $\hat{T}$, we will now derive the potential energy operator $\hat{V}$.

The final Hamiltonian operator for the quantum mechanical system of nuclei and electrons is expressed as:

$$\hat{H} = -\sum_k \frac{\hbar^2}{2m_k} \nabla_k^2 - \sum_i \frac{\hbar^2}{2m_e} \nabla_i^2 + \sum_{k<l} \frac{Z_k Z_l e^2}{r_{kl}} + \sum_{i<j} \frac{e^2}{r_{ij}} - \sum_{k,l} \frac{Z_k e^2}{r_{ik}}$$

Where $\hbar$ is Planck's constant, m_k is the mass of the kth nuclei, m_e is the mass of an electron, Z is the atomic charge of the nuclei, e is the electron charge, r_{ab} is the distance between two particles. This equation is most easily understood by term by term. The first and second terms are the kinetic energy of the nuclei and electrons respectively. The third and fourth terms are the coulombic repulsion between nuclei and the electrons respectively. Lastly, the fifth term is what holds nuclei and electron together, the coulombic attraction between nuclei and electrons.

To solve for the wavefunction efficiently, we will make use of the Born-Oppenheimer (BO) approximation. This approximation states that the wave functions of the nuclei and electrons can be treated separately because the nuclei are significantly slower than the electrons. Therefore, we can assume the nuclei are fixed while we solve the electronic wavefunction. With

this approximation, only electron repulsion term is troublesome, as it is the only many-body problem. Many-body problems are notoriously problematic. They cannot be solved exactly and therefore require numerical methods to solve.

1.3 Hartree Fock Theory

The foundational approximation of the wave function of a quantum mechanical system is called Hartree-Fock theory, named after Douglas Hartree and Vladimir Fock. This method splits the Hamiltonian into a one electron operator $\hat{h}_{ii}$ that captures electron-nuclear attraction and electron kinetic energy, the coulomb operator $\hat{J}_{ij}$ that captures electron-electron repulsion, the exchange operator $\hat{K}_{ij}$ which captures the exchange energy that is a consequence of the mathematical formulation that ensures the antisymmetry principle is satisfied, and lastly the nuclear repulsion V_{Nuc} which is a constant due to the BO approximation. The most important takeaway from this equation is the Hamiltonian equation is exact, however wave function formulation of Hartree Fock theory is a mean-field theory, therefore it cannot calculate the exact electron Coulomb correlation, $\hat{J}_{ij}$. A natural improvement to Hartree-Fock theory would be a method that approximates the electron-correlation that Hartree Fock does not account for. This brings us to Density Functional Theory (DFT) which uses exchange-correlation functionals to approximate these unknown terms.

$$E_{HF} = 2 \sum_{i=1}^{N/2} \hat{h}_{ii} + \sum_{i=1}^{N/2} \sum_{j=1}^{N/2} [2\hat{J}_{ij} - \hat{K}_{ij}] + V_{Nuc}$$

1.4 Density Functional Theory

Hohenberg-Kohn Theorems

In 1964, Pierre Hohenberg and Walter Kohn demonstrated two key results core to DFT called the Hohenberg-Kohn theorem.

The first Hohenberg-Kohn theorem states that the ground state properties of a many-electron system can be uniquely determined by a functional of the electron density rather than the positions of each electron.

The second Hohenberg-Kohn theorem is the variational principle for Hartree-Fock theory, except it applies to the electron density rather than the wave function. It states that the ground state energy of the system can be obtained by finding the wave function that minimizes the expectation value of the energy. In other words, the lowest energy electron density corresponds to the ground state electron density.

Ultimately, these theorems state the electron density alone is sufficient to describe the energy and properties of the ground state. This reduces the complexity of the problem from $3N$ spatial variables, one for each electron's coordinates, to just the Cartesian coordinates 3, the electron density at each point in space.

Kohn-Sham formalism

The Kohn-Sham formalism is essential to modern day implementation of DFT. They are a formulation of DFT that shares core elements of Hartree Fock theory, but enables the calculation of accurate energies from the electron density. The model is defined by creating a fictitious electron density assuming electrons are non-interacting that generates the same electron density as a system of interacting electrons. Remember from the first Hohenberg-Kohn

theorem that we only need the correct electron density, even if that density is obtained through an unphysical model. This approach greatly simplifies the many-body problem by sweeping the unknown kinetic energy correlation of electrons into the exchange-correlation term. This ultimately leads to an the general Kohn-Sham functional expression:

$$E_{\rho} = T_s[\rho] + \int dr v_{ext}(r)\rho + E_H[\rho] + E_{xc}[\rho]$$

Where T_s is the Kohn-Sham kinetic energy, v_{ext} is the external potential (i.e. nuclei-electron coulombic attraction). Notice here the integration the electron density over all space rather than summing the contributions of each electron in Hartree-Fock theory. E_H is the Hartree energy for electron-electron repulsion, and lastly we have the only unknown term, E_{xc} , the exchange-correlation energy. This final term accounts for the electron exchange and correlation we are familiar with from Hartree-Fock theory. Therefore, the entire goal of modern DFT is to develop exchange-correlation functionals that efficiently approximate this exchange-correlation term.

DFT functionals come in a variety of flavors, accuracies, and speeds. Quantum chemists often refer to Jacob's Ladder to describe the accuracy vs speed tradeoffs of each functional. Hartree-Fock is below the lowest rung of the ladder, as it does not account for any electron correlation, however it does compute exchange exactly, which some functionals make use of. Moving to DFT, there are 5 types of functionals we will discuss, and thankfully all are aptly named.

1. Local Density Approximations (LDAs). As the name suggests, they approximate the E_{xc} only by the local electron density and therefore are missing the big picture.
2. Generalized Gradient Approximations (GGAs). These expand upon LDAs by accounting for the gradient of the electron density, or first derivative, or in layman's terms, how quickly the electron density changes at each point in space. By accounting

for this, GGAs are non-local and have a better (but more expensive) picture to work with.

3. Meta-GGAs. These expand on GGAs by accounting for the second derivative of the electron density, again a larger picture that also relates to the electronic kinetic energy.
4. Hybrids. These are the workhorses of modern DFT, striking the fine balance of accuracy and efficiency. As their name suggests, hybrid functionals are a hybrid of DFT and Hartree-Fock theory. The DFT portion enables approximation of electron correlation, while Hartree-Fock theory enables the exact electron exchange (However, often hybrid functionals only use a portion of exact exchange as the cancellation of error with electron correlation yields superior results).
5. Double hybrids. In addition to the Hartree-Fock hybrid, these make use of second-order Møller-Plesset perturbation theory (MP2) corrections that apply to a perturbation to the Hamiltonian that accounts for non-local orbital correlation energy. This does drastically increase the computational cost of the method, but can result in remarkably accurate energies required to understand reactivity and selectivity of reactions. Both hybrids and double-hybrids can be thought of as extensions of HF theory with additional energetic terms from quantum chemistry methods to more accurately account for electron-correlation.

The DFT functional that we employ the most is a hybrid functional called PBE0 which stands for Perdew-Burke-Ernzerhof, and the 0 refers to the number of empirical parameters. As a hybrid functional it uses Hartree-Fock to compute exact exchange. This functional is favored by physicists as its parametrization is non-empirical, and therefore chosen to reproduce physical limits. Other functionals like B3LYP and the M06 series are empirical, which means they are parametrized to fit training data. These are successful and efficient when the molecules are

similar to the training set but may fail when applied to systems that differ drastically from the initial training set (akin to machine learning).

Another functional we make use of is the hybrid functional mPW1PW91. This roughly translates to a modified version of the Perdew-Wang exchange and Perdew-Wang91 correlation to fit physical limits better than its predecessor. This functional was chosen specifically to model pericyclic reactions and carbocation rearrangements as it has a literature precedent for matching experiment on these specific systems.

Lastly, we make use of the PWPB95 Double-hybrid functional to calculate precise energies of the hybrid optimized geometries. This is the highest tier of Jacob's Ladder, and hence in theory it is the most accurate. In practice, it is also incredibly accurate. It has been benchmarked to on main group and palladium chemistry alike, and has been shown to produce the most accurate results across the board.

Exchange-correlation functional limitations

Although powerful, there are of course limitations of DFT functionals given their approximate nature. Perhaps the most glaring limitation is the lack of a universal efficient functional. In practice, a functional that performs well for one system does not necessarily translate well to different system. This results in the need for extensive benchmarking to trust a functional or find an optimal functional for a desired application. Although in theory there is an exact functional, it has yet to be discovered, nor is it guaranteed to be computationally feasible for practical application.

Additional limitations include self-interaction error, where electrons are repelled by their own contribution to the electron density, which is obviously physically inaccurate.

Basis Sets

Basis sets are used to construct molecular orbital which determine the electron density. Imagine rendering a scene at different resolutions. You can use a few large pixels to quickly produce a low-resolution representation, or you can use many tiny pixels to produce an accurate but time-intensive replica. In this analogy, the true electron density is the scene you are trying to render while the basis set size is the resolution. Just as you'd choose the resolution based on the detail of the scene, the choice of basis set size is essential efficiently approximate the electron density.

For periodic crystalline materials plane waves are typical basis sets. For non-periodic calculations that we will focus on, basis sets in quantum chemistry are essentially spherical harmonics that represent atomic orbitals called STOs. It's an intuitive and efficient choice, as we can expect the electrons of a molecule to roughly occupy combinations of atomic orbitals. As an example, let's consider the historically prominent Pople basis set, 6-31g(d). To parse through it g stands for Gaussian, as in practice STOs are approximated by a combination of primitive gaussian functions that are numerically more efficient to handle. The 6 refers to the number primitive Gaussians for each core atomic orbital, which are less important than the valence electrons. The 3 and 1 represent the number of primitive Gaussians used to approximate the two basis functions to model the valence electrons. We use 2 basis functions for the valence electrons as they require more accurate description as they are predominantly involved in chemical reactivity. This is a split-valence double-zeta basis set as we treat the valence and core electrons differently, with 2 basis functions for valence electrons. In general, the more zetas the more complete the basis set. Lastly, we have the polarization functions, (d), which apply additional d orbitals to non-hydrogen atoms.

Another basis set we employ are effective core potential (ECPs), namely Ahlrich's Karlsruhe def2 series basis set. These treat core electrons as an effective core potential that shields the valence electrons. Furthermore, they are more general balanced and computationally efficient. An example that we commonly employ is def2-SVP, where the SVP stands for split-valence polarization. This is a reliable base, and is double zeta, but one can expand upon it to def2-TZVPP where the TZVPP stands for triple-zeta valence polarization, hence it has a more complete description of valence electrons and includes extra polarization functions.

1.5 Transition State Theory

To understand and predict chemical reactivity and selectivity one must understand the kinetics of a reaction. Kinetics refers to the reaction rates converting two substances or states, while thermodynamics simply refers to the relative stability of two states and which is preferred at equilibrium. To compute kinetic properties, we must relate energy to reaction rates. The equation that enables this relation is known as the Eyring equation:

$$k = \frac{\kappa k_B T}{h} e^{\frac{-\Delta G^\ddagger}{RT}}$$

Where k is the rate constant, κ is the transmission coefficient, k_B is the Boltzmann constant, T is the temperature in Kelvin, h is the Planck constant, and $\Delta G^\ddagger$ is the Gibbs free energy of activation. The preexponential coefficient is, for our purposes, a constant. The exponential term indicates the relation between energy and rate constant is exponential, so small changes in $\Delta G^\ddagger$ result in drastic changes in reaction rates. The greater $\Delta G^\ddagger$, the slower the reaction.

1.6 Conformational Sampling

All but the smallest molecules are not limited to a single configuration in space and often have access to a myriad of viable conformations. To predict and understand the molecular reactivity, we must capture relevant conformations of a molecule along a reaction path. The number of possible conformers increases drastically with the number of rotatable bonds and number of molecules in the simulation.

To sample the many configurations, methods have been developed that combine fast (at the cost of some accuracy) semi-empirical methods to perform long and comprehensive enhanced sampling dynamics of phase space. Herein we make use of Grimme's Conformer-Rotamer Ensemble Sampling Tool (CREST)^{11,12} program that employs the fast semi-empirical method, GFN2-xTB¹³. This conformational searching protocol quickly explores phase space with a flavor of enhanced sampling method called metadynamics. Metadynamics adds a history dependent potential to bias the molecule away from visited portions and toward new conformations in phase space. This requires a collective variable (CV) that boils the complex 3N phase space to 1 representative variable. In CREST, this variable is chosen as the RMSD between the current structure and previously visited minima. For conformational sampling this is a good collective variable given its generality and ability to differentiate conformers. There are additional methods involved in CREST like genetic crossing, structure optimizations, normal molecular dynamics and clustering, but this is beyond the scope of the introduction.

Conformers are then optimized using low level DFT, a step up in accuracy from GFN2-xTB. Lastly, we use expensive high level DFT to calculate single point energies on the optimized conformers, enabling high accuracy of computed relative free energies which are essential for predicting kinetic and thermodynamic properties that dictate selectivity. These high-level

methods typically produce energies within 1-2 kcal/mol of CCSD(T), the gold standard of ab initio quantum chemistry.

1.7 Applications — Catalysis, Energetics and More

Now that we have some basic understanding of the method and its origin, we can dive into its applications.

Catalysis is a powerful tool in any chemist's arsenal. It enables the conversion of a reactant to a product via a catalyst that reduces the activation energy required to interconvert the products and reactants. Notably, the catalyst is not consumed in the reaction, which means a small concentration of catalyst can effectively convert a large quantity of reactants and still be recovered. This regenerative and efficient property makes it desirable from both an economic and sustainability standpoint.

One of the earliest impacts of an artificial catalyst is the Haber process, which converts hydrogen gas and the typically inert dinitrogen to ammonia, an essential nutrient used in fertilizers that revolutionized agriculture. This reaction has too high of an activation barrier to occur at even elevated temperatures. The key ingredient was iron, which isn't included in the products, but is crucial to cleave and reform new bonds. But *how* exactly do catalysts lower the activation energy barrier? In general, the catalyst helps by forming weak or partial bonds to the substrate in place of the original bonds. This stabilizes the transition state which often involves breaking particularly strong bonds. In the case of the Haber process, it assists in cleaving the powerful $\text{N}\equiv\text{N}$ triple bond, a feat that in nature requires lightning or biological enzymes that have evolved over billions of years.

Catalysis encompasses accelerating any reaction, but the most powerful and applicable forms of catalysis are selective for a single desired product. Such reactions can be

regioselectivity, only differing from the undesired products by the location of a formed bond. A more challenging selectivity is selecting for chirality, or right/left handedness. These reactions are called enantioselective, producing a biased mixture of the two, or non-superimposable mirrored version of the product. The similarity of the products makes selectivity challenging, as they act identically except in chiral environments. Despite seemingly small differences, these products can have astoundingly different effects, especially in biological systems which are highly sensitive to chirality.

Modern day *organometallic* catalysis uses a myriad of metals combined with designed ligands that promote enhanced and/or selective reactivity. The metal we will focus on is palladium, which is exceptional at catalyzing the formation of C-C bonds. Palladium strikes a delicate balance in its affinity to the carbon substrates and ligands. It has just the right affinity to bind substrates, but not such a strong affinity that it cannot be regenerated or release the final product. Despite widespread use in synthetic chemistry, the mechanisms by which it catalyzes reactions are often misunderstood. We will provide examples by which DFT calculations reveal unconventional reaction mechanisms in palladium carbon cross coupling catalysis.

There is a common conception that DFT is "bad for metals." It contains a kernel of truth but is an overgeneralization — performance is strongly system- and functional-dependent, and the concern applies primarily to molecular transition-metal chemistry rather than to metallic solids.

Well-behaved cases are closed-shell, single-reference complexes: low-spin d^6 octahedral (Ru, Rh, Ir) and d^8 square-planar $16e^-$ complexes (Pd, Pt) are typically modeled reliably with an appropriately benchmarked functional. Trouble arises in two regimes. First, spin-state energetics: for Fe, Mn, Co complexes spanning multiple accessible spin states, the relative energies depend acutely on the fraction of exact exchange in the functional, swinging by tens of kcal/mol across

LDA → GGA → hybrid. Calibrated choices (TPSSH, B3LYP*, r²SCAN, OPBE) exist but no single functional is universal, hence the need for well-benchmarked functionals. Second, genuinely multireference systems — near-degenerate electronic states, antiferromagnetically coupled polynuclear cores like FeS₂ clusters¹⁴ — cannot be represented by a single Kohn–Sham determinant and ultimately require CASSCF/NEVPT2 (or DMRG for large active spaces).

A practical middle ground exists for systems with coupled local spins, such as diradicals. These often admit a broken-symmetry (BS) DFT treatment: an unrestricted determinant in which α and β densities spatially localize on different atoms, breaking spatial and spin symmetry. The BS determinant is not a spin eigenstate but a weighted mixture, so its $\langle S^2 \rangle$ will differ significantly from $S(S+1)$, which in other scenarios is a red flag.

Practical workflow for any open-shell calculation: use unrestricted DFT, choose an initial guess of the correct multiplicity, and run a wavefunction stability test (stable=opt) to confirm the lowest-energy electronic state. For two-electron diradicals starting from a closed-shell guess, guess=(mix,always) mixes the HOMO and LUMO to break α/β spatial symmetry. For multi-center BS systems (Fe–Fe, Cu–Cu, Fe–S clusters), guess=(fragment=N,...) with explicit per-fragment spin flips is more reliable. Check $\langle S^2 \rangle$ against $S(S+1)$ for ordinary unrestricted solutions; for BS solutions, expect contamination and apply projection.¹⁵ If functional dependence is severe, the T1 diagnostic from a CCSD(T) single-point is high (> 0.05),¹⁶ or BS-DFT itself becomes unstable, multireference methods are likely required.

Although metals have traditionally been crucial for catalysis, they aren't required. Biology is a great example, where most enzymes are metal-free. *Organocatalysts* have been designed to mimic their biological enzyme counterparts and can even outperform them in selectivity and potency. Some organocatalysts are remarkably simple, like the amino-acid proline. Modern

organocatalysts have evolved to be incredibly complex, with highly reactive Lewis acidic sites and confined pockets to direct selectivity. We will dive into an example where an incredibly complex organocatalyst manages to selectively react a remarkably unreactive substrate and reveal the interactions and origins of reactivity and selectivity.

The main application discussed herein revolves around understanding selectivity and reactivity in catalysis; however, I will also present and apply examples where we probe the electronic, magnetic, and bonding properties of a unique class of transformations called pericyclic reactions. These reactions exhibit cyclic delocalized electrons in the transition state, which stabilize the transition state in the same way that benzene's aromaticity thermodynamically stabilizes its planar equilibrium geometry. However, pseudopericyclic reactions also exist, and although the arrow pushing mechanism may suggest pericyclic behavior, they involve a lone pair in an orbital that is orthogonal to the cyclic array, breaking the cyclic delocalization.

Chapter 2 — *PeriRxn*, a Tool for Assessing Pericyclicity through Nucleus Independent Chemical Shifts and Normalized Multicenter Bond Order

This chapter is reproduced from my paper published in ACS organic letters, see publication list before the introductory chapter.

Analyses of nucleus independent chemical shifts (*NICS*) and normalized multicentered bond orders (nMCBO) along reaction coordinates were used to quantify the degree of cyclic delocalization of various reactions as a criterion for whether reactions are pericyclic. The

magnitude of the z sampled average, $\overline{NICS_{zz}}$, and nMCBO near the transition structure was found to be a good indicator of pericyclicity, but the topology of $\overline{NICS_{zz}}$ along the intrinsic reaction coordinate proved to be more informative.

Introduction

Aromaticity has long been an area of interest for physical organic chemists.^{1,17–19} The enhanced stability of aromatic ground state minima (and many excited states) is well understood, however the classification of aromaticity in transition structures (TSs) is still a subject of debate for some systems. The Woodward-Hoffmann (W-H) orbital symmetry rules predict whether formation of a product of a pericyclic reaction with a particular stereochemistry is “allowed” or “forbidden”.⁵ Although Woodward and Hoffmann famously stated there are no exceptions to these rules,⁵ over the years, numerous apparent violations of these rules have been reported.²⁰ Many of these supposed violations have been shown to be reactions not subject to the rules, such as pseudopericyclic reactions that engage orthogonal orbitals,^{21–23} stepwise reactions,²⁴ or concerted reactions where bond-making/breaking events are so asynchronous that delocalized bonding arrays are apparently not formed anywhere along reaction coordinates.²⁵ Recently, Carpenter argued that inherent penalties associated with “forbiddenness” are not always very large,²⁶ but that does not negate the issue on which we focus here: does a given reaction involve significant (to be quantified below) continuous cyclic overlap of orbitals supporting rearranging electrons somewhere along its reaction coordinate? Here we disclose a tool called *PeriRxn* for characterizing pericyclicity based on two complementary methods of quantifying cyclic delocalization along reaction coordinates: nucleus independent chemical shifts (*NICS*)^{27,28} and normalized multicenter bond orders (nMCBO).⁴

Results and Discussion

Classic Pericyclic Reactions

We use *PeriRxn* to evaluate the $NICS_{zz}$ and nMCBO behavior of classic pericyclic reactions as positive controls. Unsurprisingly, each reaction displays maximum cyclic delocalization at/near the TS, evidenced by a deep $\overline{NICS_{zz}}$ minimum (Figure 1, red). While $NICS_{zz}(1)$, i.e., $NICS_{zz}$ computed 1 Å displaced from the plane of atoms in an aromatic system, is consistently used as an indicator for cyclic delocalization,^{3,29–31} sampling $NICS_{zz}(1)$ is not practical for systems lacking symmetry (which can give drastically different magnitudes on different sides of the plane) or which possess groups close to a $NICS(1)$ point.^{2,29,30} *PeriRxn* samples along both sides of the plane in question and spans a range of distances to facilitate interpretation, in the spirit of *NICSscan* procedures.^{32–34} The presence of substantial negative $NICS_{zz}$ regions (blue in the "maps" shown in Figure 1 and following figures) above and below the plane near to the TS are characteristic of pericyclic reactions. Also as expected, nMCBO magnitude (Figure 1, green) is greatest at/near the TS, where partial bonding is shared amongst the atoms supporting the rearranging electrons. The sign of nMCBO changes for Möbius and Hückel orbital arrays, however, as is clear for the series of electrocyclic reactions with 4, 6, and 8 electrons in Figure 1C-E). Due to the multiplicative nature of nMCBO, an odd number of phase inversions (characteristic of Möbius arrays) results in a negative multicenter bond order.

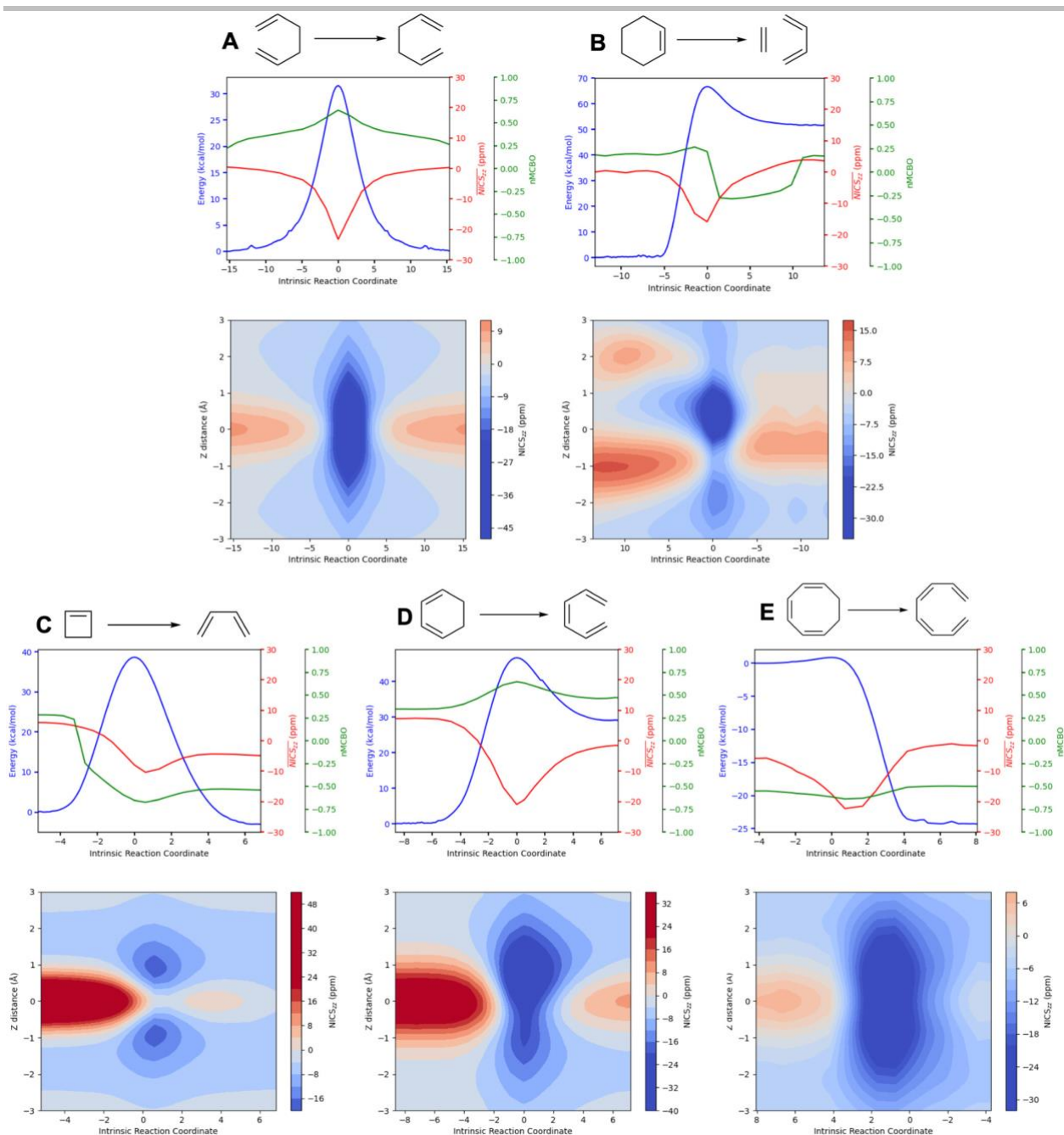


Figure 1. *PeriRxn* analysis along reaction coordinate for five typical pericyclic reactions. For each panel (A-D): Reaction of interest (top), $\overline{NICS}_{zz}$ (red), nMCBO (green), along intrinsic reaction coordinate (blue). Plot of all $\overline{NICS}_{zz}$ values as a function of z displacement and intrinsic reaction coordinate, blue is negative and red is positive (bottom). While the range of $\overline{NICS}_{zz}$ plotted for these “maps” differs for each, the color scale is the same for all of them (and all maps below). **A.** Parent Cope rearrangement. **B.** Parent Diels-Alder reaction. **C.** Electrocyclic ring-opening of cyclobutene. **D.** Electrocyclic ring-closure of 1,3-cyclohexadiene. **E.** Electrocyclic ring-opening of 1,3,5-cyclooctatriene.

Pseudopericyclic Reactions

We selected three pseudopericyclic reactions to consider, one representative of each main class of pericyclic reactions: electrocyclic, cycloaddition and sigmatropic shift.^{35–37} None of these reactions exhibit the signs of cyclic delocalization characteristic of the classic pericyclic reactions. $NICS_{zz}$ are consistently more positive than their pericyclic counterparts, and no significant $\overline{NICS_{zz}}$ minima near TSs are found. nMCBO analysis reveals a decrease in delocalization near the TS for the reaction shown in Figure 2A, the opposite of the behavior observed for the pericyclic analogue. Similarly, the reaction shown in Figure 2B exhibits the opposite behavior to its pericyclic analogue with the sign of nMCBO proceeding as $- \rightarrow + \rightarrow -$, in contrast to the $+ \rightarrow - \rightarrow +$ behavior shown in Figure 1B. The reaction shown in Figure 2C exhibits no notable change in nMCBO. These examples illustrate the distinctly different behavior of pseudopericyclic reactions from pericyclic reactions, supporting the proposal that the *PeriRxn* analysis of $NICS_{zz}$ and nMCBO can distinguish reactions with and without cyclic delocalization – the criteria for pericyclicity used here.

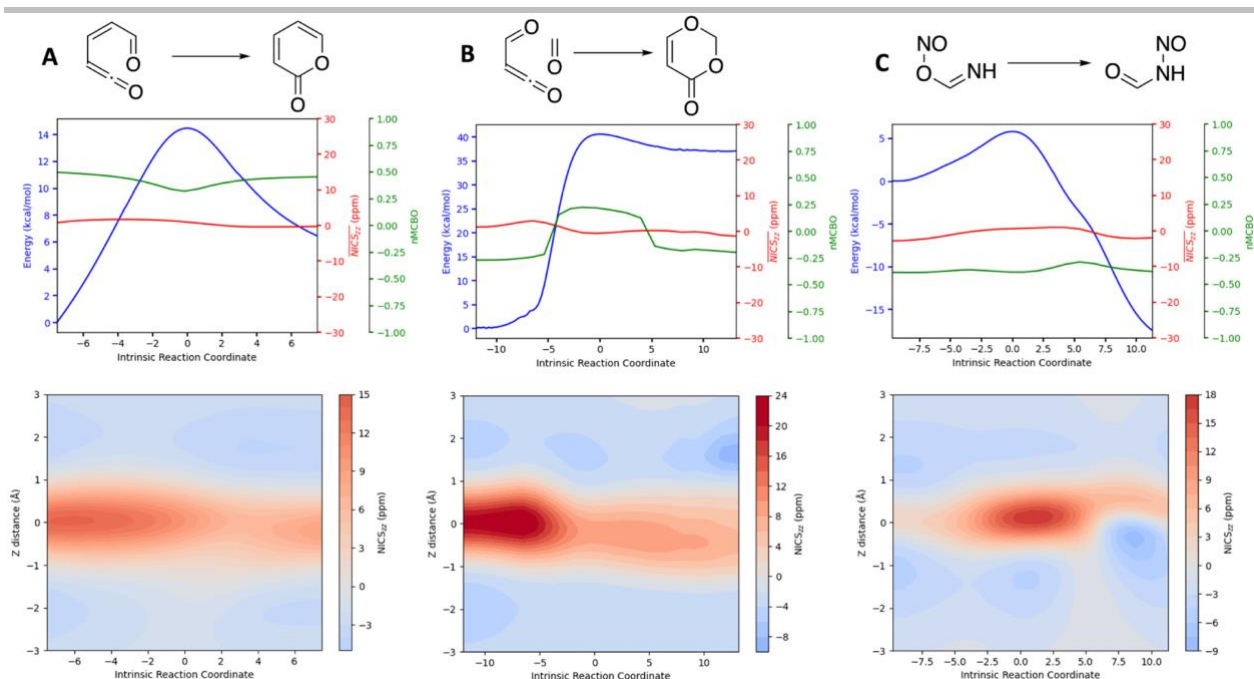


Figure 2. *PeriRxn* analysis along reaction coordinates for pseudopericyclic reactions. For each panel (**A**–**C**): Reaction of interest (top), $\overline{NICS}_{zz}$ (red), nMCBO (green), along intrinsic reaction coordinate (blue). Plot of all $NICS_{zz}$ values as a function of z displacement and intrinsic reaction coordinate, blue is negative and red is positive (bottom). **A.** (Z)-5-oxopenta-2,4-dienal cyclization. **B.** Buta-1,3-dien-1-one + formaldehyde [4+2] cycloaddition. **C.** Formimidic nitrous anhydride formal [1,3] sigmatropic shift.

