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Quantum Chemical Interrogation of Reactions Promoted by Dirhodium Tetracarboxylate Catalysts—Mechanism, Selectivity, and Nonstatistical Dynamic Effects

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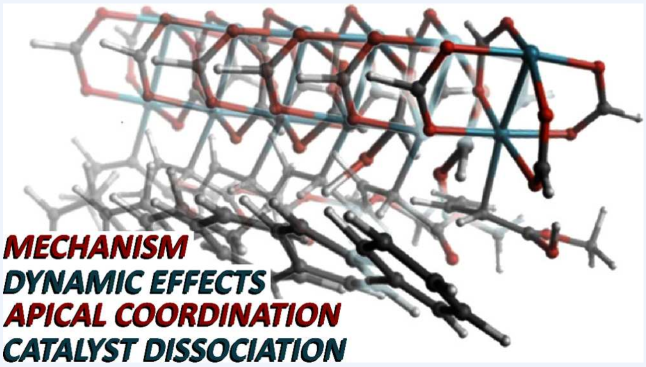

CONSPECTUS: Rh_2L_4 catalysts have risen in popularity in the world of organic synthesis, being used to accomplish a variety of reactions, including C−H insertion and cyclopropanation, and often doing so with high levels of stereocontrol. While the mechanisms and origins of selectivity for such reactions have been examined with computational quantum chemistry for decades, only recently have detailed pictures of the dynamic behavior of reacting Rh_2L_4-complexed molecules become accessible. Our computational studies on Rh_2L_4 catalyzed reactions are described here, with a focus on C−H insertion reactions of Rh_2L_4-carbenes. Several issues complicate the modeling of these reactions, each providing an opportunity for greater understanding and each revealing issues that should be incorporated into future rational design efforts. First, the fundamental mechanism of C−H insertion is discussed. While early quantum chemical studies pointed to transition structures with 3-center [C−H−C] substructures and asynchronous hydride transfer/C−C bond formation, recent examples of reactions with particularly flat potential energy surfaces and even discrete zwitterionic intermediates have been found. These reactions are associated with systems bearing π-donating groups at the site of hydride transfer, allowing for an intermediate with a carbocation substructure at that site to be selectively stabilized. Second, the possible importance of solvent coordination at the Rh atom distal to the carbene is discussed. While effects on reactivity and selectivity were found to be small, they turn out not to be negligible in some cases. Third, it is shown that, in contrast to many other transition metal promoted reactions, many Rh_2L_4 catalyzed reactions likely involve dissociation of the Rh_2L_4 catalyst before key chemical steps leading to products. When to expect dissociation is associated with specific features of substrates and the product-forming reactions in question. Often, dissociation precedes transition structures for pericyclic reactions that involve electrons that would otherwise bind to Rh_2L_4. Finally, the importance of nonstatistical dynamic effects, characterized through ab initio molecular dynamics studies, in some Rh_2L_4 catalyzed reactions is discussed. These are reactions where transition structures are shown to be followed by flat regions, very shallow minima, and/or pathways that bifurcate, all allowing for trajectories from a single transition state to form multiple different products. The likelihood of encountering such a situation is shown to be associated again with the likelihood of formation of zwitterionic structures along reaction paths, but ones for which pathways to *multiple* products are expected to be associated with very low or no barriers. The connection between these features and reduced yields of desired products are highlighted, as are the means by which some Rh_2L_4 catalysts modulate dynamic behavior to produce particular products in high yield.

KEY REFERENCES

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- Laconsay, C. J.; Pla-Quintana, A.; Tantillo, D. J. Effects of Axial Solvent Coordination to Dirhodium Complexes on Reactivity and Selectivity in C−H Insertion Reactions: A Computational Study. *Organometallics* **2021**, *40*, 4120−4132.[2] This study examined the influence of axial ligands on reactivity and selectivity, having implications for the

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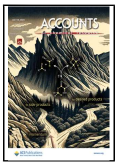

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interpretation of solvent effects, the effects of additives, and the use of ligands with additional Lewis basic groups.

- Hare, S. R.; Tantillo, D. J. Cryptic Post-Transition State Bifurcations Reduce the Efficiency of Lactone-Forming Rh-Carbenoid C−H Insertions. *Chem. Sci.* **2017**, *8*, 1442−1449.[3] This study involved the first ab initio molecular dynamics simulations on a Rh_2L_4 promoted reaction, indicating the presence of a post-transition state bifurcation and showing how nonstatistical dynamic effects can lead to unwanted side products.
- Guo, W.; Hare, S. R.; Chen, S.-S.; Saunders, C.; Tantillo, D. J. C−H Insertion in Dirhodium Tetracarboxylate-Catalyzed Reactions Despite Dynamical Tendencies Toward Fragmentation − Implications for Reaction Efficiency and Catalyst Design. *J. Am. Chem. Soc.* **2022**, *144*, 17219−17231.[4] This study involved molecular dynamics simulations that point toward the potential generality of nonstatistical dynamic effects in controlling selectivity, the importance of specific noncovalent interactions and substrate conformational control, and the differences between simple achiral catalysts and complex chiral catalysts.