Apparent Violations

Having established clear differences in behavior between pericyclic and pseudopericyclic reactions, we sought to apply *PeriRxn* to apparent violations of the W-H rules. A representative type of reaction for which asynchronicity in bond-making/breaking has been argued to provide a means of circumventing the W-H rules is the cationic [4,5]-sigmatropic shift (Figure 3B).²⁵ The example in Figure 3B was predicted to be concerted but proceed with the W-H forbidden supra/supra stereochemistry (see Supporting Information for stepwise variants). For this reaction, C–C bond formation precedes C–C bond cleavage, with TS bond lengths of 2.29 and 1.58 Å, respectively. *PeriRxn* analysis reveals a $\overline{NICS}_{zz}$ minimum near the TS, suggesting

pericyclic character, but it is promptly followed by an increase to a maximum, implying loss of cyclic delocalization. In contrast to our earlier analysis,²⁵ this finding leads us to hypothesize that the reaction proceeds via a W-H allowed homo-Cope ([3,4]-sigmatropic shift) TS, where the s-bond that ultimately migrates is not involved in the delocalized array. The TS geometry is consistent with this proposal, given the migrating s-bond is barely elongated. To test this hypothesis, we analyzed a simple homo-Cope reaction (Figure 3A). Our analysis revealed a qualitatively similar behavior between this reaction and the reactant side of the [4,5]-shift reaction coordinate. After the TS for the [4,5]-shift, the migrating C–C s-bond begins to break and pericyclic character is eliminated. The significant dip in nMCBO for the reaction in Figure 3B is correlated with the C–C bond cleavage. Here, *PeriRxn* pointed us to the intrusion of a pericyclic process in this apparent violation of the W-H rules, a phenomenon that we had previously overlooked!

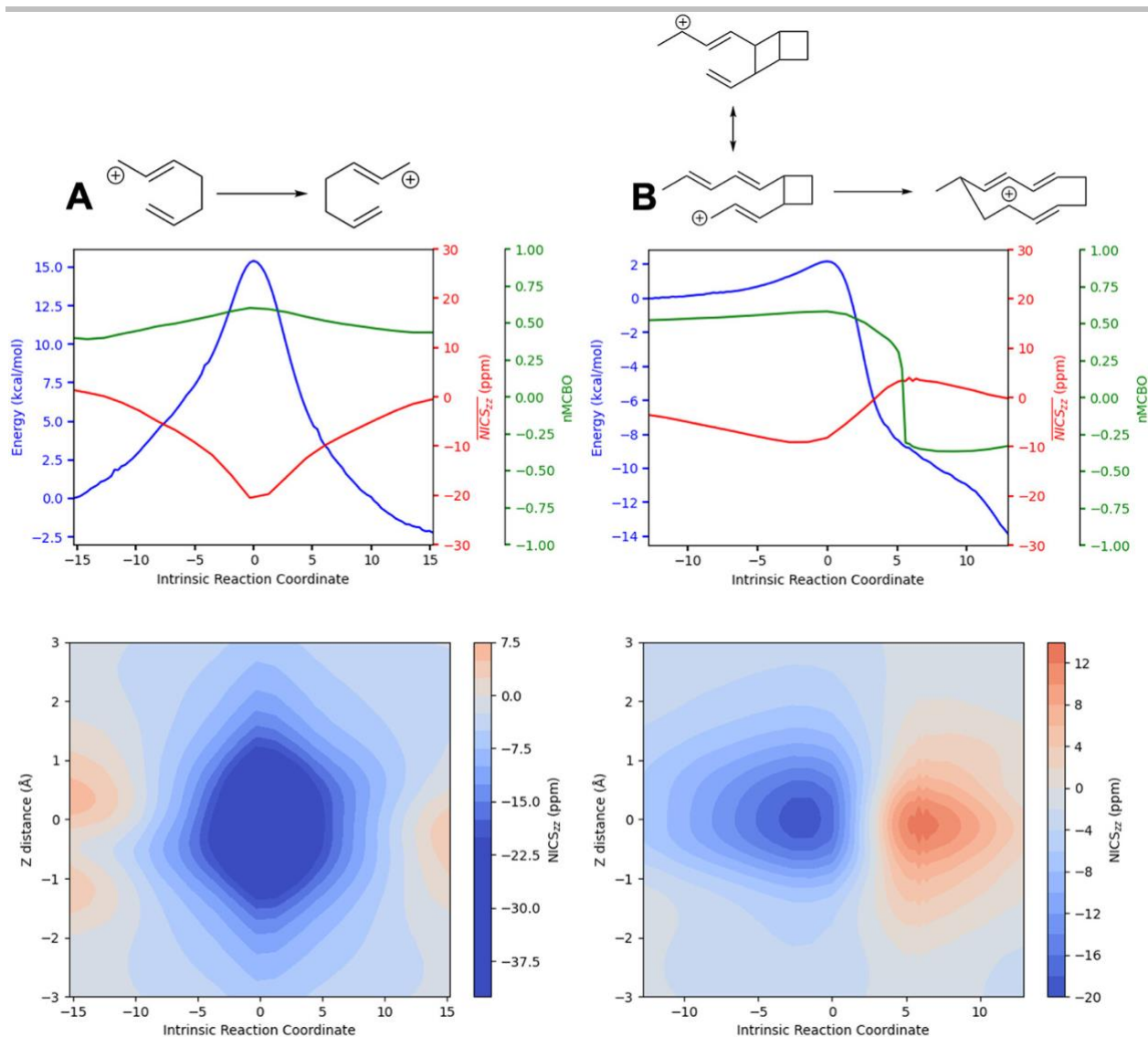


Figure 3. *PeriRxn* analysis along reaction coordinates for cationic sigmatropic shifts. For each panel (A-C): Reaction of interest (top), $\overline{NICS}_{zz}$ (red), nMCBO (green), along intrinsic reaction coordinate (blue). Plot of all $\overline{NICS}_{zz}$ values as a function of z displacement and intrinsic reaction coordinate, blue is negative and red is positive (bottom).

In Figure 4A is shown an example of a reaction with a highly delocalized TS, but one that lacks *cyclic* delocalization (a putative step in the enzyme chaperoned formation of the sesquiterpene pentalenene).³⁸ The reactant here displayed some homoallylic cation delocalization, so the reaction could be considered to be a (2 + 3) cycloaddition in which 4

electrons are involved. The π -systems involved all interact suprafacially, so cyclic delocalization should be forbidden by the W-H rules, but the reaction was computed to be concerted. Nonetheless, bond-making/breaking events were again found to be asynchronous for this reaction, and it displayed positive or minimally negative $NICS_{zz}$ across all z sampling and no significant $\overline{NICS_{zz}}$ minima at/near the TS. The reaction is not pericyclic and therefore not a violation of the W-H rules. The nMCBO undergoes several sign inversions along the reaction coordinate, however, providing further insight into the nature of the delocalization during reaction. The first corresponds to disruption of the homoallylic delocalization, the second to the delocalization accompanying bond formation, the third to the loss of delocalization as 5-membered ring s-bond is formed, and the fourth to the formation of the 4-membered ring s-bond.

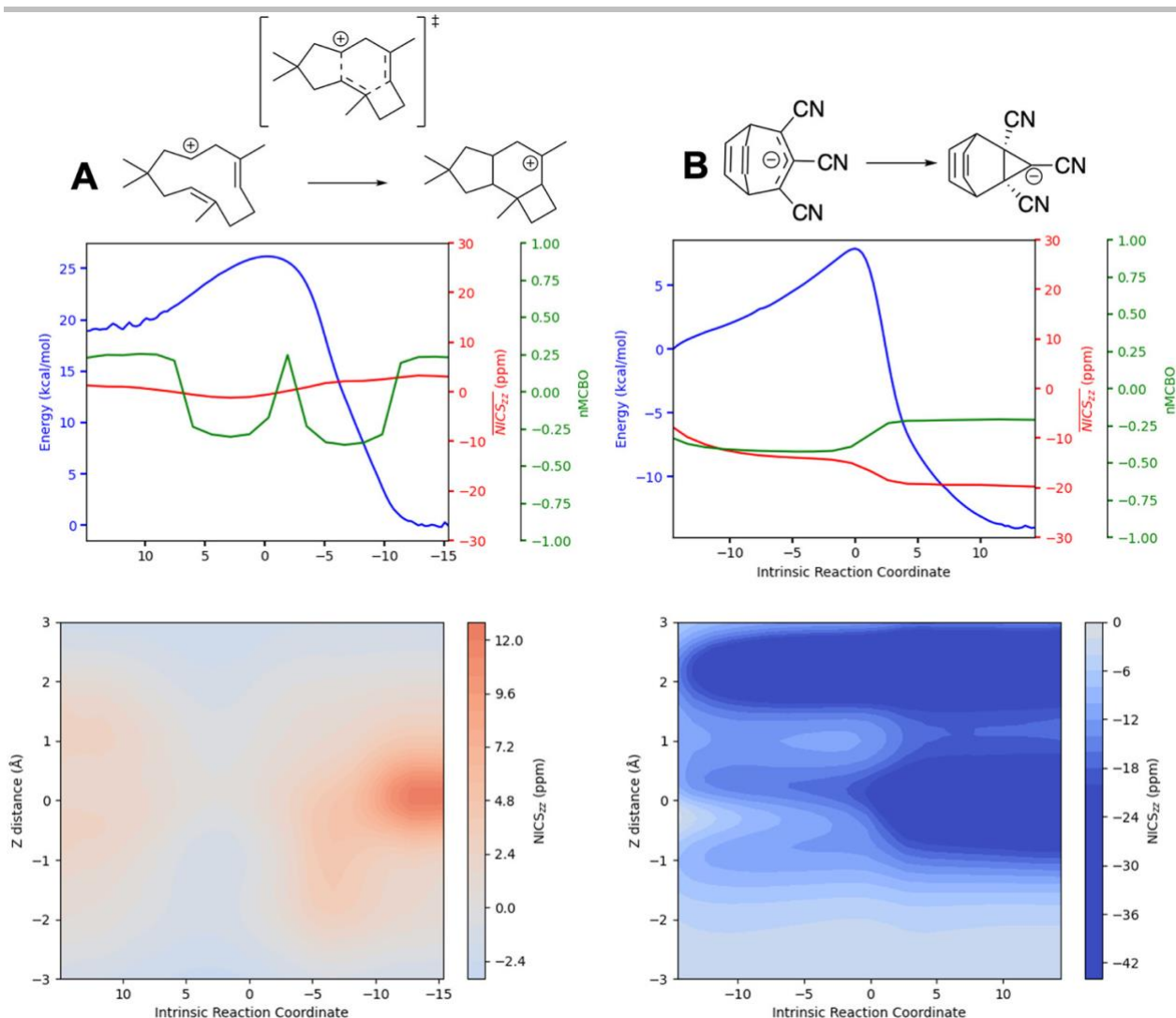


Figure 4. *PeriRxn* analysis along reaction coordinates for two additional reactions. For each panel (A-B): Reaction of interest (top), $\overline{NICS}_{zz}$ (red), nMCBO (green), along intrinsic reaction coordinate (blue). Plot of all $\overline{NICS}_{zz}$ values as a function of z displacement and intrinsic reaction coordinate, blue is negative and red is positive (bottom).

Another apparent violation of the W-H rules is shown in Figure 4B – a disrotatory 4-electron electrocyclic ring-opening.³⁹ While this reaction was originally hailed as a violation,⁴⁰ subsequent computational work revealed that its TS actually involves the conrotatory motion expected for an allowed process, followed by relaxation to the formally forbidden product later along the reaction coordinate to avoid strain.³⁹ Our analysis shows no clear $\overline{NICS}_{zz}$ minima at/near the TS, but this can be attributed to the concentrated negative charge, large s effects

near $z=0$, and the presence of a π -bond 2-3 Å above the ring. nMCBO also does not have a well-defined minimum at/near the TS, because the delocalization in the reactant for this system is also substantial. This case highlights some limitations of *PeriRxn*.

To demonstrate the use of *PeriRxn* for synthetically relevant apparent violations, we employed it to examine a ring-opening step in the synthesis of (+)-liphagal (Figure 5A), an inhibitor of the PI3K family of enzymes that have been shown to play a role in pathogenesis of diabetes and cancer.⁴¹ This reaction appears to be a forbidden disrotatory 4-electron electrocyclic ring-opening, but our analysis reveals a shallow $\overline{NICS}_{zz}$ minimum as the reaction approaches the TS, suggesting a W-H allowed process. With respect to the sp^3 carbons at the ends of the breaking σ -bond, this reaction appears to be monorotatory with the C–H group rotating “outward” while the other carbon merely moves away without rotation (Figure 6). After the TS, a twisted conformation of the diene forms. So again, the reaction avoids forbidden cyclic delocalization. Additionally, the carbonyl group participates, with its C=O bond elongating slightly at the TS, suggesting the onset of extended non-pericyclic delocalization.

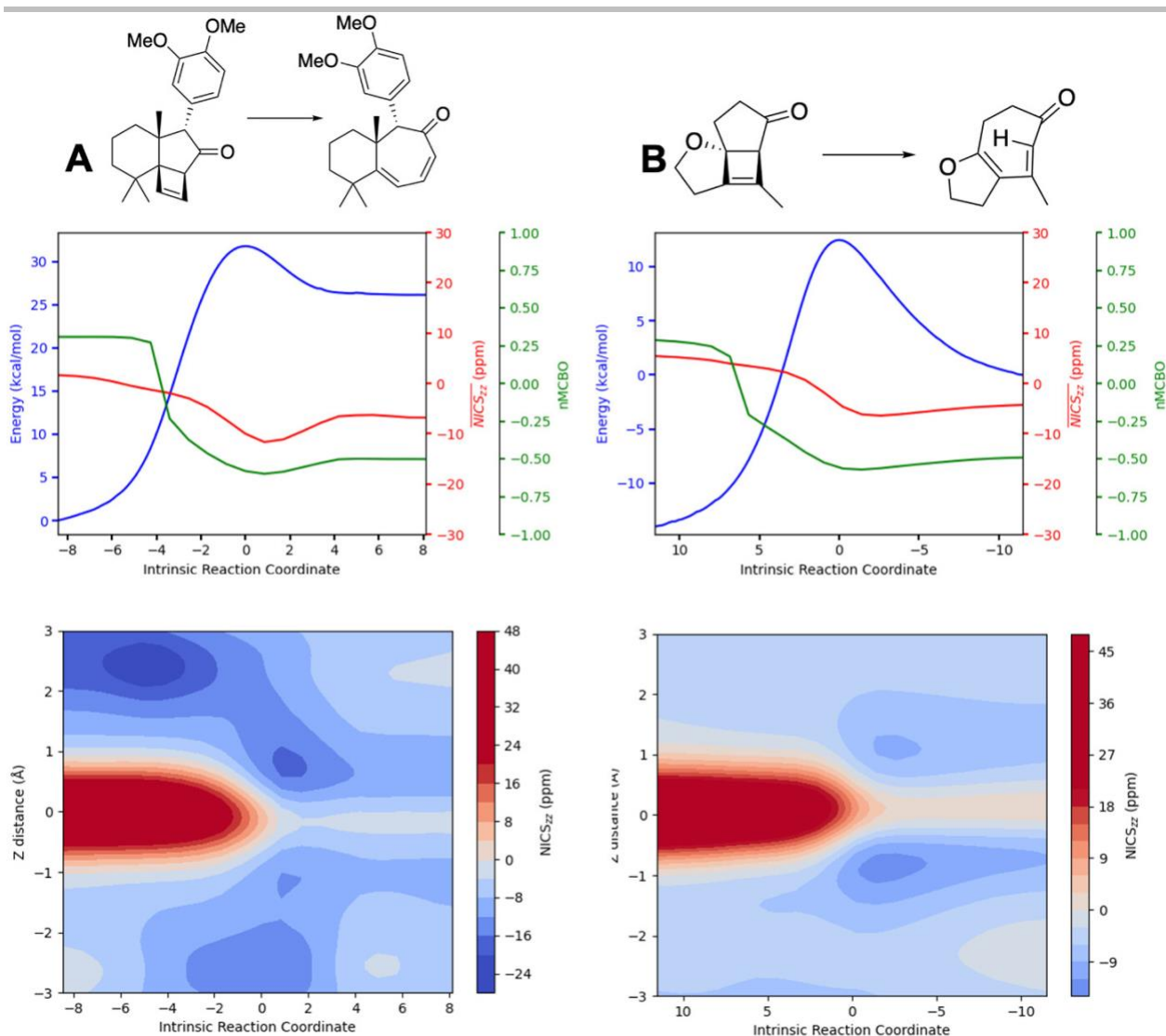


Figure 5. PeriRxn analysis along reaction coordinates for synthetically relevant apparent violations. For each panel (A-B): Reaction of interest (top), $\overline{NICS}_{zz}$ (red), nMCBO (green), along intrinsic reaction coordinate (blue). Plot of all $\overline{NICS}_{zz}$ values as a function of z displacement and intrinsic reaction coordinate, blue is negative and red is positive (bottom).

A similar cyclobutene ring-opening, but one potentially involving a photoexcited cyclobutene, is shown in Figure 5B – an *E* alkene product is shown, but a *Z* alkene is observed as the final product in solution.⁴² Since the reactant shown is generated in situ via a photochemical process, several mechanisms are plausible here. One involves a thermal conrotatory 4-electron ring-opening followed by alkene isomerization promoted by irradiation (or

another means), another involves a disrotatory photochemical 4-electron ring-opening, and a third involves a thermal but forbidden disrotatory 4-electron ring-opening. We located a conrotatory TS, but not the thermally forbidden disrotatory TS for the ground state of this system, consistent with a pathway not violating the W-H rules. Application of *PeriRxn* analysis reveals signs of delocalization, including an nMCBO topology similar to that of the conrotatory cyclobutene ring openings shown in Figure 1C.

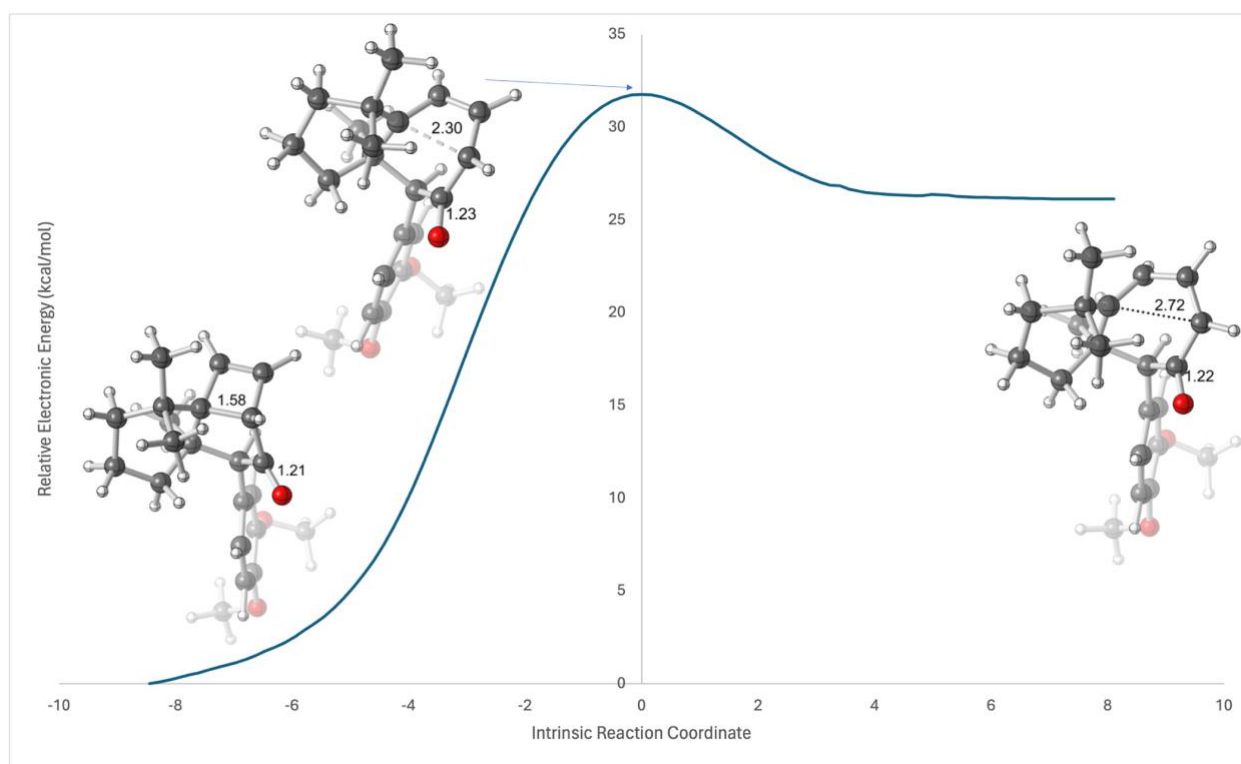


Figure 6. Intrinsic reaction coordinate diagram for the conrotatory electrocyclic cyclobutene ring opening of (+)-liphagal. Key structures are shown, with bond distances reported in Å.

Highly polarized electrocyclizations explored by Houk and co-workers were also examined (Figure 7).⁴³ For these reactions, $\overline{NICS}_{zz}$ maxima near TSs were found, consistent with paramagnetic ring current and associated antiaromatic character.^{44,45} In addition, the

nMCBO drops to negative values near the TSs for these reactions, consistent with cyclic delocalization in Möbius orbital arrays. While it could be argued that the diamagnetic ring current associated with aromaticity of the 5- and 7-membered rings in/near the TS for the system in Figure 7B influences the $\overline{NICS}_{zz}$, such an argument is not possible for the system in Figure 7A. Thus, we have no compelling evidence from *PeriRxn* that these reactions are not “true violations” of the W-H rules.

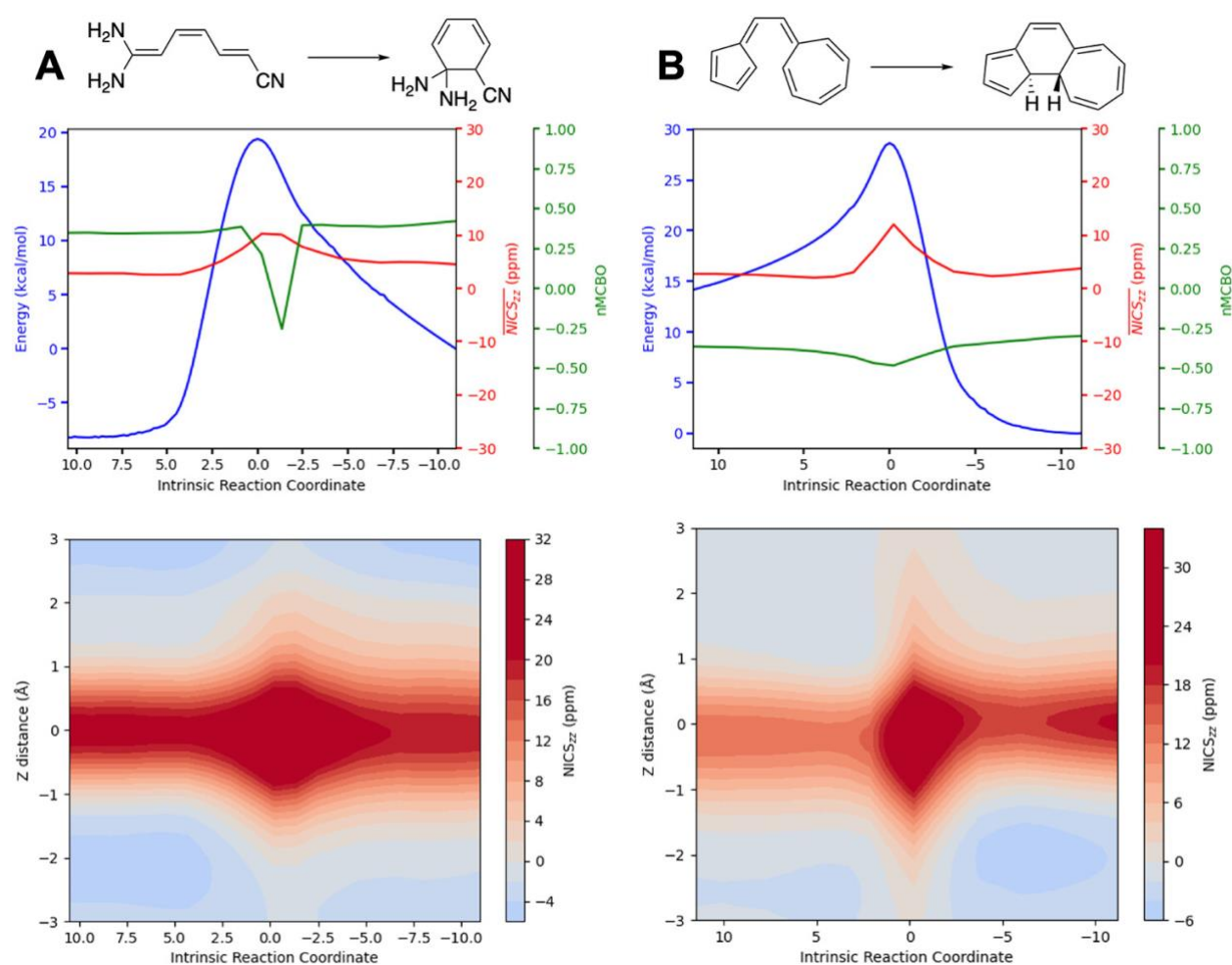


Figure 7. *PeriRxn* analysis along reaction coordinates for highly polarized electrocyclic reactions. For each panel (A-B): Reaction of interest (top), $\overline{NICS}_{zz}$ (red), nMCBO (green), along intrinsic reaction coordinate (blue). Plot of all

$NICS_{zz}$ values as a function of z displacement and intrinsic reaction coordinate, blue is negative and red is positive (bottom).

Guidelines for Interpreting Magnitudes of $\overline{NICS_{zz}}$

The magnitude of $\overline{NICS_{zz}}$ minima can serve as a proxy for the magnitude of cyclic delocalization. For standard pericyclic reactions, this magnitude typically ranges from -20 to -30 ppm, while the lowest individual $NICS_{zz}$ values range between -30 and -50 (Figure 1). A notable exception is found for cyclobutene ring-openings, with lower individual $NICS_{zz}$ magnitudes. Pseudopericyclic reactions have shallow $\overline{NICS_{zz}}$ minima at most, consistent with their lack of cyclic delocalization. Some non-standard pericyclic reactions examined here display magnitudes between -5 to -10, suggesting weaker, but not negligible cyclic delocalization. In general, interpretation of $NICS_{zz}$ magnitude must be done with caution in cases where a small ring, negative charge, and/or neighboring π -bond(s) are present.

Conclusions

Here we introduce a tool, *PeriRxn*, for characterizing pericyclicity on the basis of two measures of cyclic delocalization and argue that these should be examined along reaction coordinates, not only at TSs. In addition to the reactions described here, *PeriRxn* has been applied previously to several other reactions, including organometallic reactions.^{46–48} Our preferred method is to evaluate the shape and magnitude of properly sampled $\overline{NICS_{zz}}$ as a function of the reaction coordinate, but nMCBO provides corroborating evidence and can readily differentiate Möbius and Hückel orbital arrays. We have shown that pseudopericyclic reactions exhibit little fluctuation in $NICS_{zz}$ at any z sampling and no significant $\overline{NICS_{zz}}$ minima along

reaction paths. Most apparent violations of the Woodward-Hoffmann rules that we have examined can be rationalized as either circumventions instead of violations, or rule followers that form formally forbidden products after they are through with cyclic delocalization. Reactions with highly polarized TSs stand as the exception. We note in closing that (1) *PeriRxn* is freely available to the community via Github (<https://github.com/WillDeSnoo/PeriRxn>), and (2) the approach described here is easily extendable to trajectories from molecular dynamics simulations.⁴⁹

Computational Methods and Choice of Systems

All calculations were performed at the mPW1PW91/6-31G(d)⁵⁰ level of theory using *Gaussian16*.⁵¹ Choice of functional and basis set were justified by their extensive previous use in modeling both carbocation rearrangements and main group chemistry in general.^{52,53} Intrinsic reaction coordinate (IRC) calculations were calculated with the local quadratic approximation.^{54–}⁵⁶ Normalized multicenter bond orders were calculated with the *Multiwfn* software package.⁵⁷ nMCBOs should be interpreted with care, as non-zero bond orders are observed even when aromaticity is not involved. *NICS* values were computed at a range of points for each system using custom scripts (available in Supporting Information) where ghost atoms were placed along the vector normal to the plane of atoms potentially involved in cyclic delocalization (normal vector calculated by principal component analysis; see Supporting Information). $\overline{NICS_{zz}}$ were calculated as the average of $NICS_{zz}$ of ghost atoms placed at 0.1 Å intervals from 3 Å above to 3 Å below the plane of atoms mentioned above, to avoid effects caused by s-bonds.^{13,24,25} Wavefunction stability was tested for cases where diradical character pathways were plausible, but low energy diradical alternatives to the structures described below were not found.

Test reactions were selected to obtain a variety of classic pericyclic reactions (for which there is no current debate about their pericyclicity), pseudopericyclic reactions,^{35,36,39} and reactions that have been considered to potentially violate the W-H rules.^{39,41–43,58}

Data Availability Statement

The data underlying this study are openly available in iochem-BD at <https://doi.org/10.19061/iochem-bd-6-523>.^{59,60}

The Appendix contains methodological details on the *PeriRxn* script and additional relevant figures and discussion of the [4,5] sigmatropic shifts.

Chapter 3 — Allyl-Allyl Coupling Promoted by Catalyst Systems with two Palladium Atoms – A Plethora of Potentially Pericyclic Processes

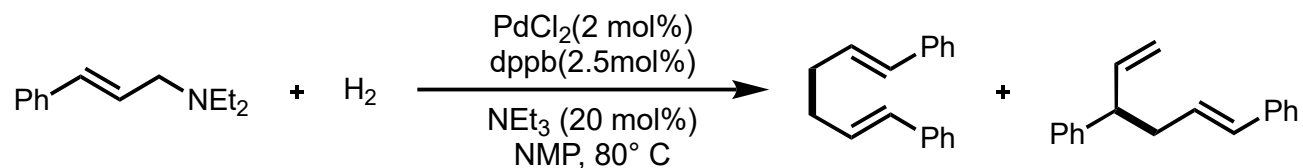
Recently, Huang and co-workers reported a catalytic reaction that utilizes H₂ as the sole reductant for a C-C coupling of allyl groups with yields up to 96%. Here we use computational quantum chemistry to identify several key features of this reaction that provide clarity on how it proceeds. We propose the involvement of a precatalyst Pd-Pd bound dimer, demonstrate the importance of ligand π – π interactions and counterions, and identify a new, energetically viable, mechanism involving two dimerized, outer-sphere reductive elimination transition structures that determine both the rate and selectivity. Although we rule out the previously proposed transmetalation step on energetic grounds, we show it to have an unusual aromatic transition

structure in which two Pd atoms support rearranging electrons. The prevalence of potential metal-supported pericyclic reactions in this system suggests that one should consider such processes regularly, but the results of our calculations also indicate that one should do so with caution.

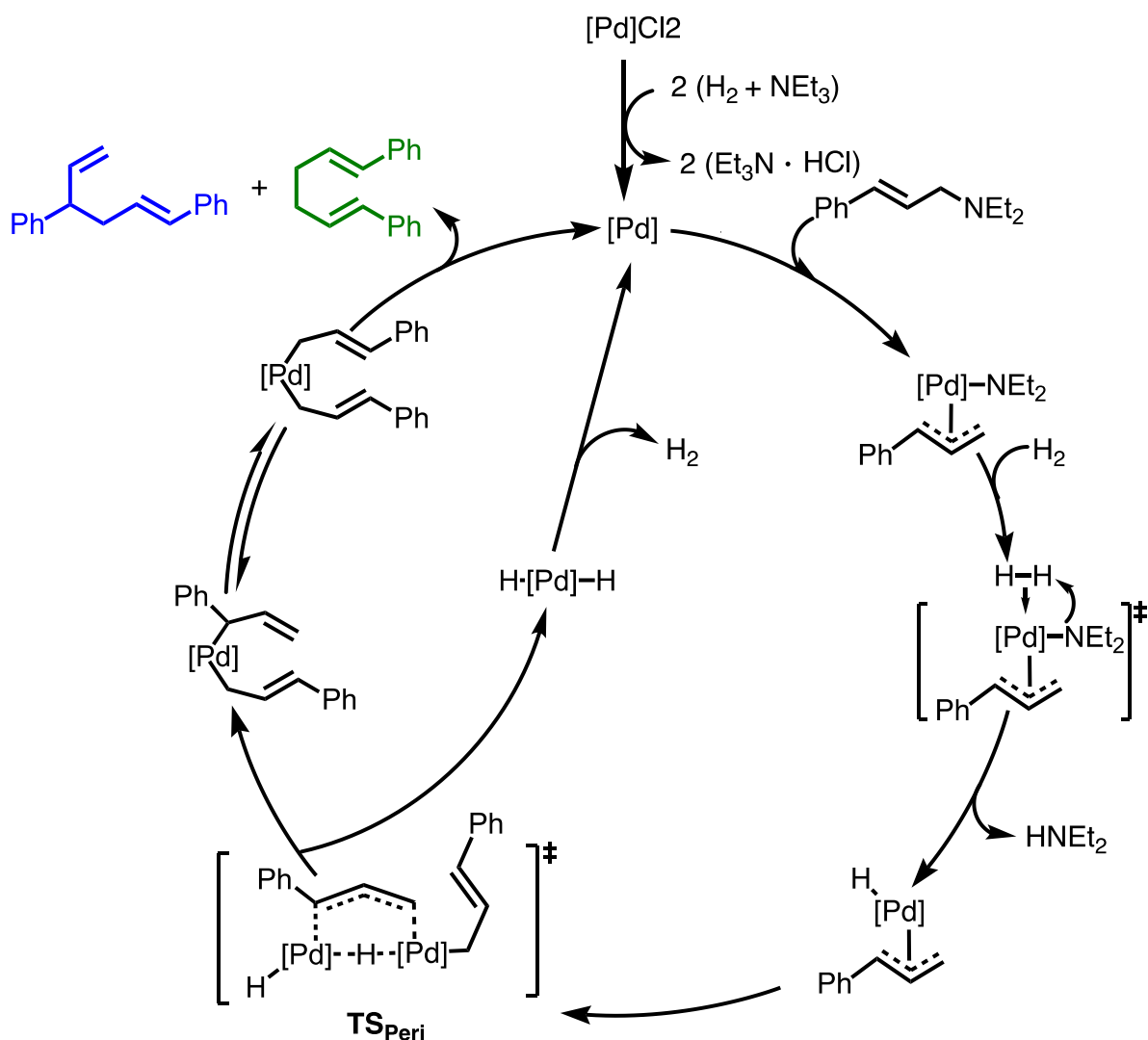
Introduction

Combining palladium catalysis and H₂ oxidation to couple allyl groups could be an empowering synthetic process. Palladium catalysts have had a profound impact on organic chemists' ability to construct C-C bonds, as recognized by the Nobel Prize awarded in 2010 for the development of palladium-catalyzed cross-coupling reactions.⁶¹ Recent developments in mechanistic understanding of these reactions enable the design of more selective and robust catalytic systems.^{62–65} Reactions that make use of H₂ as a sole reductant are ideal, due to its availability and benign nature when compared to common organometallic reductants.^{66–68} However, palladium-catalyzed allyl couplings with H₂ face a chemoselectivity challenge in that reduction of alkenes may compete.⁶⁹ Huang and co-workers recently discovered a palladium catalyst that couples allyl groups with yields of products up to 96% (Scheme 1).⁶ Here we employ high-level density functional theory (DFT) calculations to assess the energetic viability of mechanisms – previously proposed and suggested by us – for this transformation, with an eye toward the potential role of unusual pericyclic processes. This reaction is of note not just for its practical synthetic value but for the fundamental questions it raises about the roles of pericyclic reactions in organometallic chemistry. For example, we explore here transmetalation and allyl-allyl coupling steps involving two palladium atoms that may or may not be considered pericyclic (Scheme 2) and we argue that the product distribution observed experimentally is ultimately determined by metal-free pericyclic reactions. Examples of organometallic pericyclic reactions are particularly sparse for metal dimers,⁷⁰ and here we analyze in detail a case where two metals

directly support cyclically rearranging electrons. Furthermore, we propose an alternative to generally accepted palladium cross-coupling mechanisms.



Scheme 1. Reaction of interest. Newly formed bonds are bolded for clarity.



Scheme 2. Mechanism proposed by Huang and co-workers.^[10]

Palladium promoted carbon-carbon coupling chemistry often follows a typical mechanism: oxidative addition, followed by transmetalation, then reductive elimination.^{71–75} The

originally proposed pathway for the reaction studied here (Scheme 2)⁶ also falls into this mechanistic regime, however the results of our calculations reveal such a pathway to be kinetically unfeasible due to a high barrier for transmetalation (see Supplementary Information (SI)). We propose an alternative reactive pathway that avoids the difficult transmetalation step by directly forming the products via unusual outer-sphere C-C coupling reductive elimination.^{76,77} We also found an unexpected turnover-determining intermediate (**TDI**), which precedes one of two nearly degenerate bimetallic transition structures (TSs) that correspond to not only the rate-determining, but also the selectivity-determining steps.

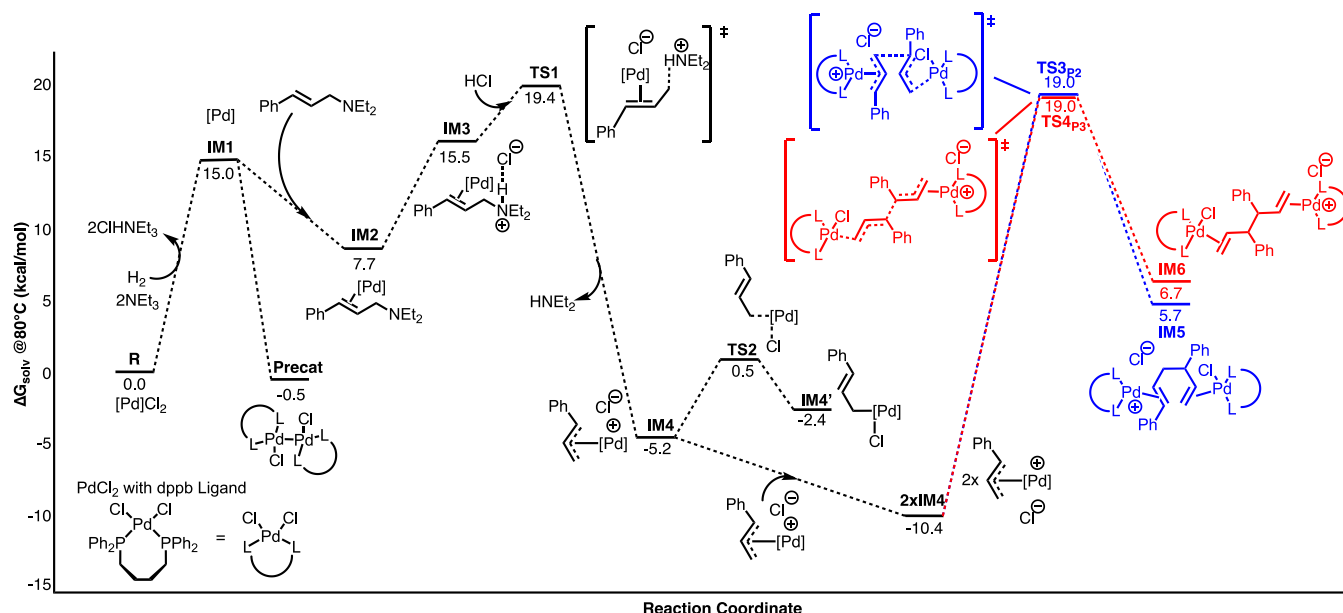


Figure 1. Proposed reaction mechanism. Computed free energies are reported in kcal/mol.

Computational Methods

Geometry optimizations were performed utilizing the PBE0 hybrid exchange-correlation density functional⁷⁸ with the D3(BJ)⁷⁹ dispersion correction in conjunction with the def2-SVP basis set⁸⁰ for all atoms using Gaussian16.⁸¹ The Integral Equation Formulism Polarizable Continuum Model⁸² (IEF-PCM) was employed for implicit solvation with a dielectric constant chosen based

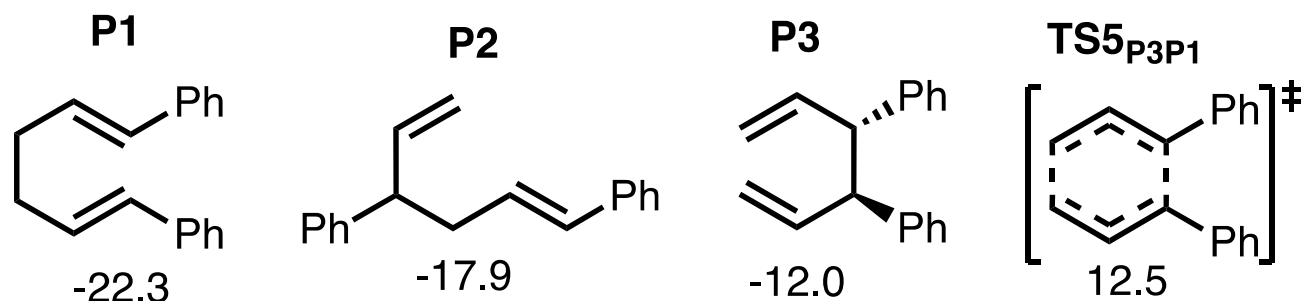
on the literature reported value for *N*-methyl-2-pyrrolidine (NMP) solvent ($\epsilon=33.0$).⁸³ Intrinsic reaction coordinate (IRC) calculations were used to confirm the connectivity between transition structures and minima (see SI for plots).^{54–56} Gas phase single point energy calculations were performed using the PWPB95 double hybrid functional⁸⁴ with D4 dispersion corrections⁸⁵ and the def2-TZVPP basis set on the PCM(NMP)-PBE0-D3(BJ)/def2-SVP geometries using the ORCA 5.0.1 software package.⁸⁶ The PWPB95 functional is highly robust for treating organometallic reactions.^[30,31] Conformational searches were performed following the iMTD-GC procedure with CREST 2.11.1¹² at the GFN2-xTB¹³ level of theory. Normalized Multicenter Bond Indices (nMCBO)⁴ and Non-Covalent Interaction (NCI) Plots⁸⁷ were calculated with Kohn-Sham wavefunctions at the PCM(NMP)-PBE0-D3(BJ)/def2-SVP level of theory using the Multiwfn⁸⁸ program and visualized with VMD.⁸⁹ Molecular geometries were visualized using Cylview 1.0b.⁹⁰

Results and Discussion

Reaction Profile Overview

The most plausible mechanism for the reaction from Scheme 2, based on our computational results, is shown in Figure 1. Pd with the 1,4-bis(diphenylphosphino)butane (dppb) ligand is abbreviated here as [Pd]. First, reduction of [Pd] in [Pd]Cl₂ (**R**) by H₂ can occur to generate a [Pd](0) species (**IM1**) and release 2 HCl. The [Pd](0) species can then combine with [Pd]Cl₂ to form a dimeric precatalyst. Second, association of (*E*)-*N,N*-diethyl-3-phenylprop-2-en-1-amine to the [Pd](0) metal center leads to **IM2**. Third, the amine group in **IM2** can be protonated by HCl to form salt **IM3**. This species then can undergo loss of diethylamine via **TS1** to form an η^3 -allyl palladium cation with a Cl[−] counterion (**IM4**). This species is the turnover determining intermediate (**TDI**).^[40] Notably, a low barrier suggests that **IM4** is in rapid equilibrium with a square planar η^1 Cl-[Pd]-allyl species (**IM4'**) that is slightly higher in free energy. Two

equivalents of **IM4** can then dimerize and form either product **P2** or **P3**, via **TS3_{P2}** or **TS4_{P3}** and **IM5/6**, followed by metal loss (see also Scheme 3). Product **P3**, not observed experimentally, is predicted to undergo an uncatalyzed Cope rearrangement to form the thermodynamically favored product **P1** (Scheme 3). Below we discuss various parts of this pathway in detail. Note that during the revision of our manuscript, Dang et. al published an allyl homocoupling that uses a photocatalyst-promoted electron transfer to form a diallyl palladium species that undergoes inner-sphere reductive elimination.⁶⁴ In contrast, our work assesses a reaction in the absence of photoredox conditions, and thus showcases different diallyl palladium reactivity that can lead to the same products.



Scheme 3. Products **P1**, **P2**, and **P3** and a Cope rearrangement TS that converts unobserved product **P3** to product **P1**. Computed free energies relative to starting materials (kcal/mol) are reported below each structure. The reference 0 for all structures is 2 equivalents of (*E*)-*N,N*-diethyl-3-phenylprop-2-en-1-amine, and one equivalent of H₂.

[Pd]-[Pd] Precatalyst

Based on kinetic studies, formation of a precatalyst was proposed, since a loss of induction period and enhanced initial reactivity was observed when [Pd]Cl₂ was subjected to 10 mol% Et₃N and 1 atm H₂ for 15 min before adding allyl substrate.⁶ This observation is consistent with an initial reduction of [Pd]Cl₂ to an activated [Pd](0) species leading to the overall observed reactivity. Our calculations revealed that formation of a lone [Pd](0) species requires 15 kcal/mol

(**IM1**, Figure 1), making it thermodynamically unstable relative to $[\text{Pd}]\text{Cl}_2$, and not a plausible precatalyst.

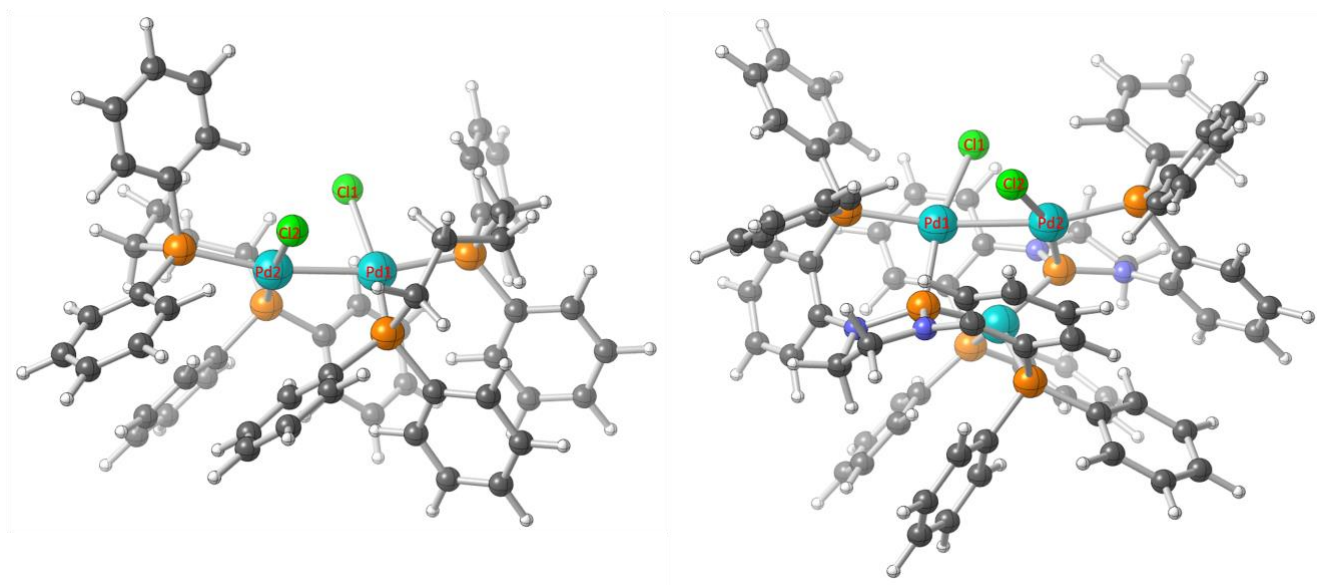


Figure 2. Optimized structures of precatalyst Pd-Pd bound dimer (left) and a reported crystal structure of a similar compound (right).⁹¹ Atom colors: Pd (cyan), P (orange), Cl (green), C(gray), N(blue), H(white).

Table 1. Geometric parameters for Cl-Pd-Pd-Cl dimers and bond orders: Laplacian bond order, (LBO) Mayer bond order, (MBO) Multicenter bond order (MCBO), and normalized multicenter bond order (nMCBO) calculated at the PCM(NMP)-PBE0-D3(BJ)/def2-SVP level of theory.

	Atoms	Pd1, Pd2	Pd1, Cl1	Pd1, Cl2	Pd2, Cl2	Pd2, Cl1	Pd1, Pd2, Cl2	Pd2, Pd1, Cl2	Cl1, Pd1, Pd2, Cl2
Crystal Structure	Geometric Coordinate	2.70 Å	2.44 Å	3.14 Å	2.44 Å	2.95 Å	75.2°	69.8°	102.0°
Optimized Crystal Structure	Geometric Coordinate	2.67 Å	2.43 Å	2.95 Å	2.42 Å	2.93 Å	70.7°	70.1°	101.9°
Pre- catalyst	Geometric Coordinate	2.59 Å	2.43 Å	3.52 Å	2.42 Å	3.17 Å	89.2°	78.1°	-99.0°
	LBO		0.34	<0.05	0.37	<0.05	N/A	N/A	N/A
	MBO		0.68	-0.09	0.90	0.14	N/A	N/A	N/A
	MCBO		0.68	-0.09	0.90	0.14	0.01	-0.0006	-0.0003
	nMCBO		0.83	-0.31	0.95	0.38	0.23	-0.18	-0.25

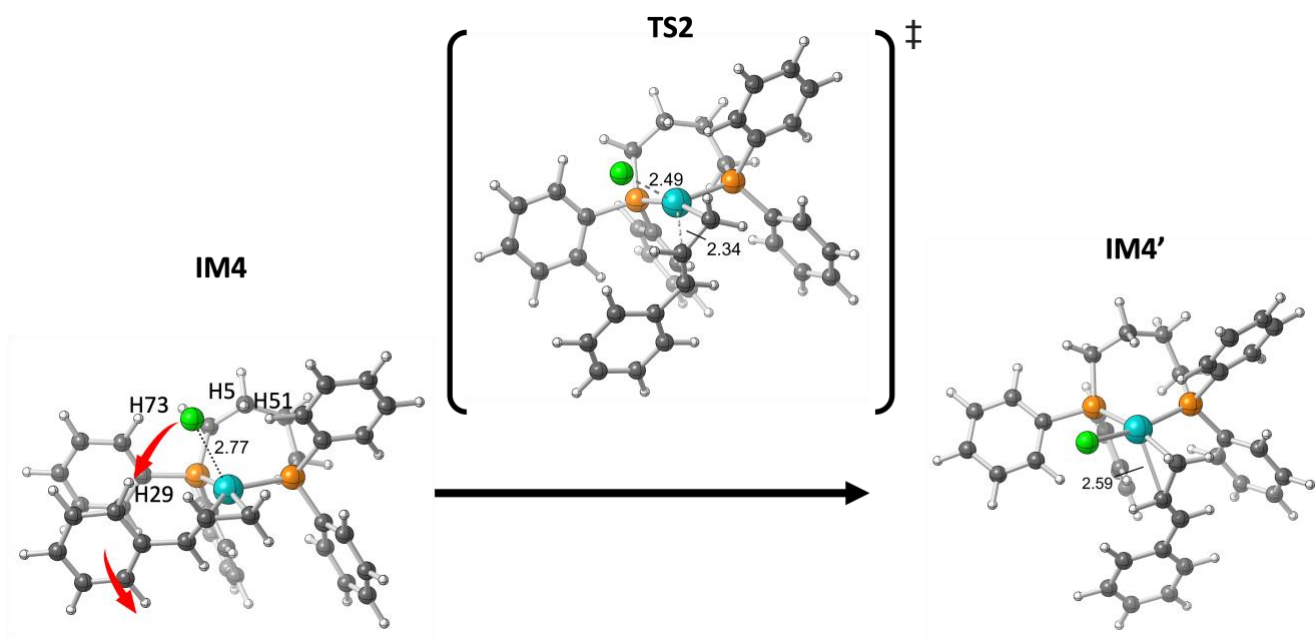


Figure 3. DFT optimized minima of ion-pair (left) and square planar (right) **TDI** and TS (center) connecting them. Atom colors: [Pd] (cyan), P (orange), C (gray), and H (white). Key distances are shown in Å.

However, addition of a second [Pd]Cl₂ species to the reduced [Pd](0) revealed a thermodynamically stable [Pd]₂Cl₂ dimer (Figure 1, **Precat** and Figure 2) that is 0.5 kcal/mol lower in free energy than the starting materials. This dimer contains a Pd-Pd bond and chlorides with acute Pd-Pd-Cl angles (Table 1). Some degree of multicenter bonding between the Cl and [Pd] atoms is suggested by nMCBOs and key bond lengths/angles (Table 1). Examples of molecules with the Cl-Pd-Pd-Cl motif have been previously reported and characterized crystallographically.⁹¹ Key geometric features of these species are retained upon optimization with the same level of theory used for our mechanistic study (e.g., Figure 2, right), further supporting the reliability of our level of theory, at least for geometries of Pd-Pd bonded species.

Deamination

After association of the substrate, HCl can protonate the amine group, turning it into a good leaving group. Loss of diethylamine produces the palladium(II)-(η^3 -allylbenzene) (**IM4**) (Figure 3). The TS for C-N cleavage (**TS1**) is shown in Figure 4.

Turnover Determining Intermediate (TDI)

Upon deamination, the resulting allylbenzene binds to palladium in an η^3 coordination mode, creating a sterically crowded metal center that cannot bind Cl tightly (Figure 3, left); the Cl-Pd bond is particularly elongated (2.77 Å). This elongation can be attributed not only to steric crowding but also to stabilization from several non-classical hydrogen bonds between the Cl and C-H bonds on aromatic rings of the ligand.^{91–93} A Mayer bond order analysis reveals non-negligible bond orders between chlorine and several C-H's (Table 2). The thermodynamic stability of the **TDI** demonstrates the importance of including the Cl⁻ counterion in the calculation.

TS1

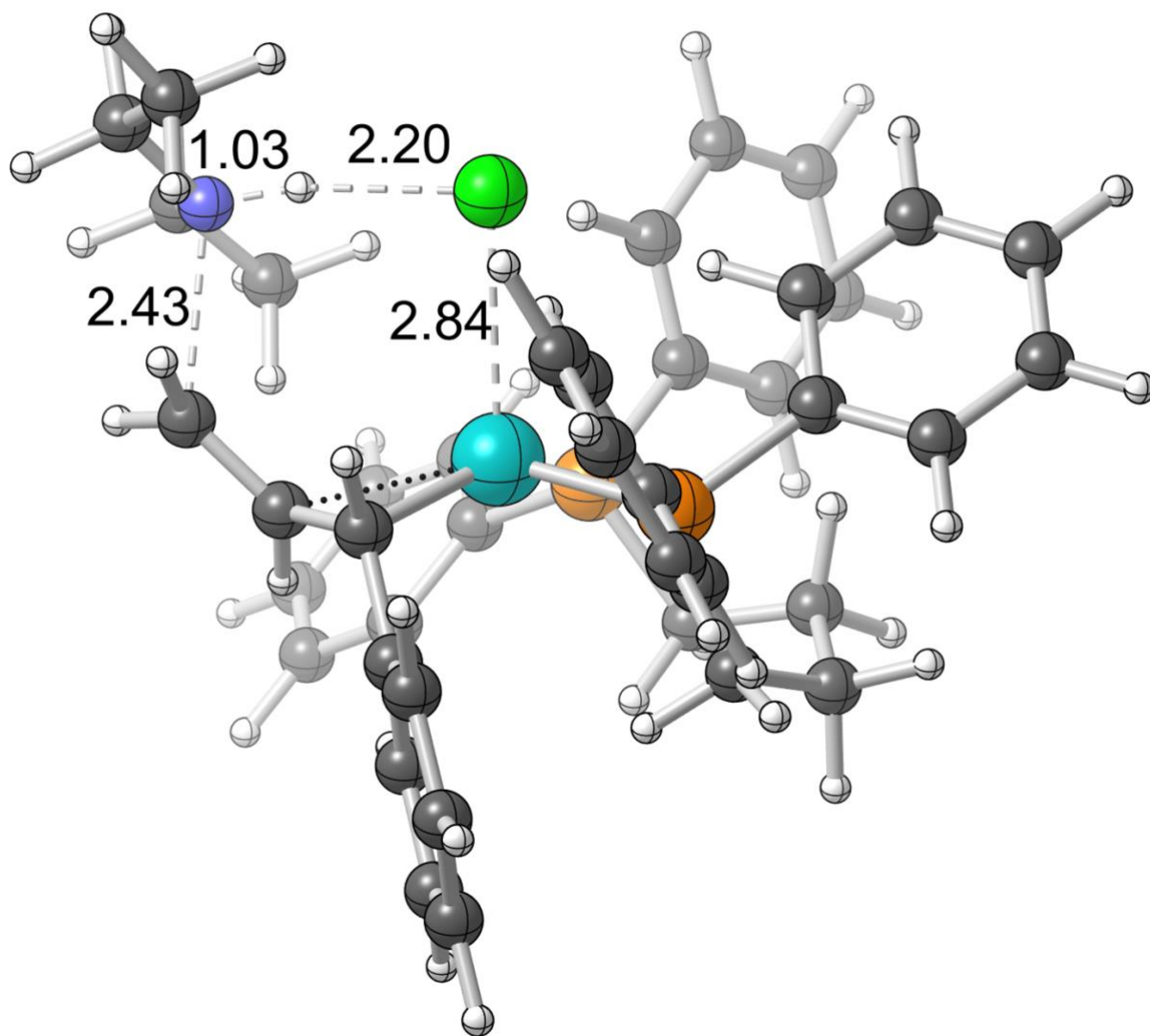


Figure 4. TS for addition of HCl/C-N cleavage to produce cationic allylbenzene palladium and diethylamine. Atom colors: Pd (cyan), P (orange), Cl (green), N (blue), C(gray), H(white). Key distances are shown in Å.

The square planar isomer (**IM4'**) involves a much shorter Cl-Pd bond (2.41 Å). Concomitant with this bond shortening, the allylbenzene loses its h^3 coordination mode. Consistent with the Hammond postulate, the TS connecting **IM4** and **IM4'** (**TS2**) appears to be late, as the Cl-Pd bond distance is more similar to that in **IM4'** than that in **IM4** (Figure 3).

Table 2. Bond lengths and Mayer bond orders (MBO) for key Cl...H-C hydrogen bonding in **TDI**.

Atoms	Cl, Pd	Cl, H51	Cl, H73	Cl, H5	Cl, H29
Geometric Coordinate	2.77 Å	2.55 Å	2.69 Å	2.71 Å	2.95 Å
MBO	0.35	0.12	0.10	0.09	0.07

To further probe long-range effects of the many phenyl groups present, single point calculations were performed without the D3 dispersion correction. Doing so led to an increase in energy of **IM4** by 9.3 kcal/mol relative to that of **R**. Similarly, a truncated system where ligand phenyl groups were substituted with methyl groups exhibited an increase of 4.8 kcal/mol. The reduced stabilities of the **TDI** complex in the non-dispersion corrected and methyl truncated models demonstrate the importance of using an untruncated model with proper dispersion corrections for systems with ligands bearing multiple aromatic groups.

The Originally Proposed Rate-Determining Pericyclic Transmetalation Step

Experimental observation of a second-order rate dependence on [Pd] suggests a rate-determining step that involves two [Pd] species.⁶ The original proposed **TS_{Peri}** (Scheme 2) involves exchange of a hydride for an allyl group via a transmetalation step involving six rearranging, cyclically delocalized, electrons. **TS_{Peri}** exhibits Craig-like σ aromaticity,^{94–96} as the atomic orbitals engaged in this rearrangement include the s orbital of the hydride, the p orbitals of the allyl fragment, and the d orbitals of the palladium atoms. Such a TS was located, and its

geometry reveals a synchronous transfer of the hydride and allyl moieties (Figure 5A). However, this process was calculated to have an activation barrier of 54.4 kcal/mol, far too high to be feasible under the reaction conditions. The large barrier is largely attributed to the high-energy Pd-H intermediates rather than the pericyclic step. The pericyclic step itself only faces a barrier of 17 kcal/mol relative to the preceding intermediate. One might ask if **TS_{Peri}** has the aromaticity expected for a pericyclic reaction. Due to the numerous aromatic groups in the ligands, it is difficult to extract only the effects associated with the reactive core, so to address this issue, the ligand phenyls were truncated to methyl groups for comparison. The full system and truncated model exhibited trends in $\overline{NICS}_{zz}$ consistent with cyclically delocalized electrons (Figure 5C, red), having dips near to the TS. An nMCBO analysis along the reaction coordinate also revealed that the highest bond order between the reactive centers occurs near the TS (Figure 5C, green). For reference, a known aromatic metallabenzene containing a diphosphine palladium unit (Figure 5B) has a $\overline{NICS}_{zz}$ value of -2.5 at the same level of theory, which is even smaller in magnitude than what is observed in the calculated TS and small model.⁹⁷

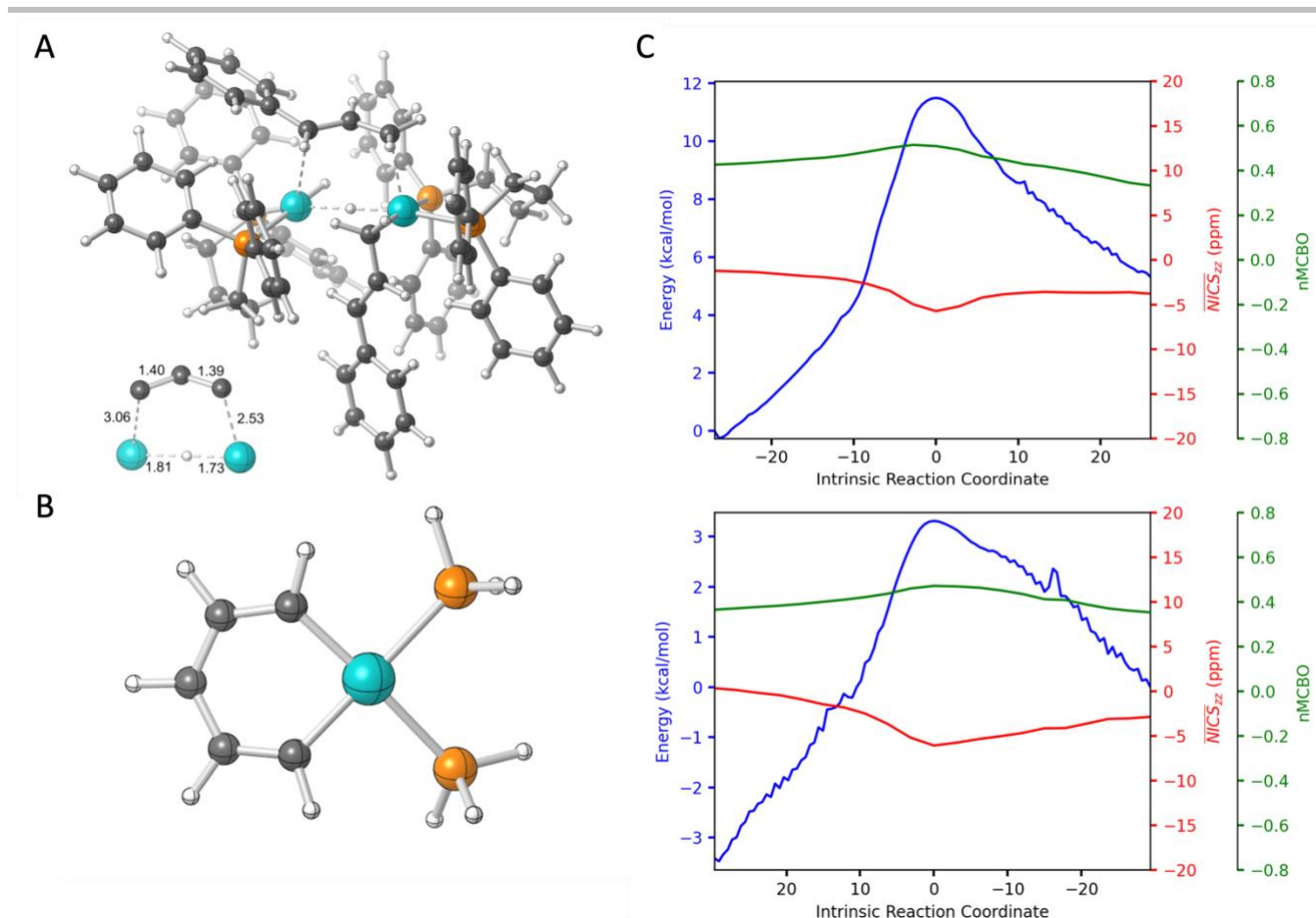
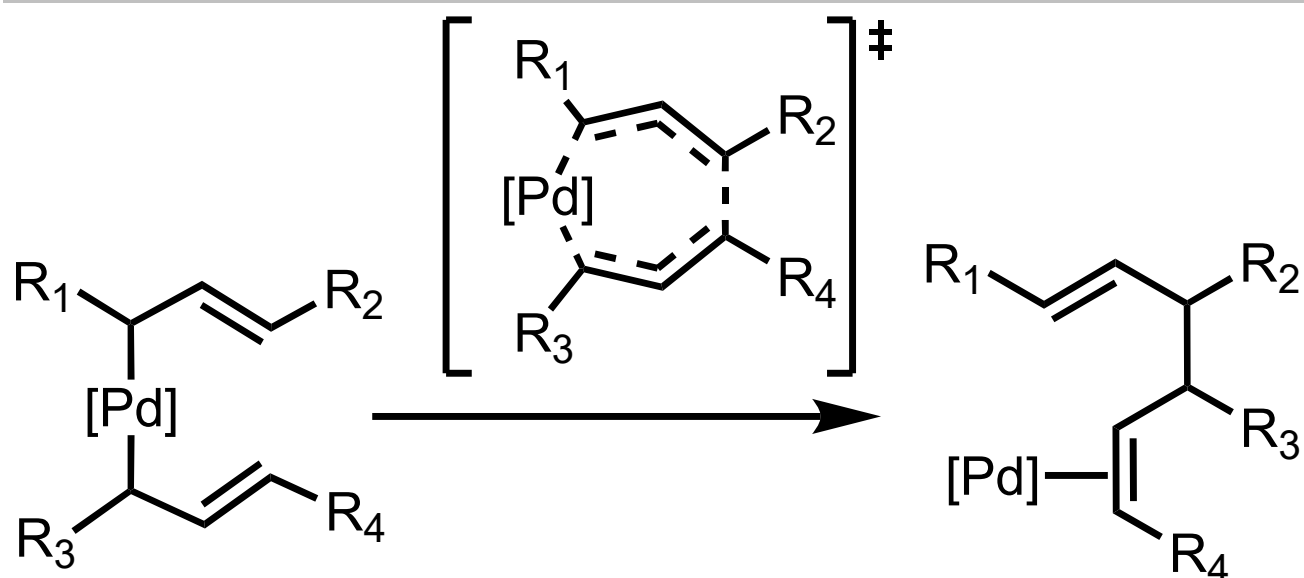


Figure 5. A: Optimized TS for previously proposed transmetalation step.^[10] Key bond lengths (Å) are highlighted in insert. Atom colors: Pd (cyan), P (orange), C(gray), H(white). **B:** Metallabenzene with phosphine ligands – a reference structure for an aromatic palladium complex. **C:** Analysis of proposed pericyclic TS (top) and methyl truncated model (bottom). Plot of energy (blue), $\overline{NICS}_{zz}$ (red), and nMCBO (green) along the IRC. $\overline{NICS}_{zz}$ was averaged from -3 to 3 Å at 0.1 Å increments.



Scheme 4. C-C bond formation from dialkyl palladium intermediate. Products: **P1** ($R_1=\text{Ph}$, $R_2=\text{H}$, $R_3=\text{Ph}$, $R_4=\text{H}$), **P2** ($R_1=\text{Ph}$, $R_2=\text{H}$, $R_3=\text{H}$, $R_4=\text{Ph}$), **P3** ($R_1=\text{H}$, $R_2=\text{Ph}$, $R_3=\text{H}$, $R_4=\text{Ph}$)

The Originally Proposed Selectivity-Determining Step

Previously, it was proposed that the reaction would proceed via a cyclic TS akin to that shown in Figure 5A, followed by transmetalation that would result in both allyl groups bound to the same palladium (Scheme 2).⁶ That bis- η^1 allyl-[Pd] species could then undergo a rearrangement resembling a Cope rearrangement with an intervening [Pd] (Scheme 4). The presence of the palladium d-orbitals facilitates this type of reaction.⁶⁵ Consistent with previous work,^{98,99} our calculations show that, if the diallyl palladium intermediate can be formed, it may undergo symmetry-allowed Pd-catalyzed [$\pi 2_s + \pi 2_s + \sigma 2_s + \sigma 2_s$] reactions to form the observed products with activation energies of 39.7, 30.3 and 28.1 kcal/mol for **P1**, **P2**, and **P3** respectively. However, to generate the necessary diallyl palladium species, the previously discussed barrier of 54.4 kcal/mol would have to be overcome. To circumvent this problem, we hypothesized that

two units of the **TDI** could combine and form the products directly. This proposed mechanism completely avoids traditional transmetalation.

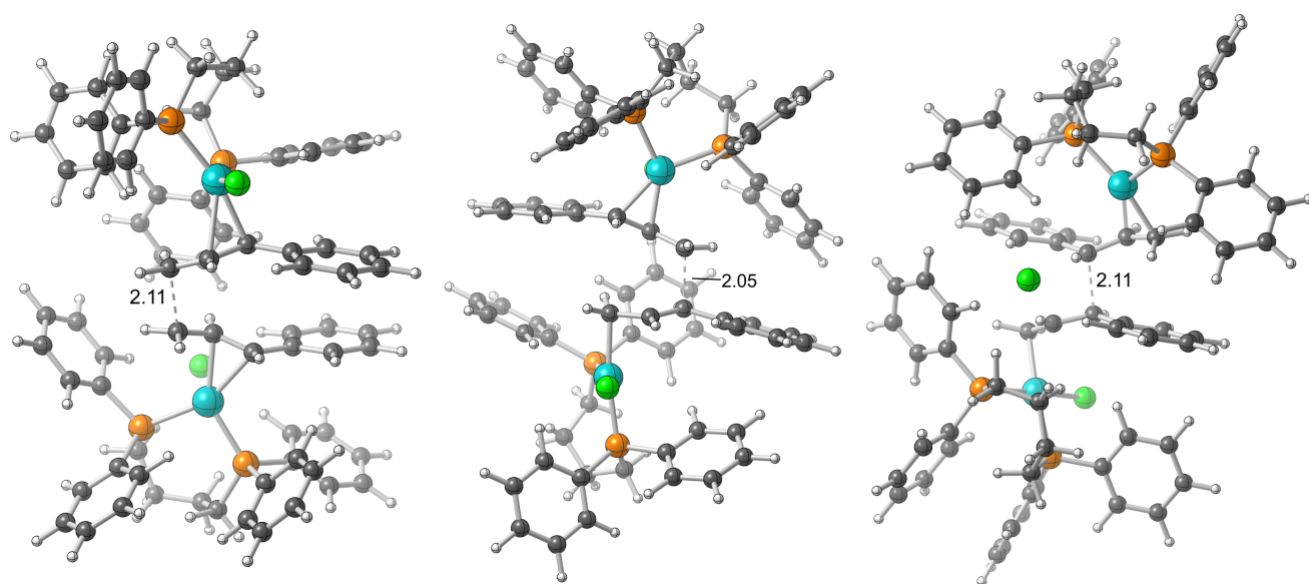


Figure 6. TSs for the turnover and selectivity determining step: **TSP1** (left) **TSP2** (middle) **TSP3** (right). Forming C-C bond distances are shown in Å. Atom colors: Pd (cyan), Cl (green), P (orange), C (gray), H (white).

Rate and Selectivity Determining Steps

The computed free energy barriers for direct formation of **P1**, **P2**, and **P3** via double outer sphere reductive elimination shown in Figures 1 and 6 were predicted to be 37.3, 29.4 and 29.4 kcal/mol respectively. The larger barrier for formation of **P1** appears to be due to steric clashes near the palladium centers. This unusual alternative to classic reductive elimination has some precedent in recent work, although that work did not involve C-C coupling.^[17] These findings

could be taken to imply that **P1** is kinetically inaccessible, however we predict that **P3** may, upon loss of [Pd], undergo an uncatalyzed Cope rearrangement to form **P1** with an activation free energy of only 24.5 kcal/mol (a palladium catalyzed Cope rearrangement was also evaluated, but the activation energy was calculated to be 4 kcal/mol higher in energy than the uncatalyzed Cope rearrangement; see appendix for details). The extremely similar free energies for **TSP2** and **TSP3** are in excellent agreement with the experimentally observed product distribution of 50/50/0 for **P1/P2/P3**.

Table 3. Mulliken (Hirshfield) [Natural Population Analysis] charges, in units of elementary charge, on carbon atoms involved in newly forming C-C bond. Difference is reported as (η^3 cation) - (square planar).

	Square Planar	η^3 Cation	Δ Charge (e)
TSP1	-0.08 (-0.073) [-0.491]	0.004 (-0.032) [-0.367]	0.084 (0.041) [0.124]
TSP2	-0.113 (-0.038) [-0.298]	0.047 (-0.026) [-0.343]	0.16 (0.013) [-0.045]
TSP3	-0.023 (-0.037) [-0.272]	0.047 (0.002) [-0.185]	0.07 (0.039) [0.087]

Table 4. SAPT0/def2-SVP results (kcal/mol).

	Electrostatics	Exchange	Induction	Dispersion	Total
TSP1	-73.9	29.3	-26.4	-10.7	-81.7
TSP2	-76.7	38.3	-28.7	-13.1	-80.2
TSP3	-91.2	42.0	-30.4	-14.1	-93.6

All three double **TDI** coupling TSs involve one η^1 , approximately square planar, palladium allyl species (**IM4'**) and one η^3 palladium allyl species (**IM4**). Mulliken, Hirshfield, and Natural population analyses of the carbon atoms involved in the forming C-C bond indicate greater negative charge on the square planar palladium (Table 3), consistent with the idea that this palladium substructure is nucleophilic while the other is electrophilic. Furthermore, chlorine anions are known to affect reactivity and selectivity in palladium allyl couplings by means of displacing the allyl fragment, which is consistent with structures and reactive roles of **IM4** and **IM4'**.^[54] Additionally, during the selectivity determining steps, the chlorine anions exhibit extensive non-classical Cl...H-C hydrogen bonding.^{92,93} For example, Figure 7 shows these interactions visualized with an NCI plot for **TSP3**, which shows a network of weak interactions. The interaction energy of the chloride counterion with the rest of the TS was analyzed by Symmetry Adapted Perturbation Theory (SAPT).¹⁰⁰ A significantly larger interaction was observed for **TSP3** compared to **TSP1** and **TSP2** (Table 4), with electrostatics being the leading term. The removal of chlorine atoms from these TSs resulted in increased free energy barriers, different predicted selectivity, and different mechanisms (see appendix), further illustrating the importance of including chlorides in computational models. In addition to chlorine interactions, π - π interactions were also revealed to be extensive in the rate and selectivity-determining steps. NCI plots reveal several face-to-face, edge-to-edge interactions that occur as both ligand-ligand, and substrate-ligand π - π interactions (Figure 7).

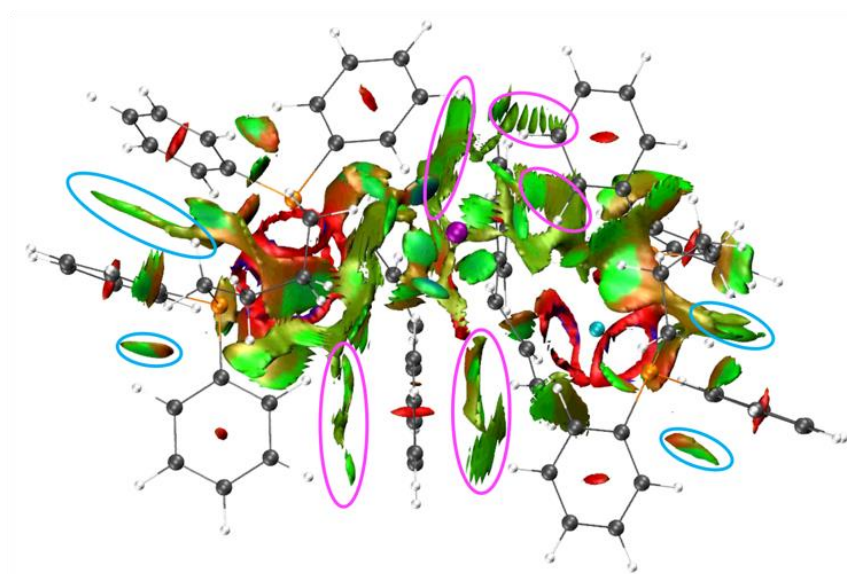
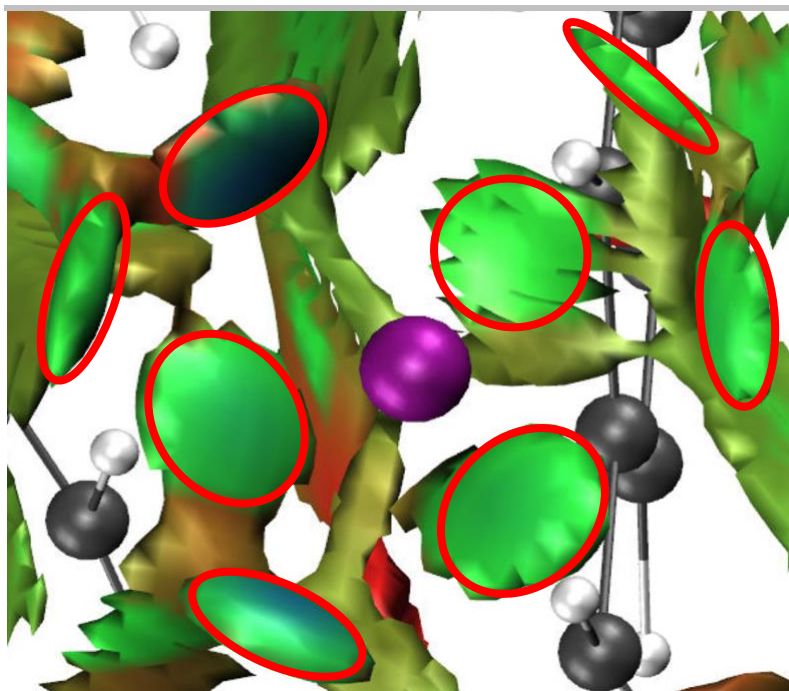


Figure 7. NCI plots of **TSP3** (bottom) and the Cl-binding region of **TSP3** (top). Red, green, and blue regions depict repulsive, weakly attractive, and strongly attractive non-covalent interactions. Cl...H-C hydrogen bonding interactions are circled in red. Ligand-ligand and ligand-substrate π - π interactions are circled in blue and pink, respectively. Pd (cyan), P (orange), Cl (magenta), C(gray), H(white).

Conclusions

Based on the results of DFT calculations, we propose a new mechanism for the [Pd]-catalyzed allyl-allyl coupling reported by Huang and co-workers.⁶ We suggest that the observed second-order rate dependence results from an outer-sphere coupling of two [Pd]-allyl monomers. We also suggest that the observed product distribution results from a metal-free Cope rearrangement of one of the initially formed products. Our results fully comport with the experimental results and highlight the pivotal roles of both ligand π - π interactions and counterion effects. In addition, we examined in detail the various possible reaction steps that could be pericyclic in nature (metal-containing, metal-supported, and metal-free), determined which processes are and are not, and predicted which have low enough barriers to contribute to the observed reactivity. We hope that our descriptions of geometric and electronic features of these unusual pericyclic reactions, whether they are found along the productive reaction coordinate or not, will encourage others to incorporate such steps in the design of new catalytic cycles.

Chapter 4 — Catalytic Asymmetric Wagner–Meerwein Shifts of Aliphatic Hydrocarbons

This chapter is reproduced from a collaboration published in Nature, see the publication list before the introductory chapter.⁷ All experimental work was performed by Benjamin List's group, with synthetic work performed by Vijay Wakchaure, isotope and kinetics work by Markus Leutzsch, and the steric map plots by Nobuya Tsuji. Dean Tantillo's research group, Croix and

I, equally contributed to elucidating the reaction mechanism, and determining key interactions that dictate enantioselectivity.

Asymmetric catalysis is an advanced area of chemical synthesis, but the handling of abundantly available, purely aliphatic hydrocarbons has proven to be challenging. Typically, heteroatoms or aromatic substructures are required in the substrates and reagents to facilitate an efficient interaction with the chiral catalyst. Confined acids have recently been introduced as tools for homogenous asymmetric catalysis, specifically to enable the processing of small unbiased substrates¹⁰¹. However, asymmetric reactions in which both substrate and product are purely aliphatic hydrocarbons have not previously been catalyzed by such super strong and confined acids. We describe here an imidodiphosphorimidate-catalyzed asymmetric Wagner–Meerwein shift of aliphatic alkenyl cycloalkanes to cycloalkenes with excellent regio- and enantioselectivity. Despite their long history and high relevance for chemical synthesis and biosynthesis, Wagner–Meerwein reactions utilizing purely aliphatic hydrocarbons, such as those originally reported by Wagner and Meerwein, had previously eluded asymmetric catalysis.

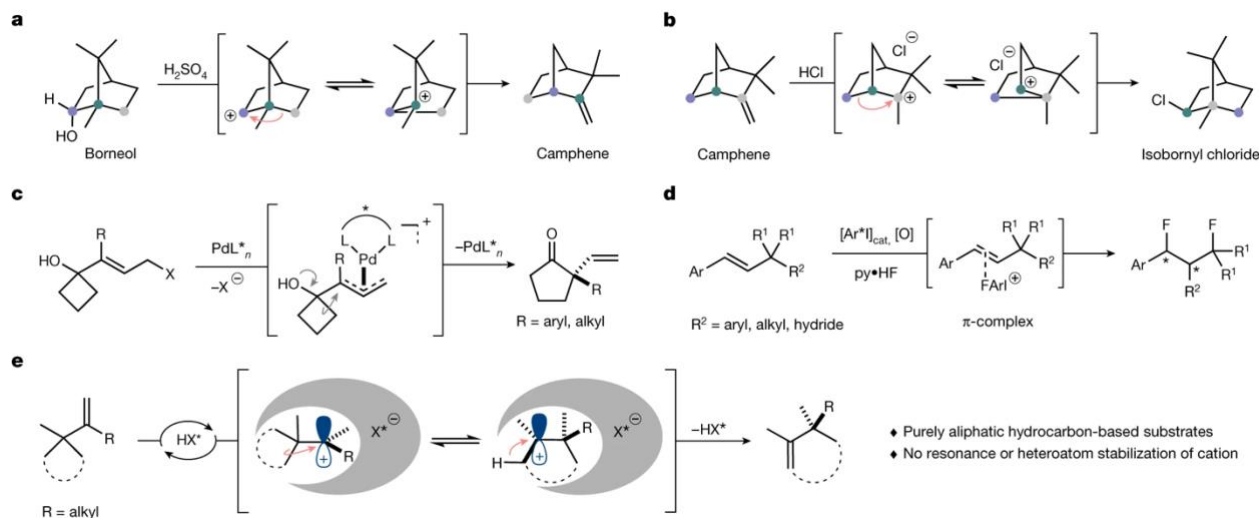


Fig. 1 | Carbocation rearrangements. a, Borneol to camphene rearrangement (Wagner 1899)¹⁰². **b**, Camphene to isobornyl chloride rearrangement (Meerwein 1922)^{103,104}. **c**, Palladium-

catalysed semipinacol rearrangement/Wagner–Meerwein shift. **d**, Aryl iodide-catalysed enantioselective 1,3-difluorination. **e**, Catalytic asymmetric Wagner–Meerwein shifts of aliphatic hydrocarbons (this work). HX*, Brønsted acid.

Since Bredig and Fiske¹⁰⁵ discovered a nonenzymatic, modestly enantioselective cinchona alkaloid-catalysed cyanohydrin synthesis in 1912¹⁰⁶, asymmetric chemical catalysis has evolved extensively and currently encompasses reactions with transition metals^{107–109}, enzymes^{110,111} and organocatalysts^{112–114}. However, the catalytic and enantioselective processing of purely aliphatic hydrocarbons is still extremely challenging. Typical substrates and reagents used in asymmetric catalysis feature heteroatoms or aromatic groups, which enhance reactivity and enable enantiodifferentiation by providing functional groups that engage in specific interactions with the catalyst. Indeed, to the best of our knowledge, Pfaltz's landmark iridium-catalysed asymmetric hydrogenation of a purely alkyl-substituted olefin stands out as the only example in which an only-aliphatic hydrocarbon is catalytically processed to give an enantiopure only-aliphatic hydrocarbon^{115–117}. We became interested in advancing hydrocarbon chemistry by investigating cationic shifts as a fundamental class of chemical and biochemical transformations. The most prominent example in this regard is the cationic Wagner–Meerwein rearrangement^{118,119}. Catalytic enantioselective Wagner–Meerwein reactions that proceed through purely aliphatic hydrocarbon-based cations, such as those originally reported by Wagner and Meerwein, have not previously been described (Fig. 1a,b)^{120–124}. Notable examples of enantioselective cationic shifts were reported by Trost and Yasukata¹²⁵, Trost and Xie¹²⁶ and Jacobsen and coworkers^{127,128}, and feature π -allyl palladium intermediates to afford enantioenriched α -vinyl cycloketones (Fig. 1c) or a hypervalent iodine-catalysed, 1,3-difluorinative reaction of β -substituted styrenes (Fig. 1d).

We have recently introduced strong and chiral confined imidodiphosphorimidate (IDPi) Brønsted acids as a new and general tool for asymmetric catalysis^{129,130}. IDPi catalysts have activated unbiased olefins in hydroalkoxylations¹³¹, hydroarylations¹³² and hydrolactonizations¹³³ and even enabled control over purely hydrocarbon-based non-classical carbocations^{134,135}. Encouraged by these results, we became tempted to challenge our IDPi motif with purely aliphatic hydrocarbon-based substrates toward highly enantioselective Wagner–Meerwein shifts and describe here the results of these investigations (Fig. 1e).

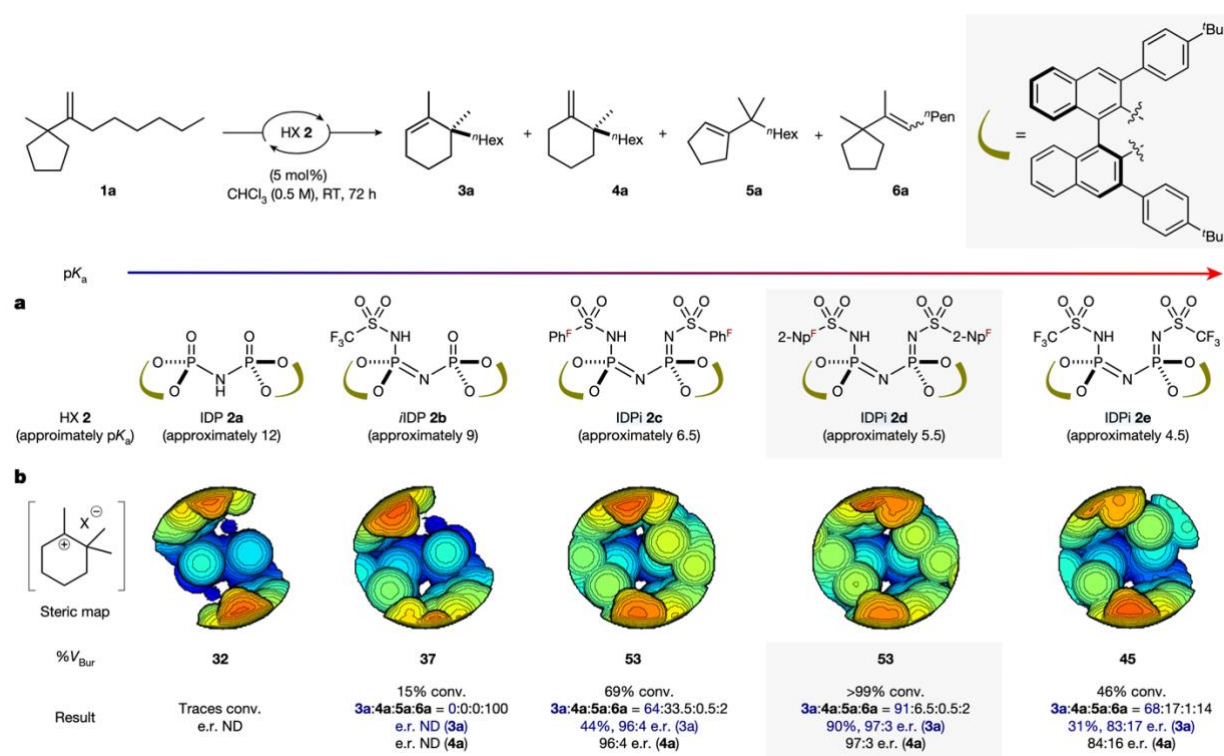


Fig. 2 | Investigation of acidity, confinement and chiral pocket size of catalyst in the catalytic Wagner–Meerwein shift. Yields and conversion were determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Side product distribution ratios were determined by crude ^1H NMR spectroscopy. The enantiomeric ratio was determined by gas chromatography analysis (Supplementary Information has details). **a**, Estimated pK_a values in CH_3CN based on the literature report for a similar catalyst^{130,136}. **b**, Calculated steric map of

simplified substrate visualized by SambVca 2.1¹³⁷. The map is viewed from the centre of the substrate and directed toward the active site of each catalyst. The colour indicates depth along the z axis; the red zone is closer to the substrate, whereas the blue zone is farther away. For the ion pair of **2b**, one of the C–H bond lengths is fixed (Supplementary Fig. 21). conv., conversion; e.r., enantiomeric ratio; IDP, imidodiphosphoric acid; iIDP, iminoimidodiphosphoric acid; ND, not determined; nHex, n-hexyl; nPen, n-pentyl; 2-NpF, 2-perfluoronaphthyl; PhF, pentafluorophenyl; pKa, negative logarithm of the acid dissociation constant; RT, room temperature; tBu, tert-butyl; %VBur, percent buried volume.

At the onset of our studies, we subjected olefin **1a** to 5 mol% of various confined chiral Brønsted acid catalysts covering a broad pKa(negative logarithm of the acid dissociation constant Ka) range at room temperature for 24 h to obtain ring-expanded cycloalkene **3a** (Fig. 2). As expected, weaker acids, such as imidodiphosphoric acid **2a**, failed to give any reactivity. Similarly, iminoimidodiphosphoric acid **2b** gave only poor conversion of substrate **1a** to furnish olefin isomerization product **6a**. By contrast, our highly acidic and confined IDPi catalyst **2c** gave product **3a** in moderate conversion and a high enantiomeric ratio of 96:4. A substantial amount of exoproduct **4a** is also formed in similar enantioselectivity and is slowly converted into the corresponding endoproduct **3a**, already suggesting that deprotonation cannot be enantiodetermining. We further observed trace amounts of product **5a** (less than 0.5%) in which a methyl group has migrated. Our highly acidic and more confined IDPi catalyst apparently suppresses olefin isomerization of the starting material to give hydrocarbon **6a** (less than 2%). Notably, a change in the sulfonamide inner core of the catalyst from pentafluorophenylsulfonyl to perfluoronaphthylsulfonyl (IDPi **2d**) delivered a drastic increase in reactivity and gave full conversion with excellent yield and enantioselectivity. We hypothesized that the high chemoselectivity, enantiocontrol and overall reactivity were enabled by the highly confined

microenvironment offered by the IDPi catalysts. To visually assess this confinement effect, buried volumes were calculated using a model ion pair of the catalysts^{138,139} (Fig. 2). A higher percent buried volume, which corresponds to a narrower pocket, may indicate that the carbocation is stabilized within the IDPi anion pocket, possibly compensating for the absence of traditional heteroatom or resonance stabilization. Indeed, consistent with these expectations, the sulfonylimidophosphoryl groups not only modulate the overall acidity but also contribute to the confinement of the catalytic active site. Notably, when compared with IDPi **2d** (53% buried volume), the even more acidic IDPi **2e**, which provides a relatively larger pocket (45% buried volume), afforded product **3a** in only poor yield. At 46% consumption of substrate **1a**, only 31% yield of product **3a** was obtained, with moderate enantioselectivity along with more olefin isomerization product **6a**. These results suggest that a fine-tuned balance between acidity and confinement is crucial to achieve high chemoselectivity, enantiocontrol and overall reactivity. After a brief screening of catalysts and reaction conditions (Supplementary Table1), we selected catalyst **2d**, CHCl₃ (4 M) and room temperature for 24 h and found that product **3a** can be obtained in both excellent yield and enantioselectivity (91%, 97:3 enantiomeric ratio).

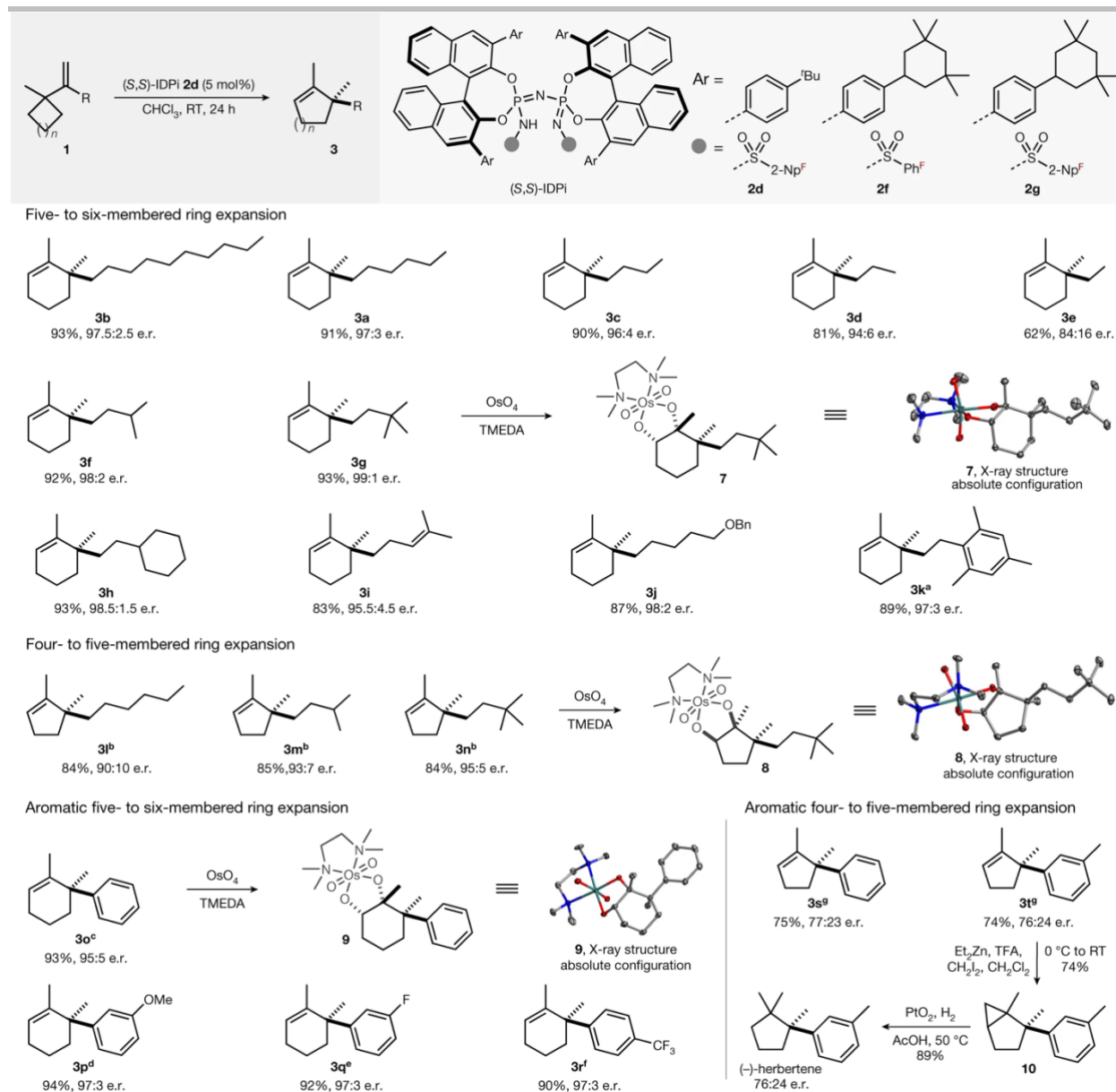


Fig. 3 | Scope of the catalytic asymmetric Wagner–Meerwein shift. Reactions were performed at 0.25 mmol scale. Isolated yields after chromatographic purification. The enantiomeric ratio was determined by gas chromatography analysis (Supplementary Information has details). ^aAt 50 °C for 24 h. ^bWith catalyst **2f** in n-hexane at room temperature for 36 h. ^cWith catalyst **2g** in methyl cyclohexane at 60 °C for 48 h. ^dWith catalyst **2g** in methyl cyclohexane at 60 °C for 72 h. ^eWith catalyst **2g** in methyl cyclohexane at 80 °C for 96 h. ^fWith catalyst **2g** in methyl cyclohexane at 90 °C for 6 days. ^gWith catalyst **2d** in methyl cyclohexane at 50 °C for 24 h. The

structure of osmate ester **7** derived from product **3g**, H atoms and the disordered atoms are omitted for clarity. The structure of one of the two independent molecules of osmate ester **8** contained in the unit cell derived from product **3n** and H atoms are omitted for clarity. The structure of osmate ester **9** derived from product **3o**, H atoms, water molecule and the disordered atoms are omitted for clarity (Supplementary Figs. 10–16). Bn, benzyl; TFA, trifluoroacetic acid; TMEDA, *N,N,N',N'*-tetramethylethylenediamine.

The substrate scope of the Wagner–Meerwein shift was assessed using a variety of alkenyl cycloalkanes that were readily converted into the corresponding ring-expanded cycloalkene products (Fig. 3). Linear and longer alkyl chains attached to the olefin gave products **3a–c** in both excellent yields and enantioselectivities. Shortening the alkyl chain to *n*-propyl (**3d**) retained the high enantioselectivity, but moderate enantioselectivity was obtained with an ethyl group (**3e**, 84:16 enantiomeric ratio). The incremental reduction in enantiomeric ratio (**3b** → **3a** → **3c** → **3d** → **3e**) is consistent with either simple steric repulsion or dispersive interactions of the *n*-alkyl groups contributing to the enantioselectivity. To our delight, branched alkyl substituents at the olefin exhibited high yields and excellent enantioselectivities (**3f–h**). A substrate bearing an alkene substituent was also tolerated, providing product **3i** with an enantiomeric ratio of 95.5:4.5 in 83% yield. *O*-benzyl and aryl group functionalities at the alkyl chain can be utilized successfully (**3j** and **3k**). We also investigated the analogous four- to five-membered ring expansion using IDPi **2f**, and both linear and branched alkyl substituents at the olefin gave the desired products in high yields and good to high enantioselectivities (**3l–n**). Apart from aliphatic hydrocarbons, aryl-substituted substrates also react. For example, five- to six-membered ring expansion with IDPi **2g** provided the corresponding products **3o–r** with different stereoelectronic properties in both high yields and enantioselectivities. Aryl-substituted substrates in the four- to five-membered ring expansion reacted with moderate yields and

enantioselectivities (**3s** and **3t**). As expected, both the three- and six-membered ring substrates under the optimal condition are unreactive. To illustrate the synthetic utility of this asymmetric transformation, a short enantioselective total synthesis of (–)-herbertene¹⁴⁰ was developed. First, product **3t** was converted into cyclopropane **10** by a Simmons–Smith reaction in 74% yield, and hydrogenolysis delivered (–)-herbertene in 89% yield. X-ray diffraction analysis of osmate esters derived from ring expansion products **3g**, **3n** and **3o** allowed the unambiguous determination of the absolute configurations of these products¹⁴¹. The stereochemistry of all other products has been assigned by analogy.

To gain insight into the reaction mechanism, we synthesized enantiopure (greater than 99:1 enantiomeric ratio), ¹³C-labelled exoproduct **11** and subjected it to the reaction conditions (Fig. 4a). Olefin isomerization of olefin **11** with IDPi **2d** gave endoproduct **12** in a greater than 99:1 enantiomeric ratio. Similarly, its enantiomer, ent-**11** (98.3:1.7 enantiomeric ratio), reacted at slightly slower rate (mismatched case) and gave product ent-**12** in 98.4:1.6 enantiomeric ratio. In both cases, we did not observe side products resulting from [1,2]-methyl or [1,2]-n-hexyl shifts. Although these results could be interpreted as implying irreversible ring expansion, our computational results indicate that this is not the case (see below). We also subjected the corresponding olefin isomer **6a** and alcohol **13** to the reaction conditions (Fig. 4b). In contrast to substrate **1a**, which afforded the desired product **3a** in excellent yield and enantioselectivity, both substrates **6a** and **13** gave product **3a** in only moderate yield and slightly lower enantioselectivity. In both cases, the substrate is less reactive, and an alternative pathway (for example, the reaction proceeding through protonated alcohol or a concerted pathway that is less enantioselective) might occur. Alternatively, the means by which the carbocation is generated may affect the subsequent rearrangement through a non-equilibrium process (see below). Furthermore, we investigated the reaction progression of ¹³C-labelled substrate **1a'** with IDPi **2d**

by ^{13}C nuclear magnetic resonance (NMR) spectroscopy (Fig. 4c). ^{13}C NMR data acquired at the beginning of the reaction show the formation of endproduct **3a'** and exoproduct **4a'** in almost equimolar amount. After approximately 2 h, product **4a'** slowly converts into the thermodynamically favoured product **3a'**. Although the formation of product **3a''** through an [1,2]-n-hexyl group migration after the ring expansion was not detected, traces of both a methyl-migrated side product **5a'** (less than 0.5%) and the olefin isomerization product **6a'** (less than 2%) were detected. The consumption of starting material **1a'** shows a characteristic first-order exponential decay, which has been observed for other intramolecular IDPi-catalysed reactions, for which only one substrate molecule is involved in the rate-limiting step of the reaction^{133,142}. Additionally, the catalyst concentration remained constant, and no substantial chemical shift changes were observed during the reaction in the ^1H and ^{13}C NMR spectra. The reaction order of catalyst **2d** was determined with variable time normalization analysis^{143,144} from ^1H NMR concentration profiles and was found to be first order as well (Supplementary Information has further details). Reactions performed at five different temperatures ranging from 15 °C to 55 °C enabled us to determine the thermodynamic parameters of the reaction with the Eyring equation. An enthalpy of activation $\Delta H^\ddagger = 12.5 \pm 0.5 \text{ kcal mol}^{-1}$, a negative entropy of activation $\Delta S^\ddagger = -30.3 \pm 1.6 \text{ kcal mol}^{-1} \text{ K}^{-1}$ and a free energy of activation $\Delta G^\ddagger_{298\text{K}} = 21.5 \pm 0.7 \text{ kcal mol}^{-1}$ were determined (Fig. 4d).

On the basis of these experiments, we can propose a plausible reaction mechanism (Fig. 4e). Accordingly, the catalytic cycle is initiated with the protonation of olefin **1a'** by IDPi **2d** to provide an alkyl-carbocation that is highly confined within the IDPi anion cavity as a contact ion pair (I), followed by an enantiodetermining five- to six-membered ring expansion, which affords ion pair II. We assume that the protonation of the substrate is the overall rate-limiting step of the reaction as covalent adducts have not been observed by ^{31}P NMR spectroscopy during the

reaction monitoring. Additionally, the negative activation entropy is in the range of various reported literature values for protonation of olefins^{133,145}. Kinetic deprotonation gives an isolable exocyclic product **4a'** that can reversibly be protonated to regenerate ion pair **II**. Finally, deprotonation from ion pair **II** furnishes the thermodynamically preferred endocyclic product **3a'** and regenerates catalyst **2d**. Before the ring expansion, ion pair **I** could isomerize to furnish trisubstituted **6a'** or convert to methyl-migrated ion pair **III**, which upon deprotonation, leads to side product **5a'**. Alternatively, ion pair **II** could undergo a [1,2]-n-hexyl shift to provide ion pair **IV**, which upon deprotonation, would lead to side product **3a''**. Similarly, ion pair **II** could undergo a [1,2]-methyl shift followed by deprotonation to provide the side products **14a'** and **15a'**. Although these hypothetical side reactions did not occur in the five- to six-membered ring expansion, in the corresponding four- to five-membered ring expansion, we did observe the [1,2]-methyl shift and [1,2]-n-hexyl shift side products.

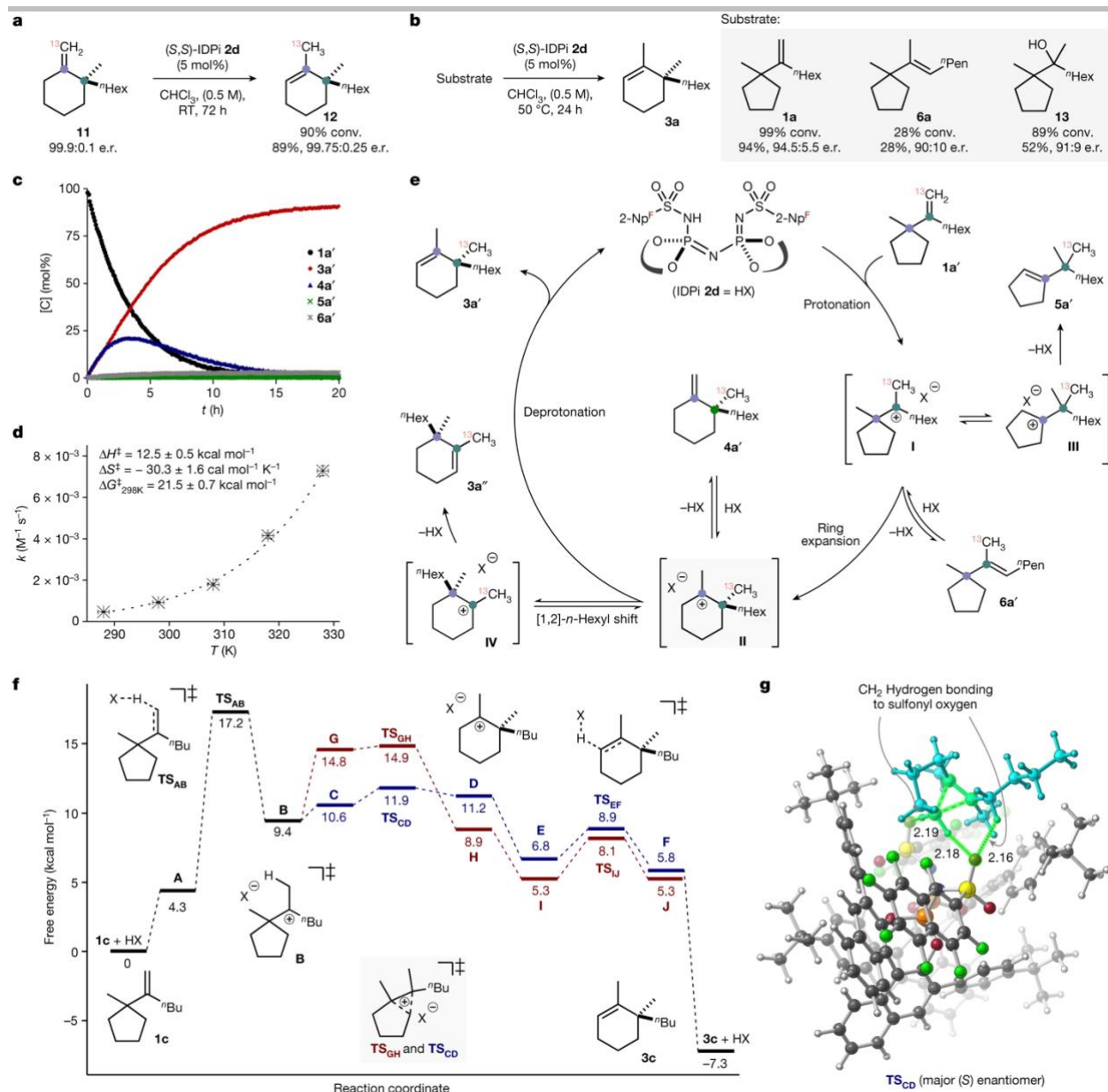


Fig. 4 | Mechanistic and computational studies. **a**, ^{13}C -labelled exocyclic olefin isomerization. **b**, Wagner–Meerwein shift with olefin isomers and corresponding alcohol. Yields and conversion were determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Olefin isomer **6a** contains 3% inseparable side product **5a**. **c**, Reaction of ^{13}C -labelled substrate **1a'** catalyzed by IDPi **2d**. Reaction profile monitored by ^{13}C NMR spectroscopy. **d**, Eyring plot obtained for the reaction of IDPi **2d** with substrate **1a**. **e**, A plausible catalytic cycle. **f**, Density functional theory-derived free energy profile (CPCM(CHCl_3) ω B97X-D4/def2-

TZVPP/CPCM(CHCl₃)-B3LYP-D3(BJ)/def2-SVP). The red path denotes the path to R enantiomer, and the blue path denotes the path to S. HX = **2d**. Structures **B**, **C** and **G** are different conformations. **B** is connected directly to **TSAB**, **C** is connected directly to **TSCD** and **G** is connected directly to **TSGH** (Supplementary Information has additional details on the conformational landscape of this complex system). **g**, Computed **TSCD** (major (S) enantiomer). Bond lengths shown are in angstrom (Å).

Density functional theory calculations support the proposed mechanism and lead to a model for the origin of enantioselectivity. Our calculations (CPCM(CHCl₃)- ω B97X-D4/def2-TZVPP// CPCM(CHCl₃)-B3LYP-D3(BJ)/def2-SVP) (Supplementary Information has details and references) on the conversion of substrate **1c** suggest that the rate-determining step is protonation of the olefin, which has a predicted free energy barrier of 17.2 kcal mol⁻¹ (Fig. 4f). The enantioselectivity-determining step is the subsequent five- to six-membered ring expansion, and the origin of enantioselectivity emerges out of a balance of non-covalent interactions within the confined chiral pocket, consistent with an induced-fit model^{146,147}. Specifically, favourable dispersion interactions and C–H $\cdots$ O hydrogen bonds seem to play key roles (Fig. 4g; Supplementary Information has additional details)^{148,149}. The lowest-energy transition state structures leading to R (**TSGH**, red path) and S (**TSCD**, blue path) products differ in free energy by 3.0 kcal mol⁻¹, which is in reasonable agreement with the experimental enantiomeric ratio of 96:4 (which equates to a difference in free energy barriers $\Delta\Delta G^\ddagger$ of approximately 1.9 kcal mol⁻¹) (Supplementary Information has further discussion and other levels of theory). Note that although the barrier for the favoured ring expansion step is very small, the overall barrier from predecessor conformer B is slightly larger. Although we cannot rule out the inhibition of conformational equilibration owing to the catalyst architecture or non-statistical dynamic effects here (the differences in enantioselectivity in Fig. 4b are at least consistent with such effects), we

note that transition structures connected directly to carbocation conformer **B** lead to a prediction of the same sense of enantioselectivity (Supplementary Information has additional discussion). Ring expansion is followed by a facile deprotonation of the cation and energetically downhill dissociation to form the final product **3c**. These results are consistent with an overall mechanism of the IDPi-catalysed rearrangement consisting of the following steps: (1) rate-determining protonation; (2) subsequent enantioselectivity-determining ring expansion; and (3) facile deprotonation to afford the final product after catalyst-substrate dissociation—a mechanistic scenario not unlike that found for terpene synthase enzymes for which the difficult chemical step is carbocation generation and stereoselectivity is controlled by the shape of the carbocation binding site¹⁵⁰.

The high-acidity and confined chiral microenvironment of our IDPi catalysts enables the handling of purely aliphatic hydrocarbons in catalytic asymmetric Wagner–Meerwein shifts that proceed through unstabilized ‘classical cations’. We believe that the presented approach bears great potential for related reactions of aliphatic hydrocarbons.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41586-023-06826-7>.

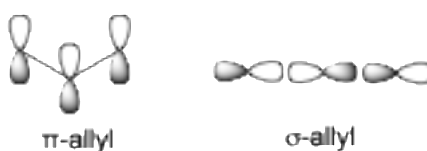
Chapter 5 — Kinetic Stabilization of σ -Allyl Cations

Theoretical attempts to create a kinetically stable σ -allyl cation over the past five decades have yet to yield a structure that could be studied experimentally. Herein, we discuss the design of a boron substituted framework that can support σ -allyl cations with predicted half-lives on the order of months at 77 K. The design of such a system required the counterintuitive use of functional groups that thermodynamically destabilize carbocations. Although it is not directly applicable, it enhances the understanding of designing kinetically stability into inherently unstable molecules. Additionally, the unique electronic and reactive properties of this molecule have inspired further study of unique functional groups (B-C-N borirenes) and applications that are not discussed herein but are an ongoing point of research.

Introduction

The search for hypervalent carbon compounds has been an ongoing challenge since the discovery of CH_5^+ in 1952.¹⁵¹ However the σ -allyl cation species, featuring a linear 3-center 2-electron bonding array (Scheme 1) has remained elusive. The first σ -allyl carbocation species was postulated in 1980 and featured three stacked *tert*-butyl groups, i.e., $(\text{C}(\text{CH}_3)_3)_3^+$ (**1**, Figure 1).⁸ Nearly two decades later, in 1999 a framework was proposed that encapsulates the central carbocation in a rigid polycyclic framework (**2**), however this σ -allyl structure was a transition structure rather than a minimum (the Si

analog of this σ -allyl cation was shown to be a minimum¹⁵²).¹⁵³ In 2014, Schleyer and co-workers proposed a σ -allyl cation minimum — $\text{C}(\text{CH}_3)_5^+$, **3** — where the two apical methyl substituents exhibit elongated bonds.⁹ However, this species was shown to be too short-lived to be observed experimentally, decomposing into methane and ethane with a half-life of $< 10^{-5}$ seconds at 10 K due to heavy atom tunneling and zero point energy (ZPE) vibrations.¹⁰ These results spurred us to search for a σ -allyl cation with an appreciable lifetime. Herein we propose σ -allyl species with ZPE corrected electron energy barriers for decomposition eight times higher than that for **3**, and with a predicted half-lives, including tunneling, on the order of months at 77 K.



Scheme 1. Key orbital interactions for π -allyl vs σ -allyl bonding.

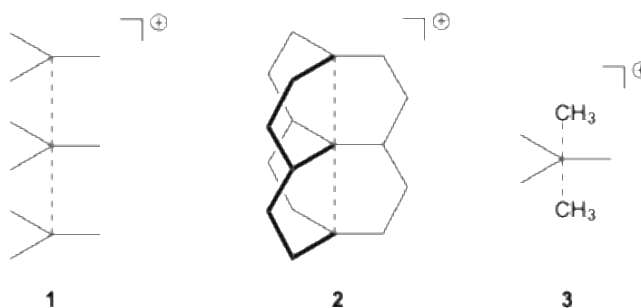


Figure 1. Previously postulated sigma σ -allyl carbocations **1**, **2**, and **3**.

Methodology

All geometry optimization, frequency, natural bond orbital (NBO 3.1),^{154–156} and intrinsic reaction coordinate (IRC)^{54–56} calculations were performed with Gaussian16 Rev. B.01⁸¹ using the M06-2X¹⁵⁷ functional and 6-31G(d)^{158,159} basis set. Results were benchmarked to DLPNO-CCSD(T)/Def2-TZVPP^{80,160} and ω B97X-V/Def2-TZVPP single points, both computed using ORCA 6.1 (see ESI).^{86,161} Quantum mechanical tunneling CVT/SCT rate constants were calculated using Polyrate 4¹⁶² and Gausssrate.¹⁶³ Example input files can be found in the ESI. Mayer bond orders¹⁶⁴ and normalized multicenter bond orders/multicenter indices (nMCBO/MCI)^{165,166} were calculated using Multiwfn.¹⁶⁷ Ring current density plots were created using SYSMOIC,¹⁶⁸ details of the calculations are provided in the SI.

Results

We began our search for a kinetically stable σ -allyl cation by leveraging three main design principles: (1) Thermodynamic stabilization of σ -allyl species. (2) Kinetic destabilization of degradation pathways. (3) Reduction of quantum mechanical tunneling by widening of barriers for decomposition reactions.^{169–172} We first focused on barrier heights (principles 1 and 2). We kept the axial carbon atoms unchanged from **3** to maintain primary carbocation character at the termini of the 3-carbon substructure, hoping to promote delocalization and increase barriers for C–C cleavage, i.e., loss of H_3C^+ would be very unfavorable. This approach left only the equatorial substituents available for modification. Use of π -donating substituents (e.g., ethene groups or incorporation into a

rigid phenalene framework) promoted fragmentation of the C $\cdots$ C $\cdots$ C unit, as such groups could attack the terminal H₃C⁺ groups, even when bulky. These structures tended to exhibit σ -allyl transition structures rather than minima (see ESI). These transition structures lead to true post-transition state trifurcations (PTSTs),^{173,174} where one axial methyl group migrates to one of the three neighboring equivalent alkenes (e.g., Figure 2). We therefore sought to avoid intramolecular nucleophilic attack and increase delocalization of the two electrons in the 3-center 2-electron array by addition of π -*accepting* substituents to the central carbon.

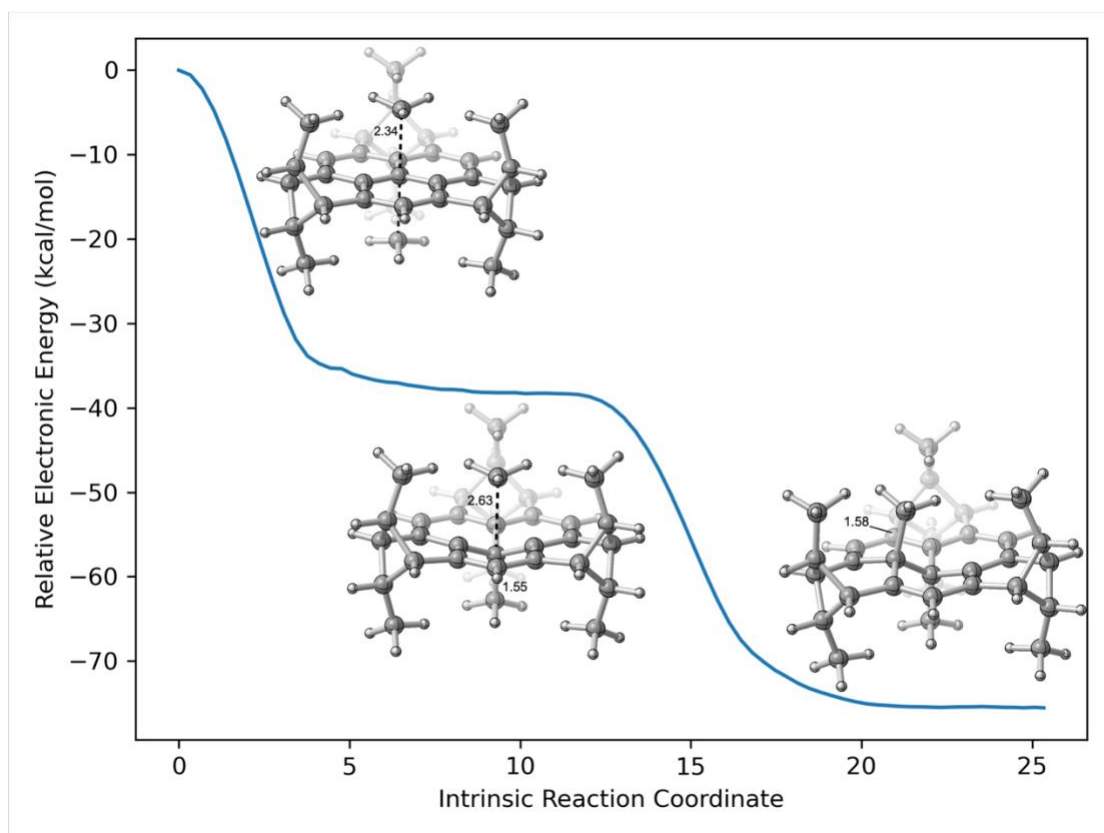


Figure 2. Intrinsic reaction coordinate diagram for a σ -allyl transition structure leading to a post-transition state trifurcation. Atom colors: H (white), and C (gray). Selected distances in Å are shown

From a kinetic standpoint, we had to dissuade degradation pathways, which consistently involved nucleophilic attack on the axial methyl groups. Installing boron atoms at all three equatorial positions, we constructed a borate version of the phenalene backbone (Figure 3, left). To gauge the carbocation destabilizing effect of the framework, we computed hydride affinities of the framework alone, in the absence of axial methyl groups. This framework exhibits an incredibly high hydride affinity, greater than that of a methylium cation (-360.8 and -356.5 kcal/mol, respectively). This framework led to a σ -allyl cation as a minimum on the potential energy surface (PES)! In this structure, the angle between the three carbon atoms is 156° rather than 180° , reducing the point group symmetry from D_{3h} to C_{2v} . The D_{3h} symmetric structure was a second order saddle point rather than a minimum or transition structure. This loss of symmetry appears to result from a favorable donor-acceptor interaction between a C–B bond and the partially empty sp^3 methyl orbitals. We quantified this interaction with NBO analysis, which showed a donor-acceptor interaction energy of 142 kcal/mol. To put this value into perspective, the strength of the next largest donor-acceptor interaction, corresponding to an oxygen lone pair donating to an empty boron p orbital, was only 78 kcal/mol; i.e., this structure is effectively bridged (C–C–B angles $< 90^\circ$, C–B distances ~ 2 Å), like non-classical carbocation with cyclic 3-center 2-electron bonding arrays.^{175–180} In pursuit of greater linearity, we substituted the oxygen atoms with NH groups, but this only increased the bond angle to 160° (**5**, Figure 3). A more significant change involved replacement of the O(BH)O motif with NH(O)NH, which led to a 168° C–C–C angle (this molecule loses its horizontal mirror plane due to puckering; **6**, Figure 3). For all three of these structures, the C $\cdots$ C $\cdots$ C delocalized structure remained a PES minimum.

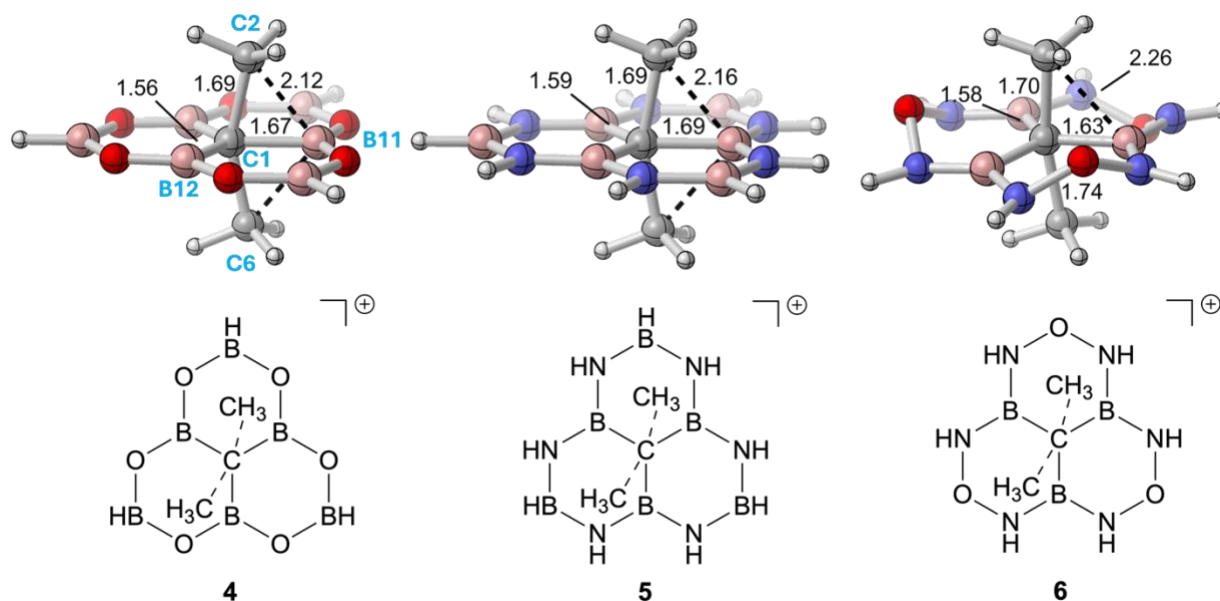


Figure 3. Structures of minima for three σ -allyl cations: **4**, **5**, and **6**. Atom colors: H (white), B (pink), C (gray), N (blue), and O (red). Selected distances in Å are shown. Atom labels are depicted in light blue.

Mayer bond order and nMCBO analyses for **4** demonstrated an array of partial bond orders. Not only are the C1–C2 bonds computed to be partial single bonds, but the C2–C1–C6 nMCBO of 0.296 suggests a delocalized bonding array comparable to 3-center 2-electron arrays in acyclic $C\cdots H\cdots C$ carbocations (atom numbers in Figure 3).¹⁸¹ The strongest 3-center 2-electron array involves C2, C1 and B11, with a nMCBO of 0.459, consistent with the geometric distortion and orbital interactions mentioned earlier. Charge analysis was performed to determine where the cationic character is most localized. Mulliken, NPA, Hirshfield and CHelpG charge models indicate the electropositive boron atoms have the most positive character, and the apical carbons have greater cationic character than the central carbon (see ESI).

Table 1. Select Mayer bond orders, multicenter bond orders, normalized multicenter bond orders, bond distances, and bond angles. Atom numbering is shown in Figure 3.

Atoms	Mayer Bond Order	Multicenter Bond Order	Normalized Multicenter Bond Order	Bond Distance/Angle
C1-C2	0.705	0.705	0.840	1.69 Å
C1-B11	0.553	0.553	0.744	1.67 Å
C1-B12	0.826	0.826	0.909	1.56 Å
C2-B11	0.137	0.137	0.370	2.12 Å
C2-C1-C6	N/A	0.026	0.296	156.3°
C2-C1-B11	N/A	0.096	0.459	78.2°
C2-C1-B12	N/A	0.020	0.270	96.0°

The potential (anti)aromatic and character of this compound also was of interest. The boron-oxygen cyclic array contains 12 electrons, an antiaromatic electron count. However, if the two electrons in the σ -allyl species contribute to cyclic delocalization it could exhibit aromatic character instead. We created current density plots of **4**, H substituted, and its fully truncated derivatives using occupied π molecular orbitals and the highest energy occupied π molecular orbital.¹⁸² The fully truncated derivative exhibits a global paratropic (counterclockwise) ring current suggestive of antiaromatic character, consistent with the Möbius 12 electron count. What appear to be diatropic (clockwise) ring currents are observed circulating the exterior of the molecule, however these can be

attributed to local oxygen lone pair currents rather than global ring currents. **4** the H substituted derivative show similar but weaker global paratropic currents, which we attribute to the hyperconjugation or weak delocalization of the σ -allyl bond. The diatropic ring current density around the center is attributed to the CH₃ units being out of plane and overlapping with the sampling region 1 Å above the plane.

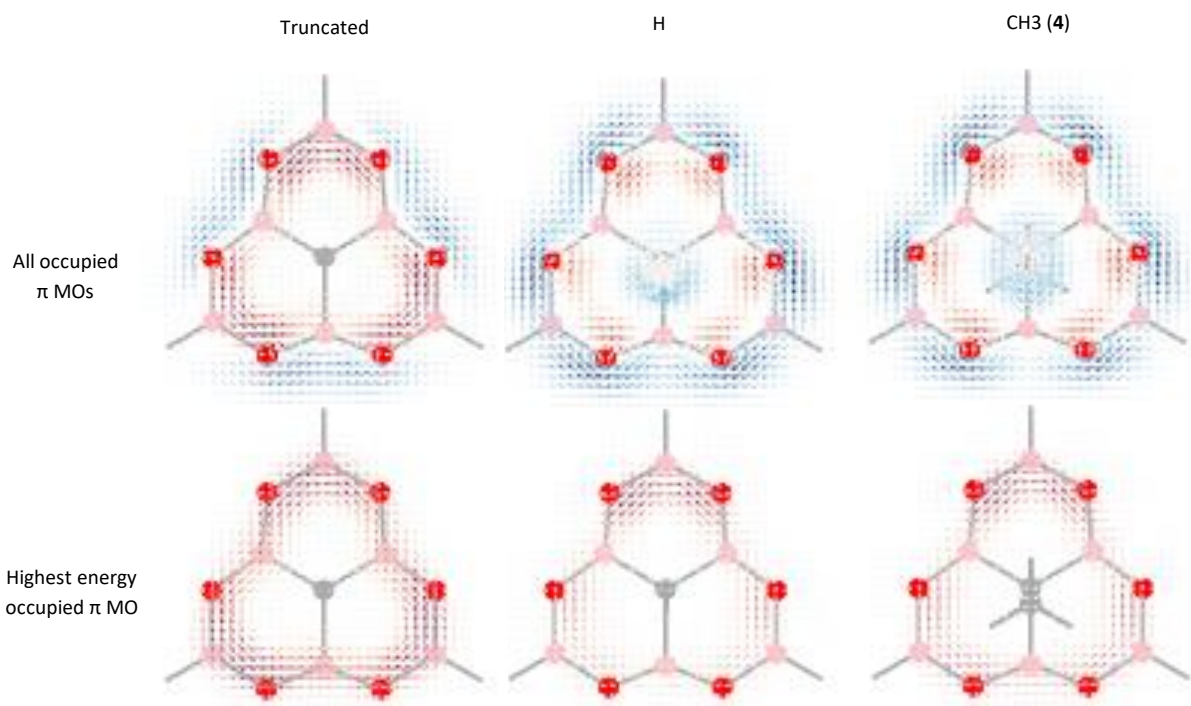


Figure 4. Current density map of fully truncated (left), H substituted (middle), and unaltered versions (right) of **4**. Current densities plots from electrons in all occupied π molecular orbitals (top) and from electrons in the highest energy π molecular orbital (bottom) are depicted. Counterclockwise paratropic ring currents are red and clockwise diatropic ring currents are blue. Atom colors: B (pink), C (gray), and O (red). Current density arrows are colored blue (clockwise) and red (counterclockwise) based on the direction with respect to the origin.

But is **4** (and its relatives) likely to be persistent enough to allow detection?¹⁸³ Most importantly, the only unimolecular degradation pathway found for **4** involved a ZPE corrected electron energy barrier of 7.4 kcal/mol, over four times higher than the degradation barriers for $\text{C}(\text{CH}_3)_5^+$.^{9,10} This degradation pathway formally involves a C–B bond attacking an axial carbon leading to C–C bond cleavage (Figure 5). This pathway also exhibits a symmetric post-transition state bifurcation (PTSB)^{184–188} where either oxygen atom may attack the residual carbocation without a barrier (see plateau region of IRC). Systems **5** and **6** display even larger ZPE corrected electronic energy barriers: 12.8 and 11.9 kcal/mol, respectively.

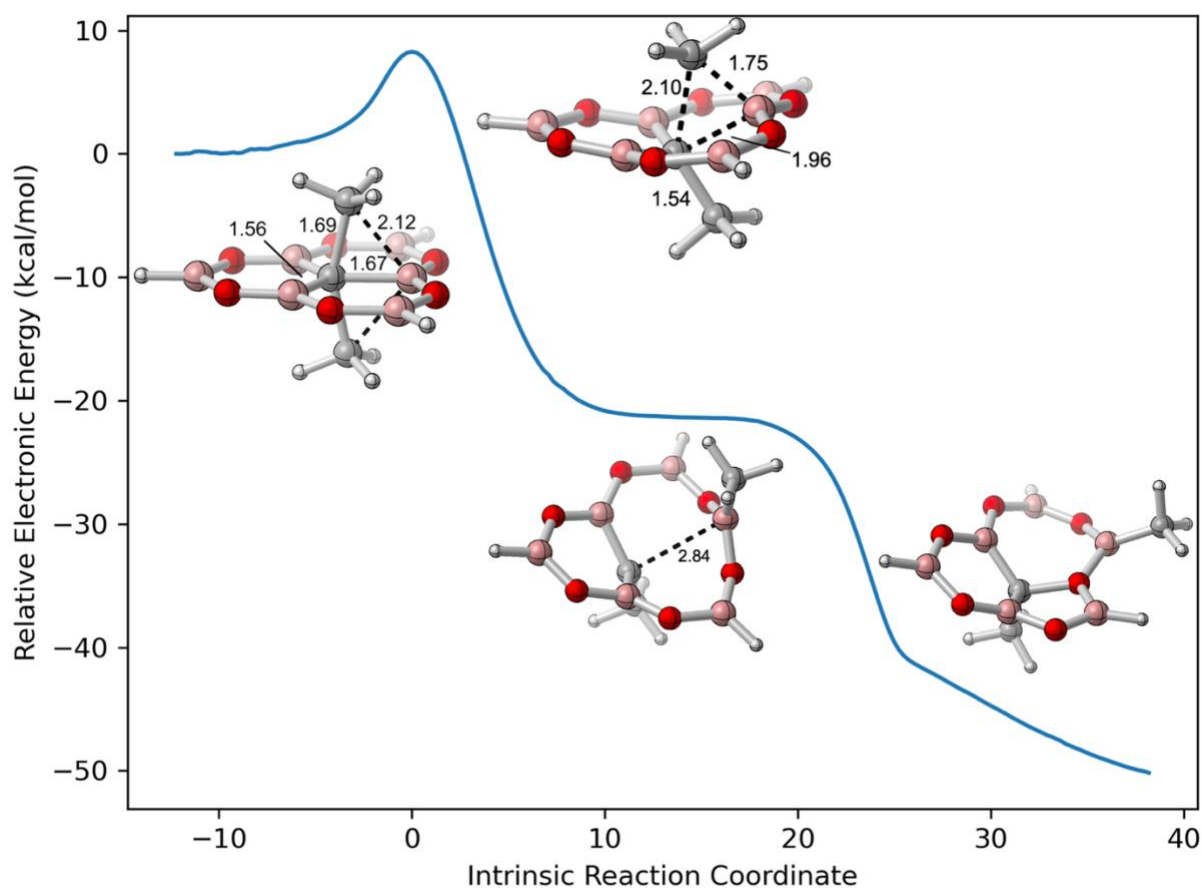


Figure 5. Intrinsic reaction coordinate diagram for unimolecular decomposition of **4**. Atom colors: H (white), B (pink), C (gray), and O (red). Selected distances in Å are shown.

Lastly, we computed the effects of quantum mechanical tunneling on the rate of the reaction in Figure 5. Computed SCT half-lives are many orders of magnitude longer than those for **3** (Table 2).¹⁰ The half-life at 80 K is predicted to be $\sim 10^7$ seconds, on the order of months, suggesting that **4** would be kinetically stable enough to be examined at liquid nitrogen (77° K) or lower temperatures. Moreover, **4** could be a powerful methylating reagent, potentially lasting long enough to react with external nucleophiles. Molecule **5** is predicted to persist for millions of times longer than the age of the universe ($4.26\text{E}+17$ s) at 77K!

	<i>Molecule 4</i>		<i>Molecule 5</i>	
T (° K)	k_{SCT} (s^{-1})	$t_{1/2}$ (s)	k_{SCT} (s^{-1})	$t_{1/2}$ (s)
10	7.34E-12	9.44E+10	2.34E-80	2.97E+79
20	2.28E-11	3.04E+10	3.08E-51	2.25E+50
50	1.19E-10	5.84E+09	2.15E-33	3.22E+32
77	4.69E-08	1.48E+07	4.39E-25	1.58E+24
80	2.25E-07	3.08E+06	1.03E-23	6.74E+22
100	1.12E-03	6.19E+02	1.24E-16	5.58E+15
150	1.48E+02	4.69E-03	4.34E-07	1.60E+06
200	5.98E+04	1.16E-05	2.84E-02	2.44E+01
298	2.36E+07	2.93E-08	1.78E+03	3.89E-04

300	2.57E+07	2.70E-08	2.07E+03	3.35E-04
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Table 2. Computed reaction rates (k_{SCT}) and half-lives ($t_{1/2}$) of **4** and **5** accounting for tunneling effects at a series of temperatures.

Conclusions

We propose a new type of framework to support σ -allyl cation delocalization with unprecedented kinetic stability. These compounds are predicted to persist long enough to be characterized experimentally at low temperatures. Ironically, kinetic stabilization required incorporation of some of the most thermodynamically destabilized carbocation structures, including H_3C^+ and B_3C^+ .

Author contributions

A.L. computed quantum tunneling effects on reaction rates and half-lives. W.D. designed the new molecular framework, carried out most quantum chemical calculations, and drafted the manuscript with input from D.T., who conceived the project and carried out some quantum calculations on **5**. W.D. and D.T. wrote the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix

Chapter 1 PeriRxn

Aromatic Plane Definition and Probe Placement

The aromatic plane of a molecule is determined via Principal Component Analysis (PCA) applied to the Cartesian coordinates of its aromatic atoms. The two principal vectors corresponding to the largest eigenvalues define the plane (xy-plane), while the third eigenvector (smallest eigenvalue) defines the normal axis (z-axis), perpendicular to the aromatic plane. Sampling points for Bq (ghost atom) probes are generated along this z-axis at 0.1 Å intervals, spanning from +3.0 Å to -3.0 Å relative to the plane.

Modification for Cycloaddition Systems

For cycloaddition reactions, aromatic atoms are given in two fragments, the aromatic plane is initially defined using PCA on the first fragment (containing n atoms). The second fragment is then translated along the z-axis to achieve coplanarity with the first fragment. The combined centroid of both fragments is calculated and subsequently displaced along the z-axis by half the initial translation distance of the second fragment. The translation of the second fragment is only used for defining the z-axis, and the relative atom positions are not altered for nmr calculation.

Tensor Alignment for NICSzz Calculation

The raw NICS_{zz} values reported in the output log file may not be aligned with the PCA-defined z-axis. To ensure proper orientation, the full 3×3 shielding tensor is extracted and rotated such that its principal axes coincide with the PCA-derived coordinate system, where the z-axis is orthogonal to the aromatic plane.

Normalized Multicenter Bond Order (nMCBO)

nMCBO by default not independent of direction $\text{nMCBO}(A,B,C) \neq \text{nMCBO}(C,B,A)$. To achieve consistent results independent of direction, the forward and backward nMCBO's are averaged by setting "iMCBOtype" in settings to 1.

1. [4,5] sigmatropic shifts continued.

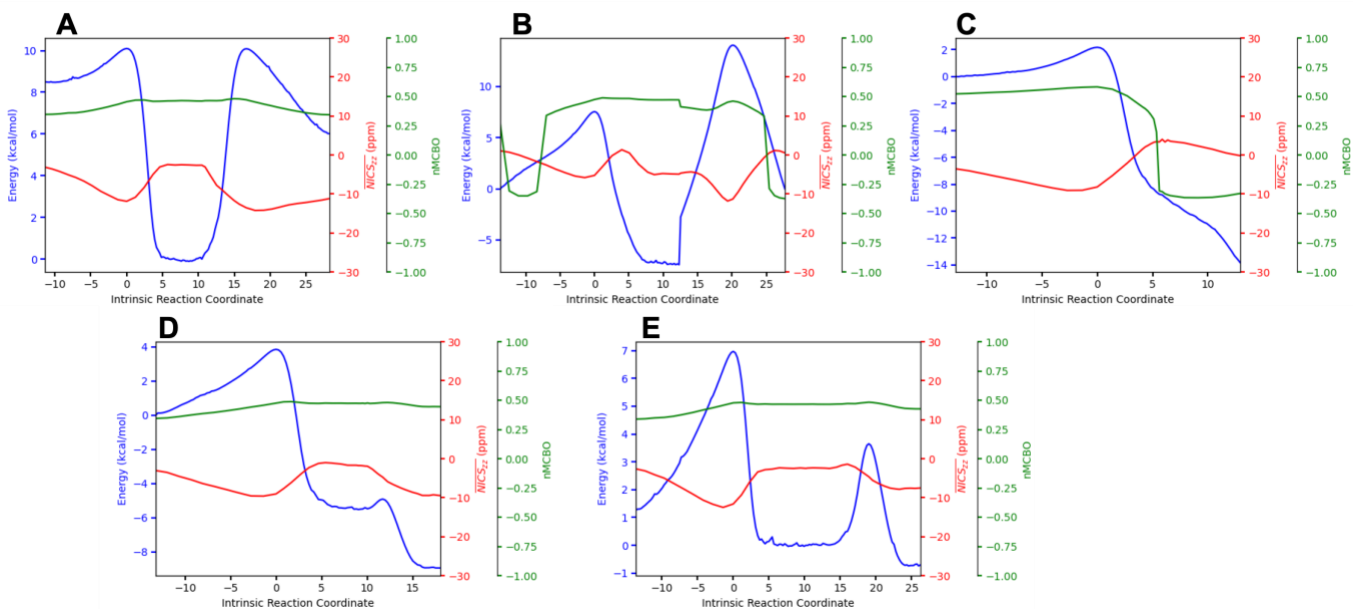
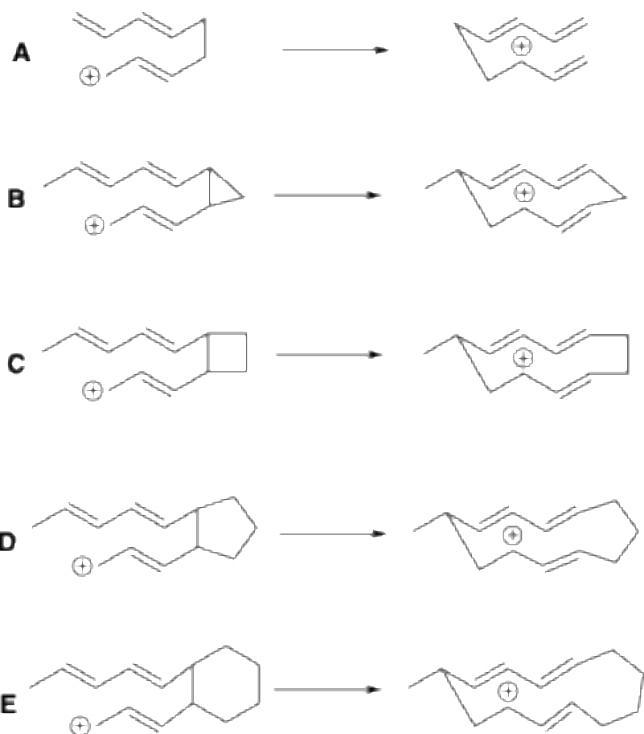


Figure S2.1. *PeriRxn* analysis along reaction coordinates for cationic [4,5] sigmatropic shifts with varied tethers. Panels are as follows: Parent (A), and carbon tether lengths of 1 (B), 2 (C), 3(D) and 4(E). $\overline{NICS}_{zz}$ (red), nMCBO (green), along intrinsic reaction coordinate (blue). Plot of all $NICS_{zz}$ values as a function of z displacement and intrinsic reaction coordinate, blue is negative and red is positive (bottom).

Each [4,5] sigmatropic shift begins with a small decrease in $\overline{NICS}_{zz}$, suggesting an increase in cyclic delocalization, and the stepwise versions display a second $\overline{NICS}_{zz}$ minima at the second transition state. This can be attributed to the pericyclic homo-cope like rearrangement as discussed in the main text. This suggests that even the stepwise pathways (A,B,D,E) produce a seemingly forbidden product, via a sequence of two allowed pericyclic reactions as shown below for the parent system A.

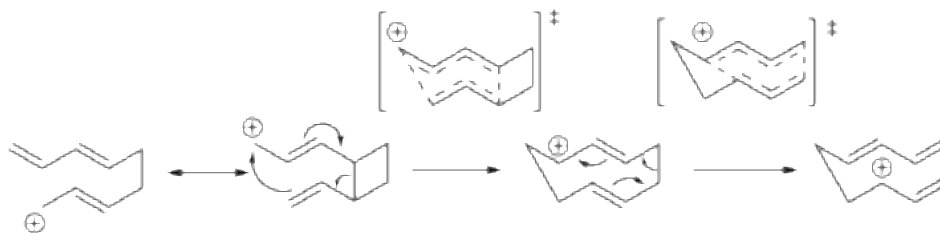


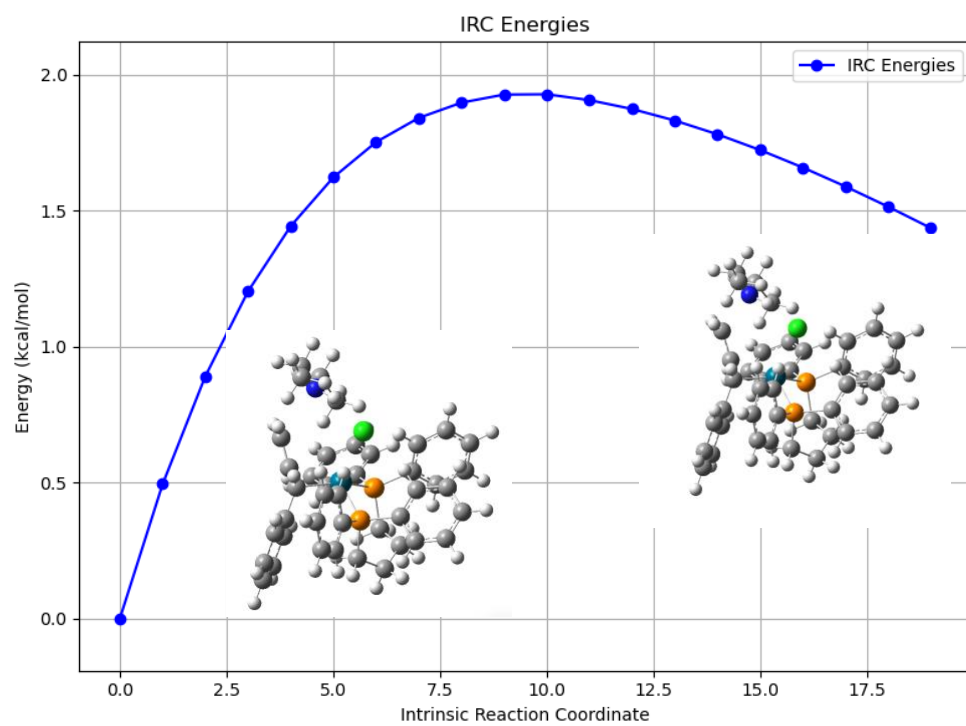
Figure S2.2. Stepwise mechanism for the parent [4,5] sigmatropic shift, producing a Woodward Hoffmann orbital symmetry forbidden product. Both elementary steps can be seen as pericyclic, akin to a homo-cope transition state.

Intrinsic

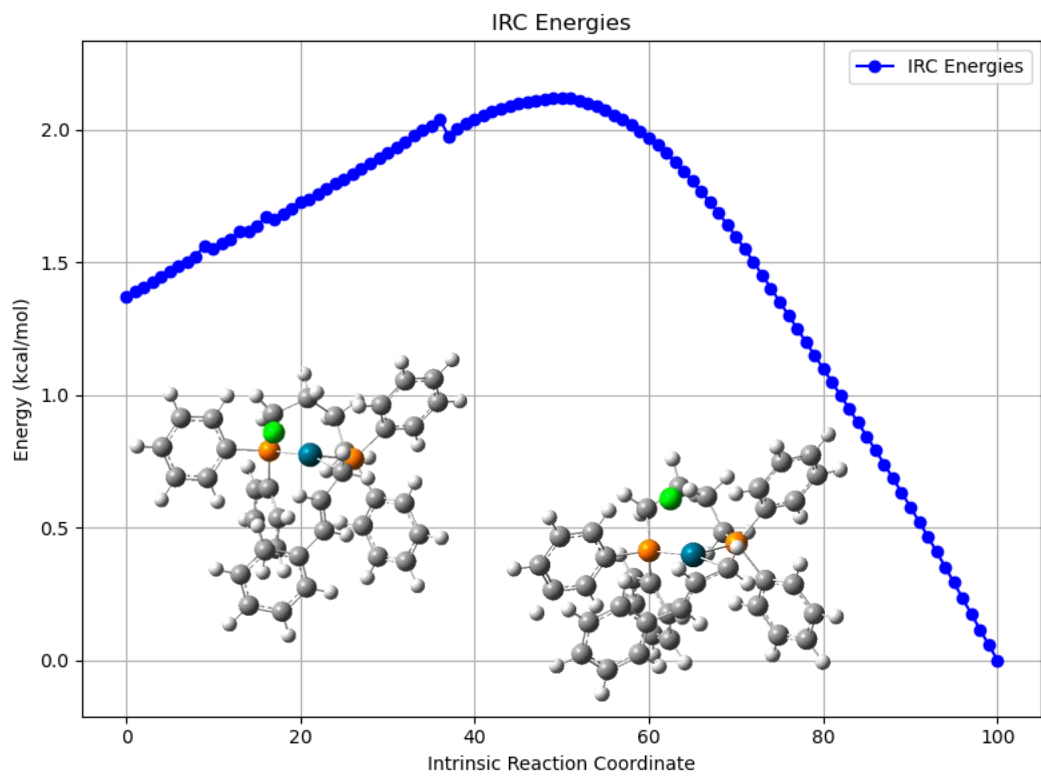
Reaction

Coordinate

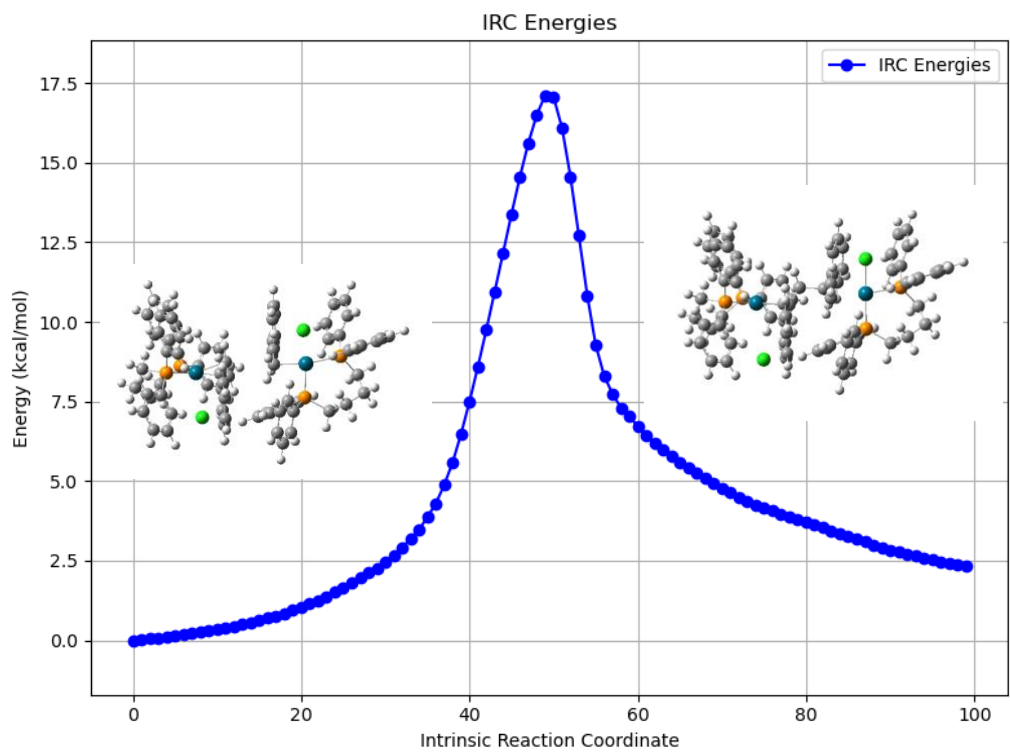
Calculations



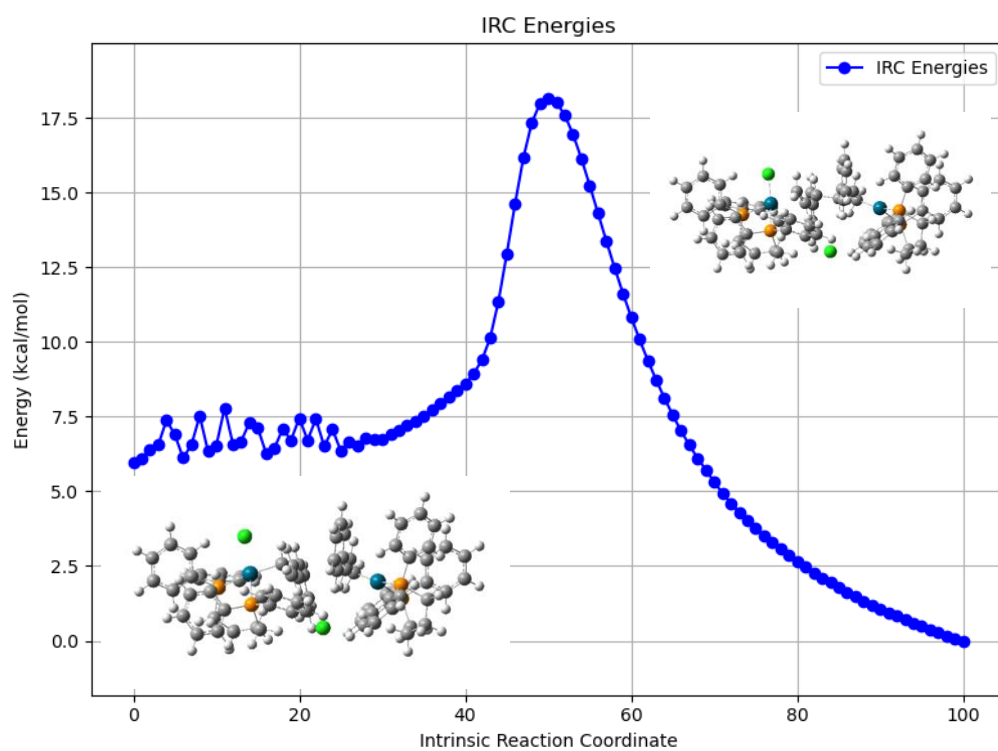
TS1 IRC



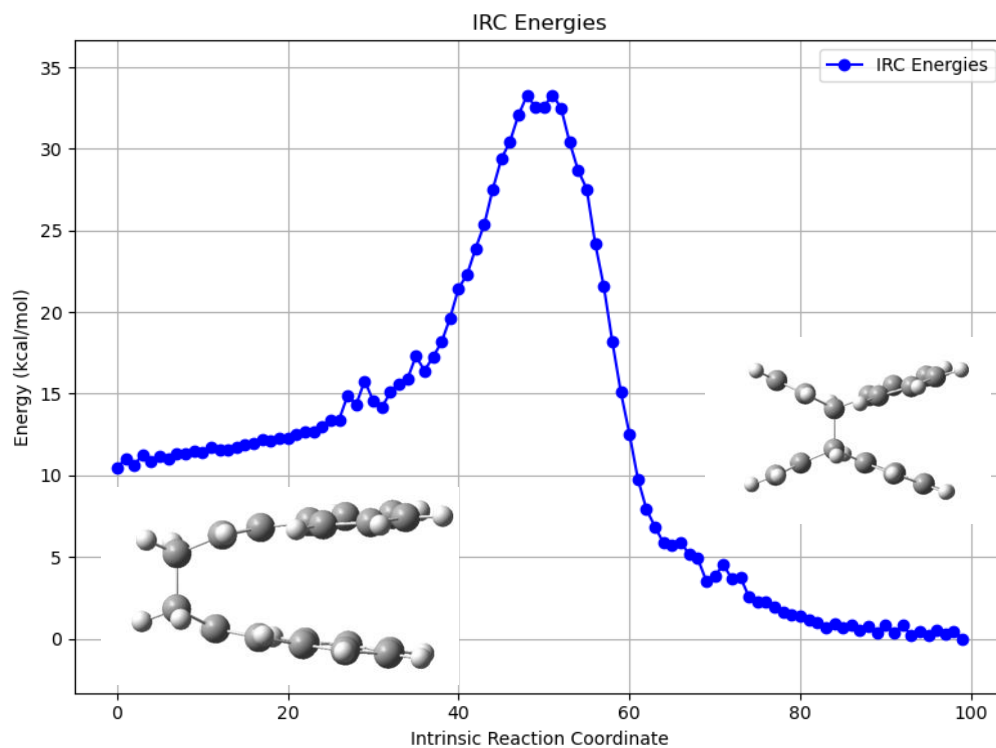
TS2



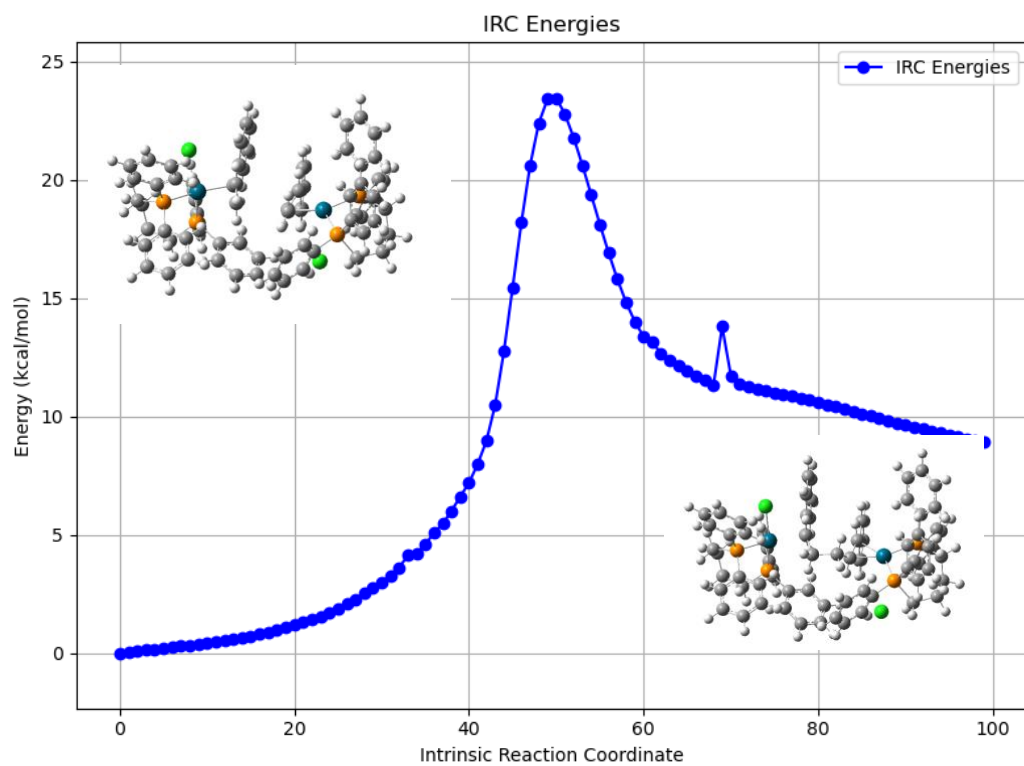
TS3_{P2}



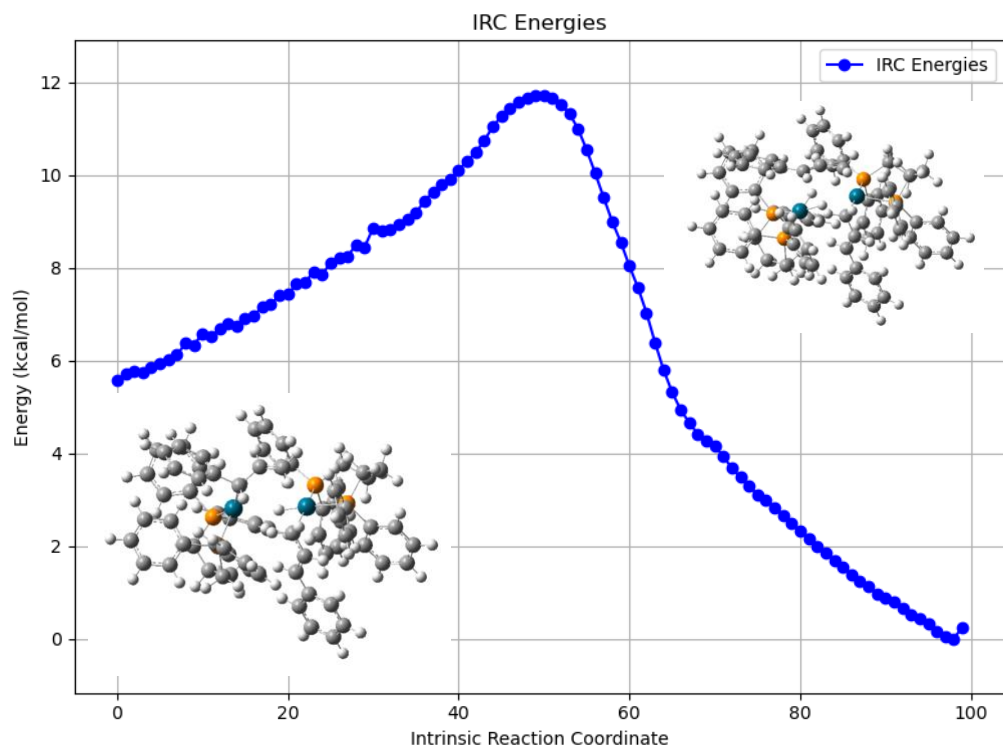
TS4_{P3}



TS5_{P3P1}



TS6_{P1}



TS7_{TM}

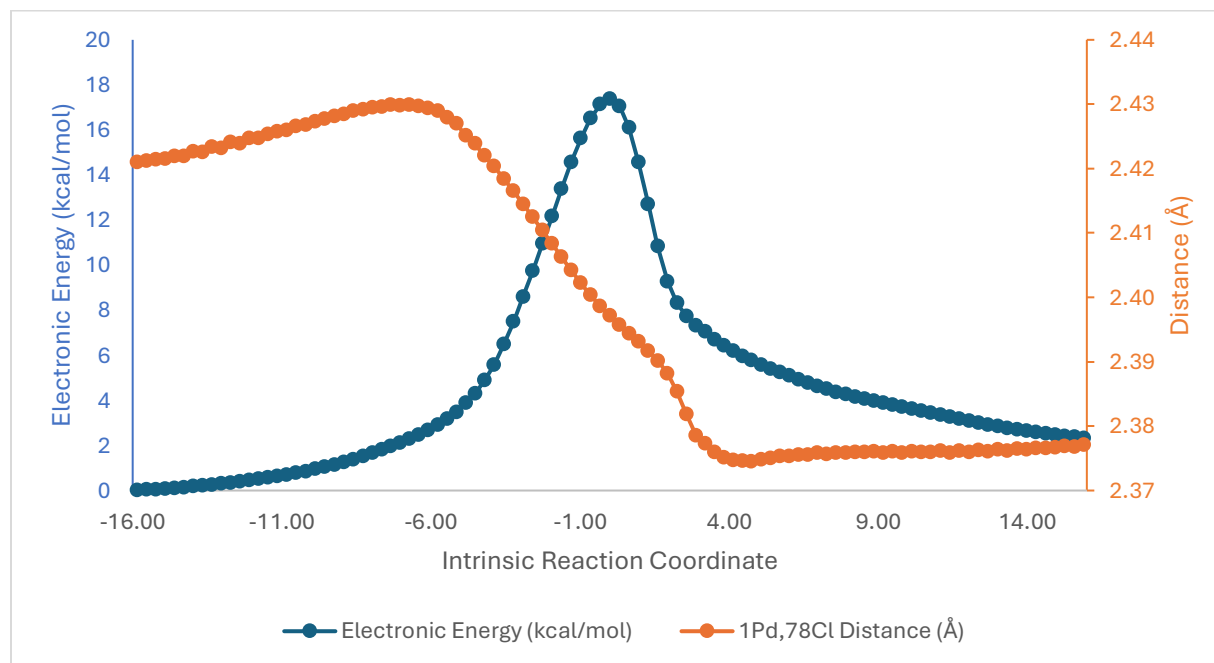


Figure S2.3. Cl-Pd Bond distance along TS3_{P2} IRC

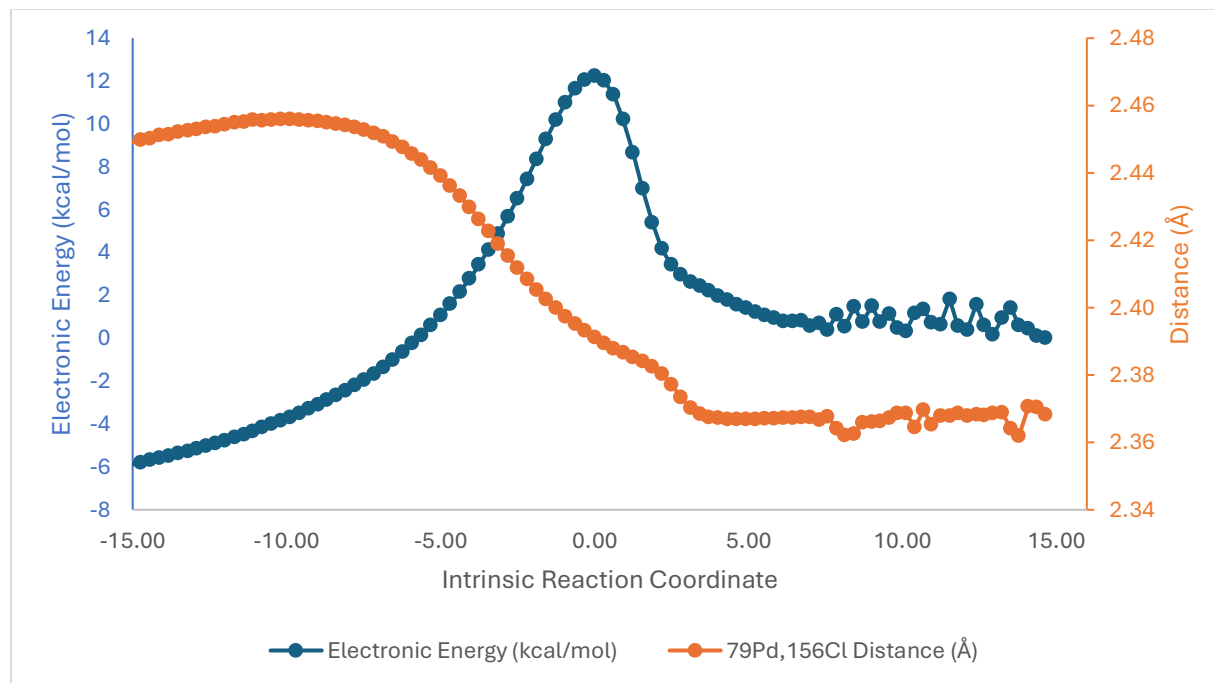


Figure S2.4. Cl-Pd Bond distance along TS4_{P3} IRC

Chapter 2 Allyl-Allyl Coupling Promoted by Catalyst Systems with two Palladium Atoms – A Plethora of Potentially Pericyclic Processes

1. All geometry optimizations and frequency calculations can be found at the following iochem-bd links:

- a. Plausible mechanism: <https://iochem-bd.bsc.es/browse/review-collection/100/314023/8779456cf644c040f3f5e59c>
- b. Originally proposed pericyclic pathway: <https://iochem-bd.bsc.es/browse/review-collection/100/314045/f190543b311a24757317b1b6>

- c. Methyl-truncated model: <https://iochem-bd.bsc.es/browse/review-collection/100/314056/0029a8085bda914bd7ce0e45>

Table S3.1. Computed Energies

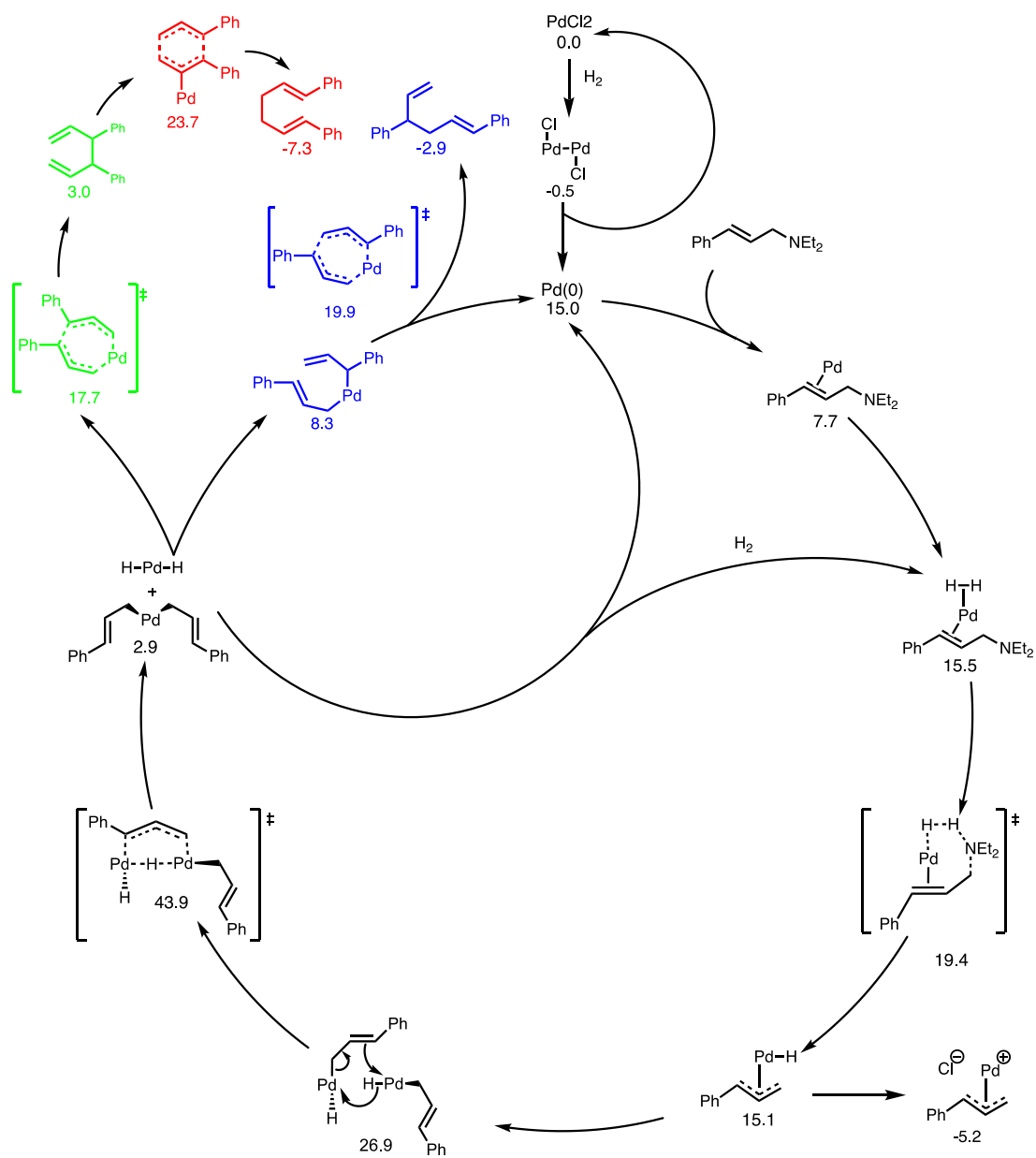
- d. All reported relative energies are reported in G_{final} , the definition of which is reported below.

$$G_{final} = G_{corr} + E_{solv,low} - E_{gas,low} + E_{gas,high}$$

Name	E solv, low	E gas, low	G corr	E gas, high	G final
Precat	-4704.15004	-4704.119118	0.866757	-4708.383005	-4707.54717
IM1	-1892.063578	-1892.052107	0.415302	-1893.936731	-1893.5329
R	-2812.012236	-2811.975853	0.417931	-2814.371161	-2813.989613
IM2	-2452.628465	-2452.615445	0.692399	-2455.303573	-2454.624194
TS1	-2453.775381	-2453.728089	0.711211	-2456.443156	-2455.779237
IM3	-2453.7851	-2453.753531	0.708792	-2456.462596	-2455.785373
H ₂	-1.163994	-1.163827719	-0.00435	-1.169054028	-1.173570309
PhAllylNEt ₂	-560.510675	-560.506186	0.245381	-561.3206583	-561.0797663
NEt ₃	-291.86153	-291.8598904	0.16792	-292.2820902	-292.1158098
IM4	-2699.779173	-2699.757761	0.560106	-2702.401684	-2701.86299
TS2	-2699.773126	-2699.74956	0.560242	-2702.390472	-2701.853796

IM4'	-2699.778422	-2699.753465	0.559818	-2702.393393	-2701.858532
IM6(P3)	-5399.57984	-5399.534486	1.151894	-5404.805219	-5403.698679
IM7(P2)	-5399.581112	-5399.517877	1.154707	-5404.79165	-5403.700178
TS6 _{P1}	-5399.541953	-5399.49278	1.149385	-5404.766766	-5403.666554
TS3 _{P2}	-5399.555089	-5399.509765	1.149366	-5404.78312	-5403.679078
TS4 _{P3}	-5399.557181	-5399.517208	1.149808	-5404.788885	-5403.67905
HNEt ₂	-213.388747	-213.386165	0.116439	-213.6989598	-213.5851028
ClHNEt ₃	-752.41615	-752.3925966	0.179311	-753.074773	-752.9190154
P1	-695.442849	-695.4355915	0.25549	-696.4465904	-696.1983579
P2	-695.434823	-695.4269459	0.255686	-696.439183	-696.1913741
P3	-695.424744	-695.4186355	0.256705	-696.4325685	-696.181972
TS5 _{P3P1}	-695.388619	-695.381866	0.257149	-696.3933561	-696.1429601
TSPeri_Methyl	-4480.789271	-4480.7632	1.165855	-4485.519813	-4484.380029
TSCopePd	-2587.496156	-2587.481707	0.700011	-2590.368161	-2589.682599
Dimer_Methyl	-2949.647768	-2949.624378	0.758736	-2952.159112	-2951.423766
PdClAllyl_Methyl	-1934.216813	-1934.193502	0.359707	-1935.724714	-1935.388318
PdCl ₂ _Methyl	-2046.458905	-2046.425135	0.218638	-2047.70742	-2047.522552

PdCl ₂ Dimer_Methyl	-3173.022311	-3172.991065	0.46171	-3175.032858	-3174.602394
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Scheme S3.1. Originally proposed mechanism with. Energies are reported in kcal/mol. PdCl₂ is the relative 0.0.

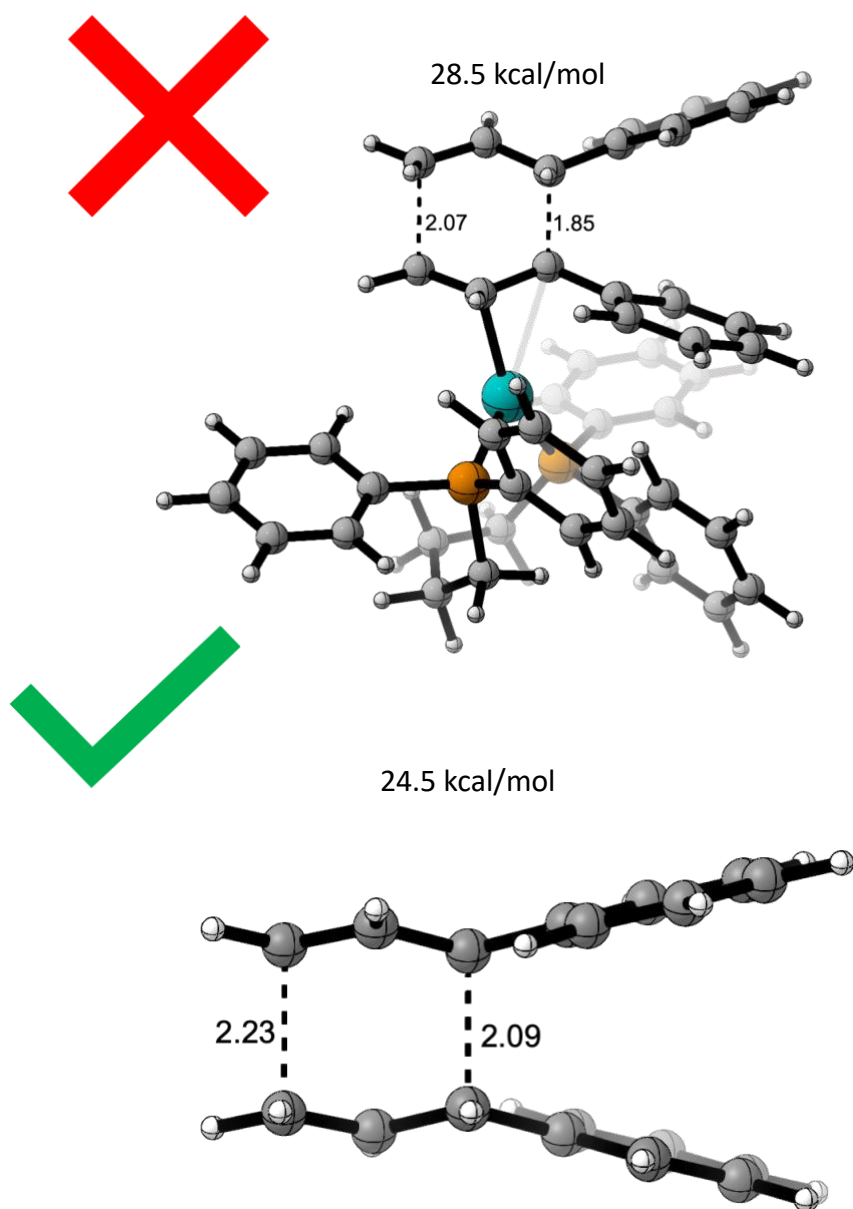


Figure S3.1. Comparison of Pd catalyzed and uncatalyzed Cope rearrangements. Activation energies are reported relative to the resting state (TDI).

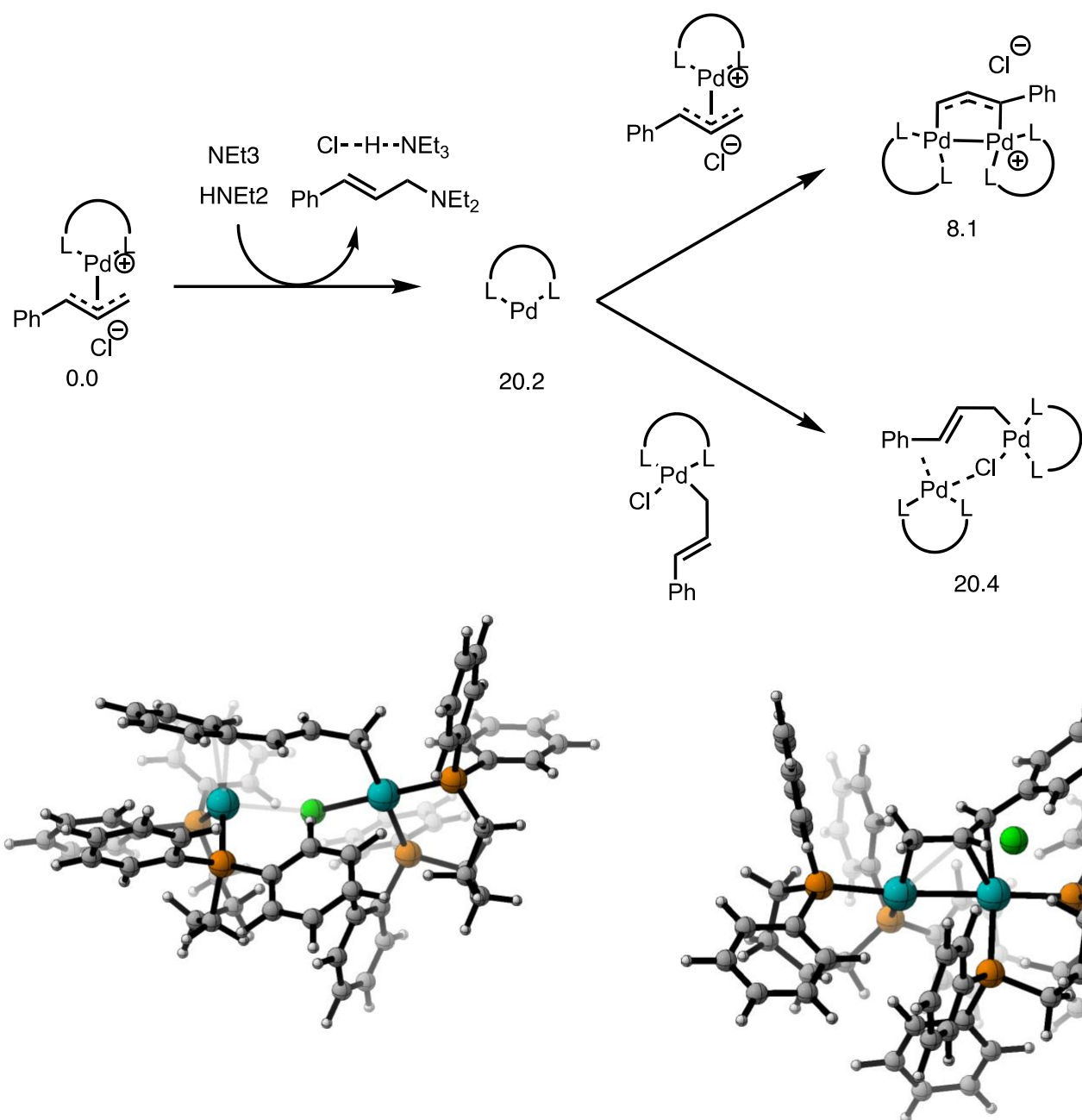


Figure S3.2. Structure of allyl-bridged Pd dimer interr

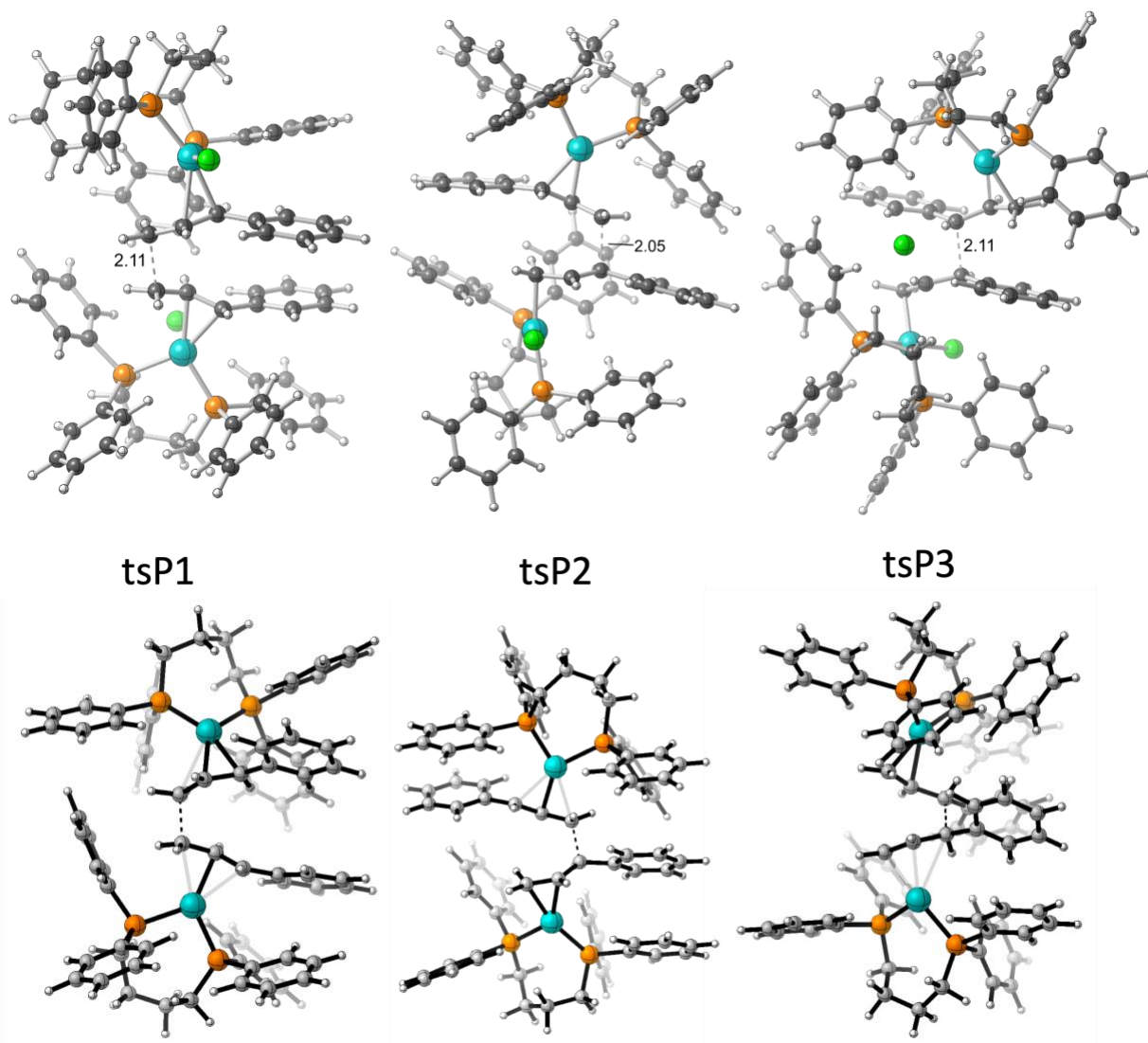


Figure S3.3. Structure and analysis of TS6_{P1}, TS3_{P2}, TS4_{P3} without Cl anions

Table S3.2. Selectivity/rate determining transition state comparison of model with and without chloride.

	with Cl	w/o Cl
TS6 _{P1}	37.3	41.1

TS3 _{P2}	29.4	42.6
TS4 _{P3}	29.4	48.3

Comparing selectivity transition states with and without chlorine reveals the important role of the chlorine anion in predicting kinetics. In the absence of chlorine, all kinetic barriers are significantly higher, the predicted product ratio favors P1, and the mechanism of P1 formation is directly through TS6_{P1} rather than through TS4_{P3} and a subsequent cope rearrangement. The change in preferred mechanism can be rationalized as less destabilization of the TS as TS6_{P1} uses 2 η^3 like Pd monomers which are less destabilized by loss of Cl⁻. Furthermore, TS4_{P3} involves the most C-H...Cl non-covalent interactions, thus anion removal highly destabilizes the structure.

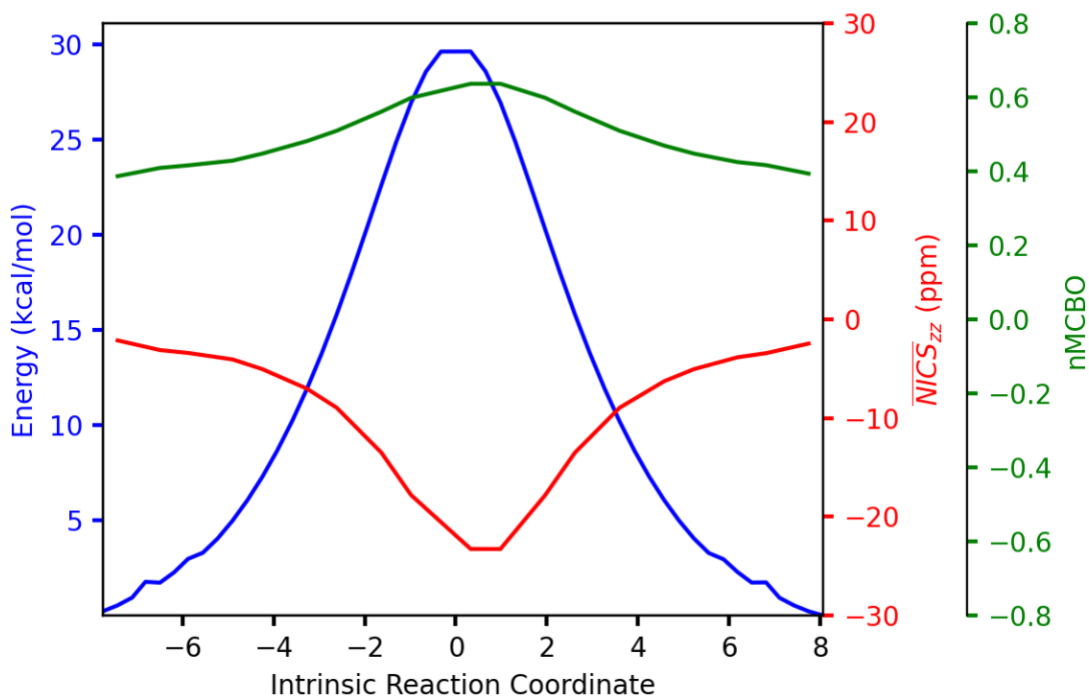


Figure S3.4. Standard cope rearrangement with $\overline{NICS}_{zz}$ and nMCBO analysis for comparison.

This analysis on a standard cope rearrangement demonstrates the typical behavior of pericyclic reaction. Just as in the main paper, ghost atoms used to probe $\overline{NICS}_{zz}$ are placed from 3 Å above and below the plane of aromatic atoms, at a 0.1 Å increment. Notice that nMCBO increases whereas $\overline{NICS}_{zz}$ decreases when approaching the transition state. Note that the magnitude of $\overline{NICS}_{zz}$ is significantly lower than a singular $NICS_{zz}(0)$, -45.2 ppm, as sampling farther results in a weaker effect that dilutes the averaged $NICS_{zz}$ values.

Catalytic Asymmetric Cationic Shifts of Aliphatic Hydrocarbons

An initial, approximate structure for the catalyst was constructed from the crystal structure of a similar IDPi catalyst.¹⁸⁹ This was used as a starting point for conformer and stationary point searches.

Conformational searches were performed on all transition structures following the iMTD-GC procedure using the Conformer-Rotamer Ensemble Sampling Tool (CREST).¹² Key bonds (breaking or forming) were constrained with a harmonic potential using GFN2-xTB.¹³ Metadynamics duration was manually set to 100 ps. Conformers from the first cycle of iMTD-GC were filtered using isostat with a 0.25 kcal/mol and 10 Å cutoff. Remaining conformers were then optimized with DFT in Gaussian 16⁵¹ unless specified otherwise: we used the B3LYP¹⁹⁰ functional, def2-SVP⁸⁰ basis set and Grimme's D3 correction¹⁹¹ with Becke-Johnson damping⁷⁹ in a conductor-like polarizable continuum model, C-PCM(chloroform).^{192,193} The remaining conformers were then optimized

followed by subsequent single point computations at M06-2X,¹⁵⁷ wB97X-D¹⁹⁴ (G16) and wB97X-D4⁸⁵ (in ORCA)^{86,161}, all with the def2-TZVPP basis set. All three functionals include quantum mechanical dispersion, a major contributor to non-covalent interactions, and have been shown to be reliable functionals in similar previous studies¹⁹⁵. Thermochemistry analysis was set to a default temperature of 298.15 K. These results revealed that the qualitative trends remained the same.

Conformational searches for the non-covalently bound ring expansion step were performed with a spherical log fermi potential around the system to prevent the substrate from dissociating from the complex in CREST (see below for more details).

Three-dimensional depictions of transition structures were generated using *CYLview*.¹⁹⁶ Noncovalent interaction (NCI)⁸⁷ plots were generated using *Multiwfn*.⁵⁷

All computed and reported structures in the main text can be found on ioChem-BD at the following DOI: [<https://doi.org/10.19061/iochem-bd-6-262>]⁵⁹

Additional Results:

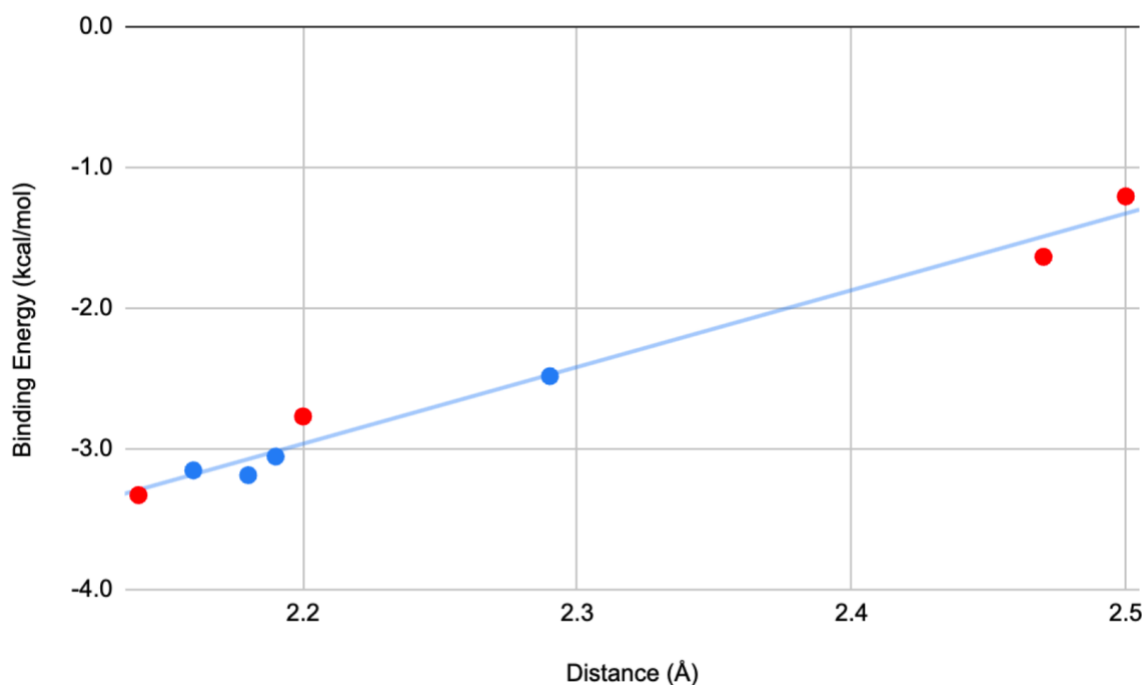


Figure S4.1. Binding energies computed from the electron density at bond critical points between 4 shortest hydrogen bonds as a function of H $\cdots$ O distance. The binding energies were computed as $(BE = -223.08 * \rho + 0.7423)$, where ρ is the electron density at the BCP. Blue points are from S TS, red points are from R TS. $R^2=0.979$.

Interpretation of Reaction Profile

The lowest energy ring expansion conformers (**C** and **G** in Fig. 4f) require the substrate to undergo a conformational change (from **B**) in the anionic pocket, the barrier of which is unclear. Therefore, we also considered the immediate ring expansion directly from the intermediate following the lowest- energy protonation transition structure (i.e., **B**, found by an intrinsic reaction coordinate (IRC) calculation). These ring expansion transition structures would assume that the protonated intermediate does not equilibrate and proceeds to ring expansion before being able to sample other conformer modes in the

anionic pocket. These transition structures for *R* and *S* have free energy barriers of 16.9 and 12.1 respectively, still favoring *S* over *R*.

While some elementary steps in the proposed mechanism are uphill in energy, the overall process is predicted to be downhill. We are also assuming here that product release makes the reaction irreversible and thereby prevents equilibration, i.e., that the product ratio should be determined by the relative free energies of competing ring-expansion TSs, not products following them. This contention cannot be proven, since it is notoriously difficult to predict dissociation barriers for solution reactions, but it seems reasonable that dissociation of complex **F** would be faster here than reversion to **B** and conversion to **H** via **TSGH** (a predicted overall barrier in the reverse direction of at least 9 kcal/mol; see above).

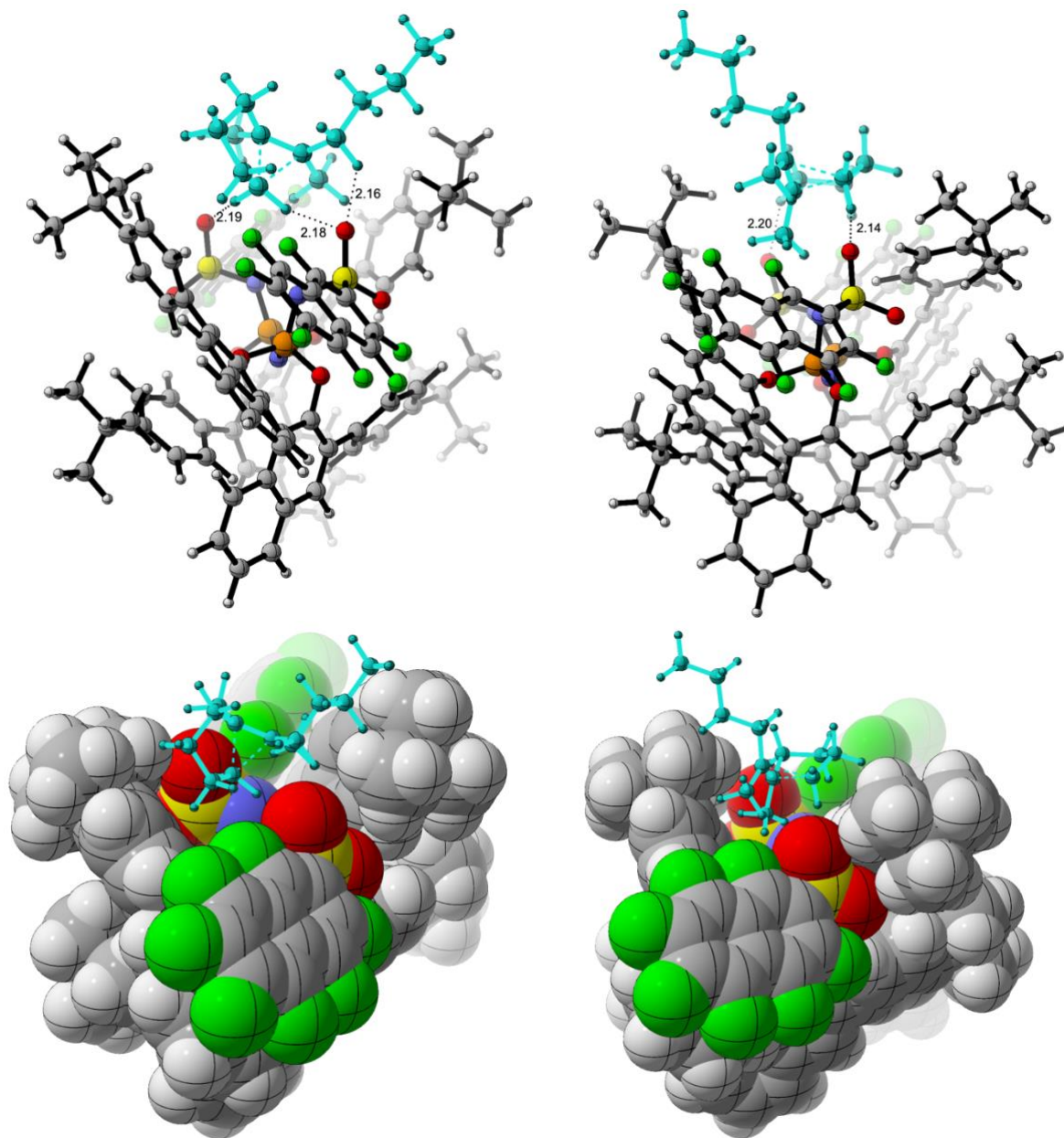


Figure S4.2. Structures of lowest energy ring expansion conformers. Ball and stick models (top), space-filling of catalyst (bottom). S conformer (left), R conformer (right).

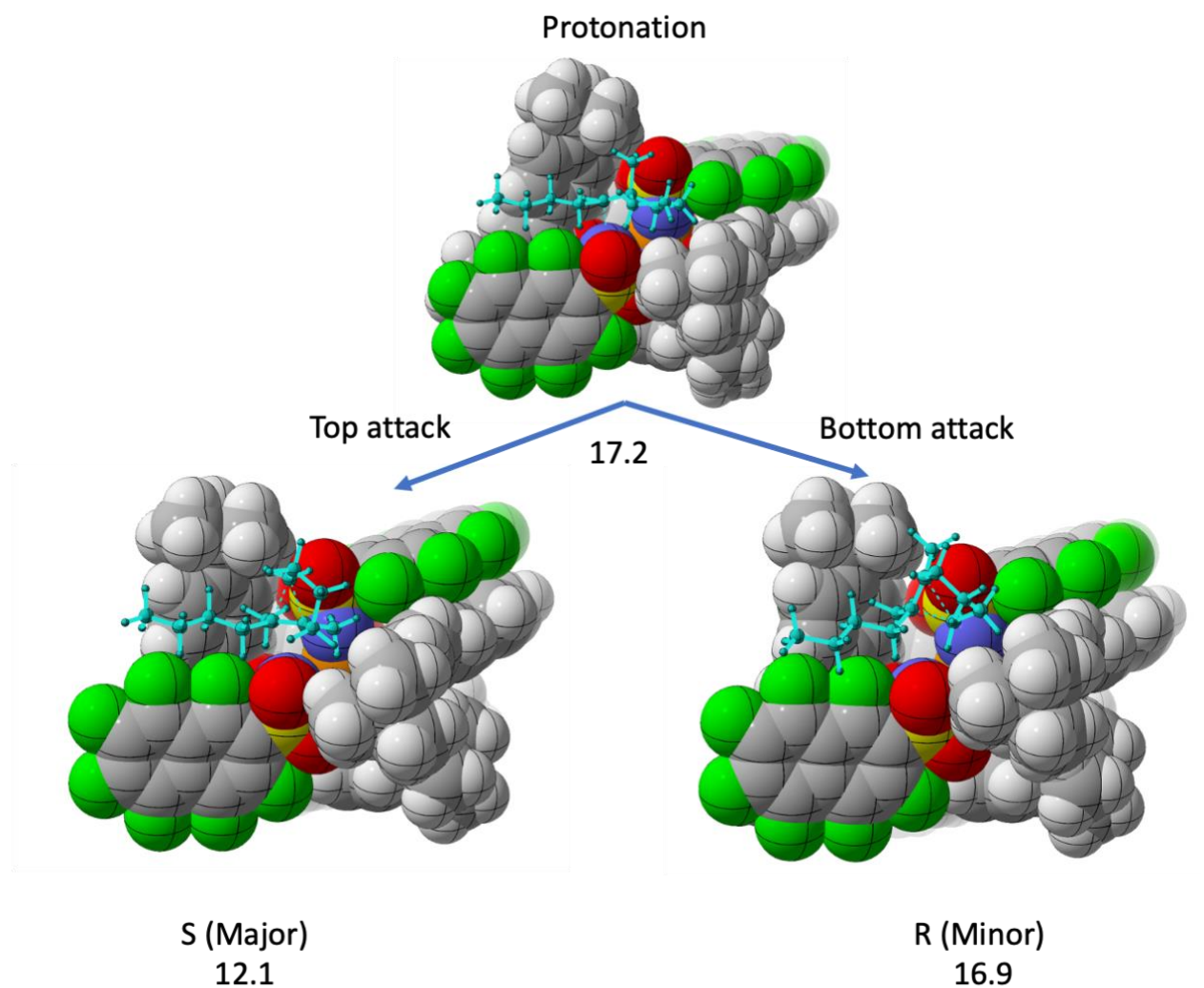


Figure S4.3 Ring expansion from **B** without significant conformational change. All structures depicted are transition states.

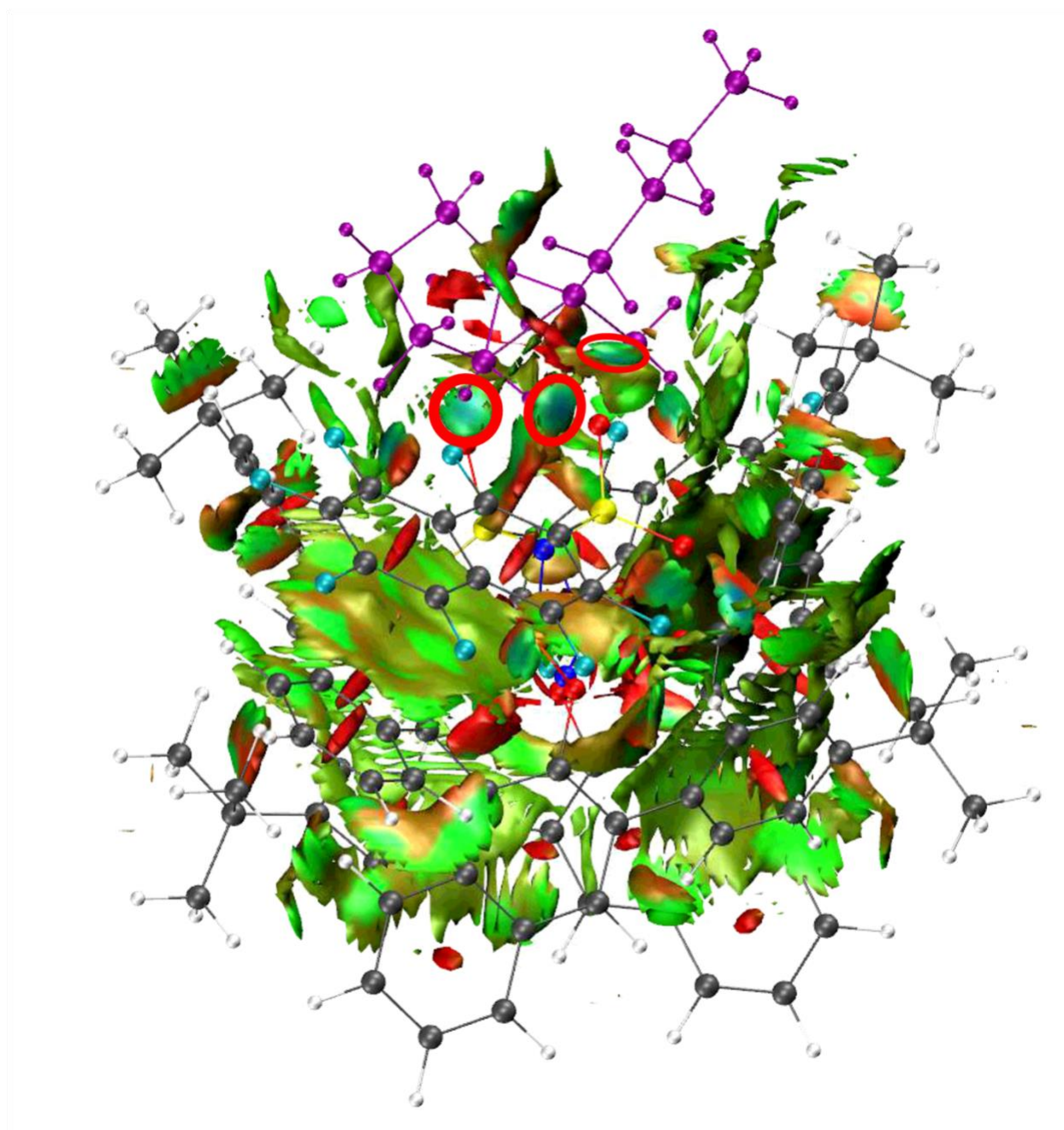


Figure S4.4. Non-Covalent Interaction plot of the lowest energy S ring expansion conformer. Interactions are colored as strongly attractive (blue), weakly attractive (green), and repulsive (red). Key hydrogen bonding interactions between substrate and catalyst are circled in red. Substrate is colored purple for clarity.

Confining potential example syntax:

\$wall

potential=logfermi

sphere: auto,all

\$end

Constraints:

TS_AB:

C176, H84: 1.34Å

N40, H84: 1.38Å

TS_CD:

C171, C180: 1.91Å

C180, C179: 1.94Å

TS_GH:

C171, C181: 1.90Å

C171, C181: 1.90Å

TS_EF:

H218, O43: 1.35

H218, C212:1.31

S5, S41: 5.80

TS_IJ:

O43, H218: 1.30Å

C212 ,H218:1.38Å

N4, N40: 3.52Å

Energies of Structures

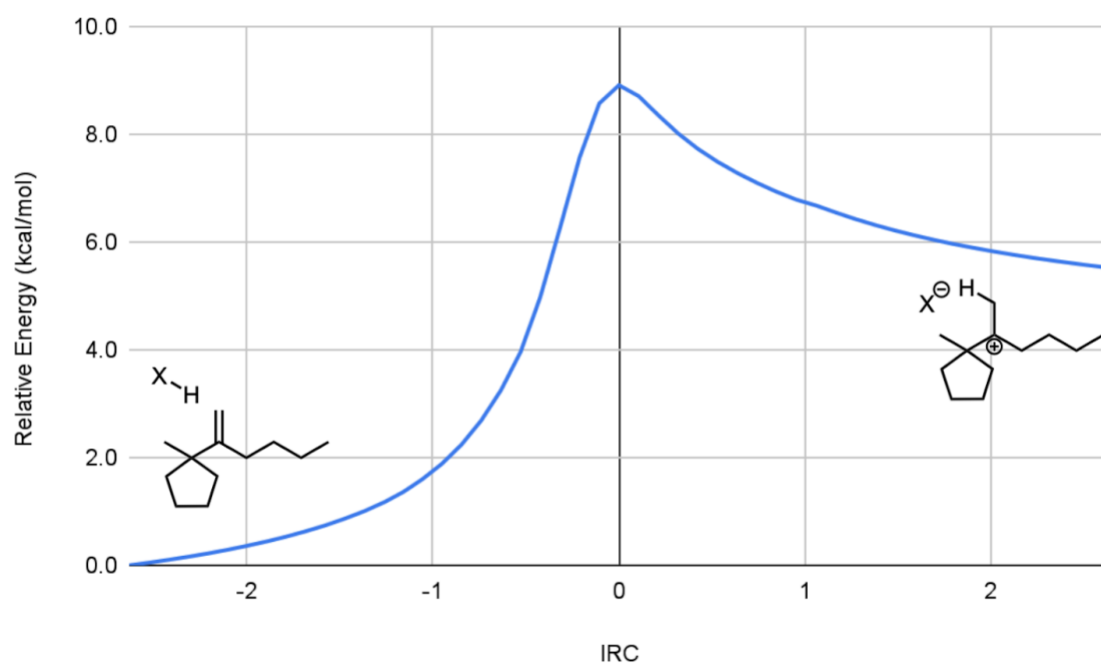
Table S4.1: Absolute Electronic (E) and Gibbs Free Energies (G) in Hartrees.

STRUCTURE	E B3LYP	E M06-2X	E WB97XD	E WB97X-D4	G B3LYP	G M062X	G WB97XD	G WB97X-D4
X-H	-7493.336	-7497.756	-7498.184	-7498.649	-7491.966	-7496.386	-7496.815	-7497.279
1C	-470.236	-470.456	-470.555	-470.578	-469.963	-470.183	-470.282	-470.305
A	-7963.609	-7968.225	-7968.766	-7969.245	-7961.940	-7966.556	-7967.097	-7967.576
TS_AB	-7963.594	-7968.205	-7968.746	-7969.222	-7961.928	-7966.538	-7967.080	-7967.556
B	-7963.603	-7968.216	-7968.759	-7969.237	-7961.934	-7966.547	-7967.090	-7967.568

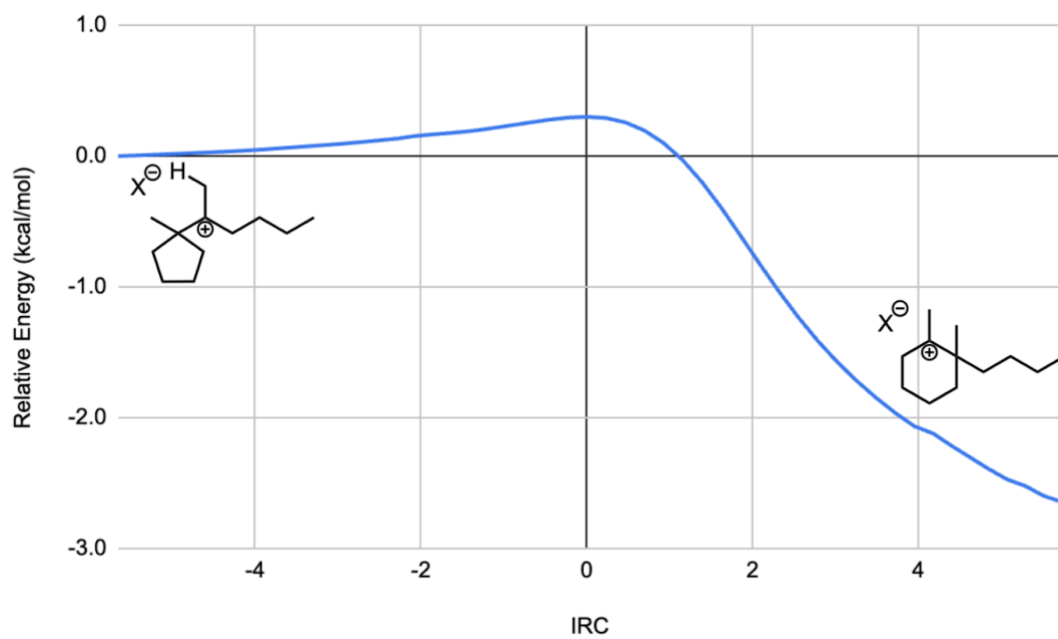
C	-7963.590	-	-7968.752	-7969.233	-7961.924	-7966.544	-7967.086	-7967.567
			7968.211					
TS_CD	-7963.589	-	-7968.752	-7969.233	-7961.921	-7966.544	-7967.084	-7967.564
			7968.213					
D	-7963.598	-	-7968.756	-7969.235	-7961.928	-7966.543	-7967.086	-7967.566
			7968.213					
E	-7963.612	-	-7968.765	-7969.243	-7961.941	-7966.554	-7967.094	-7967.572
			7968.224					
TS_EF	-7963.605	-	-7968.757	-7969.234	-7961.939	-7966.553	-7967.092	-7967.569
			7968.219					
F	-7963.612	-	-7968.765	-7969.243	-7961.943	-7966.559	-7967.096	-7967.574
			7968.228					
G	-7963.588	-	-7968.748	-7969.229	-7961.919	-7966.540	-7967.080	-7967.560
			7968.209					
TS_GH	-7963.588	-	-7968.749	-7969.229	-7961.919	-7966.542	-7967.080	-7967.560
			7968.211					
H	-7963.602	-	-7968.758	-7969.239	-7961.933	-7966.549	-7967.089	-7967.570
			7968.218					
I	-7963.607	-	-7968.765	-7969.243	-7961.939	-7966.552	-7967.096	-7967.575
			7968.221					
TS_IJ	-7963.601	-	-7968.758	-7969.237	-7961.935	-7966.554	-7967.092	-7967.570
			7968.220					
J	-7963.610	-	-7968.767	-7969.245	-7961.940	-7966.560	-7967.097	-7967.575
			7968.230					
3C	-470.251	-470.469	-470.567	-470.590	-469.977	-470.195	-470.293	-470.316
TS_BDCO	-7963.593	-	-7968.754	-7969.233	-7961.925	-7966.547	-7967.086	-7967.564
NF			7968.216					
TS_BHCO	-7963.586	-	-7968.745	-7969.225	-7961.917	-7966.538	-7967.077	-7967.557
NF			7968.206					
TS_CD2	-7963.588	-	-7968.751	-7969.231	-7961.920	-7966.543	-7967.082	-7967.563
			7968.212					

Intrinsic Reaction Coordinate Diagrams

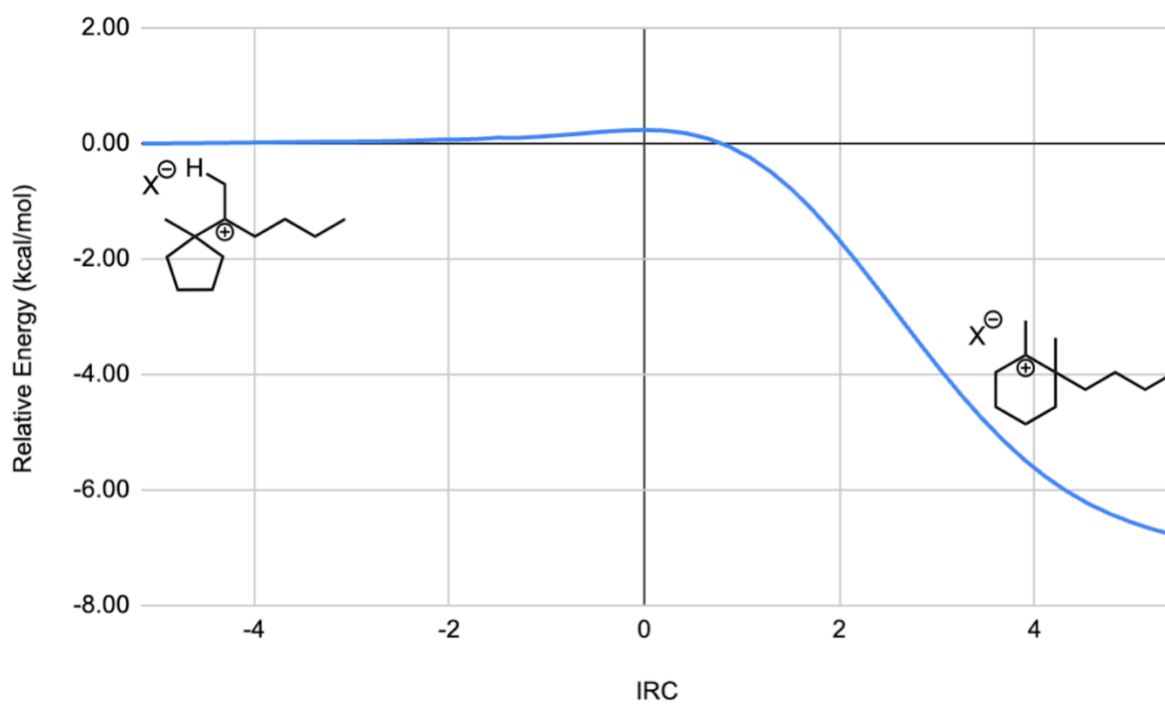
TS_{AB}



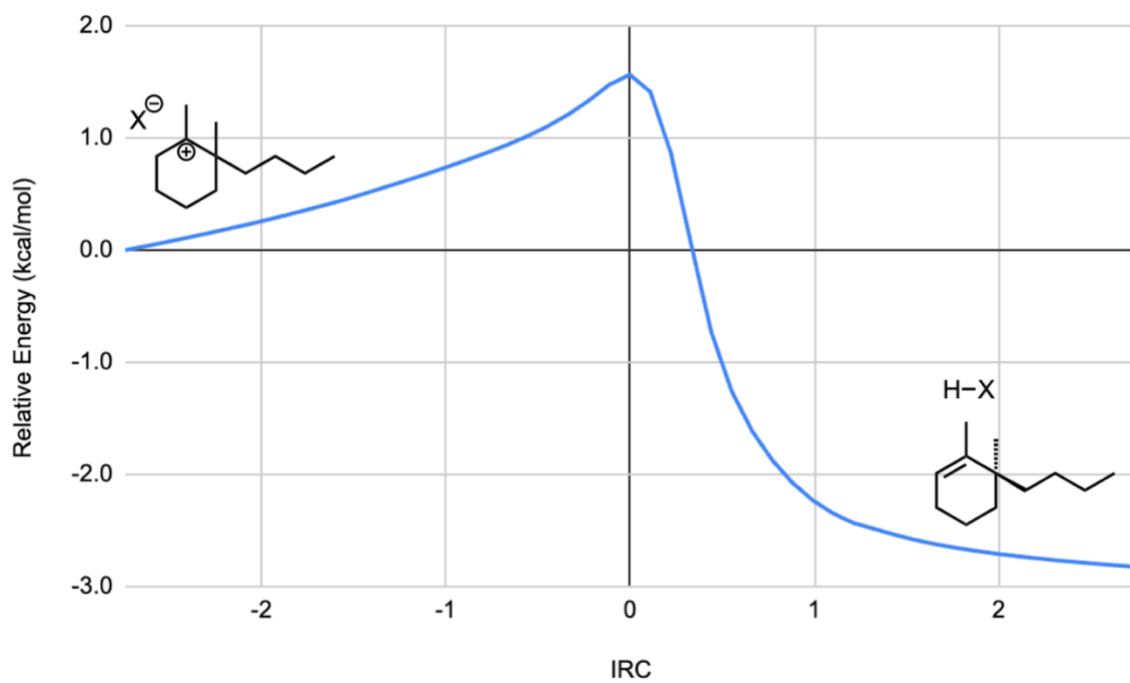
TS_{CD}



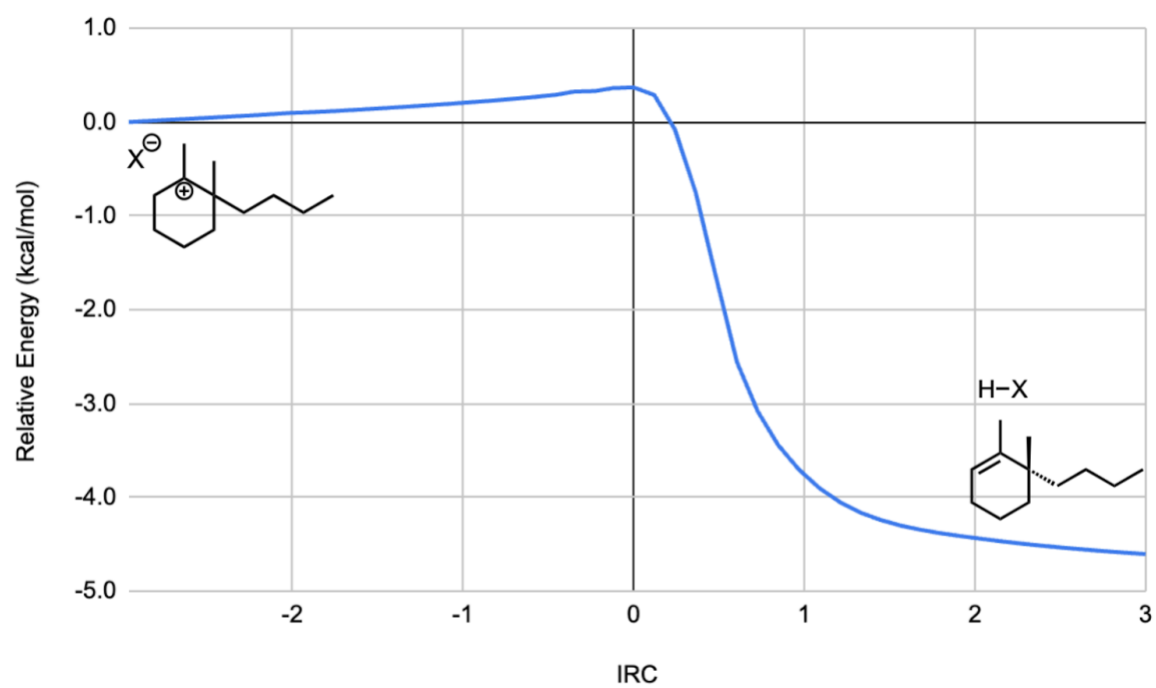
TS_{GH}



TS_{EF}



TS₂



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