■ SETTING THE STAGE

Mechanisms of Rh_2L_4 catalyzed reactions have been subjected to scrutiny using computational chemistry for approximately three decades,[5] with the most attention being paid to C−H insertion reactions.[6] In the seminal work of Taber and co-workers, molecular mechanics calculations were shown to be capable of reproducing the sense of diastereoselectivity for several $Rh_2(OAc)_4$ catalyzed intramolecular C−H insertion reactions.[7] These computations made use of constrained distances and angles to capture the geometry of the $Rh_2(OAc)_4$ substructure optimized independently with ZINDO[8] and to constrain forming/breaking bonds to a 4-center transition structure geometry (Figure 1). The agreement between experimentally observed diastereoselectivities and the computational results provided support for the reasonability of a 4-center transition structure.

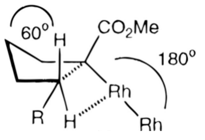


Figure 1. Taber's 4-center transition structure model. Reproduced from ref 7. Copyright 1996 American Chemical Society.

The 4-center model has not been borne out in studies using density functional theory (DFT), however. Nakamura and co-workers' early work using the B3LYP/6-31G(d)-LANL2DZ method (with some benchmarking against MP2(FC)) to model C−H insertion into simple alkanes by the catalyst model $Rh_2(HCO_2)_4$ indicated that a 3-center model (Figure 2) is more likely (in addition to mapping out the pathway for [Rh] carbene formation from a diazo compound and showing that N_2 loss can be rate-limiting).[9] This study also pointed out that the C−H insertion reaction coordinate involved asynchronous events—initial hydride transfer to the carbene carbon followed by C−C bond formation—even though the process was concerted.[10] This study was followed up by calculations on larger systems making use of the PM3(tm) semiempirical method with constraints based on DFT results on small models,[11] including some overlap with the systems studied previously by Taber. Later studies (as described below) have shown the generality of the concerted 3-center transition structure model associated with asynchronous hydride transfer and C−C bond forming events.

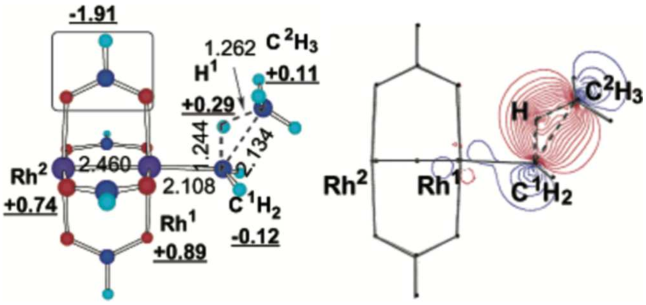


Figure 2. Left: Computed transition structure for C−H insertion into methane (selected bond lengths shown in Å and natural charges shown underlined). Right: Key orbital showing 3-center delocalization in the C−H insertion transition structure. Both images reproduced from ref 9. Copyright 2002 American Chemical Society. Similar geometries and orbitals were found for other systems examined in ref 9.

Transition structures for other Rh_2L_4 catalyzed reactions such as *β*-hydride migration, cyclopropanation, ylide formation, epoxide formation, cycloaddition, and [2,3] sigmatropic shifts also have been computed with DFT (e.g., Figure 3).[12] Many of these processes also were found to be concerted with asynchronous events. Related examples are discussed below.

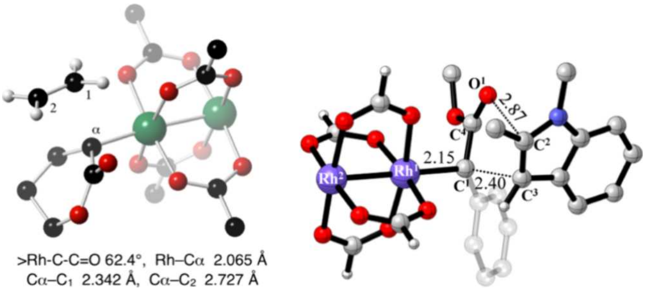


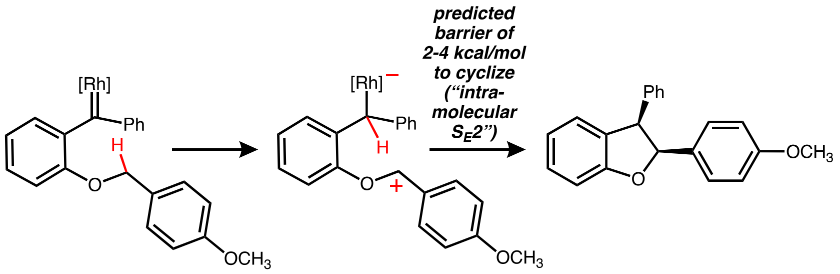
Figure 3. Representative transition structures for other Rh_2L_4 promoted reactions. Reproduced from ref 12a,e. Copyright 2011 and 2015 American Chemical Society.

In contrast, computational studies on Rh_2L_4 catalyzed reactions involving nitrenes have confirmed that they are generally electronically more complex than those involving carbenes. In particular, triplet states can be involved, allowing radical reactivity to be expressed,[13] while this type of reactivity generally is not observed for [Rh] carbenes.

■ DOING A TWO-STEP?

As described above, Rh_2L_4-promoted C−H insertion generally follows a concerted mechanism, but H transfer and C−C bond formation events can, however, occur quite asynchronously. Can the extreme of this scenario occur where these two events are actually separated by a barrier, i.e., there is a zwitterionic intermediate? Since initial hydride transfer to the carbene carbon would leave a carbocation center behind, *π*-donor substituents at this position could potentially provide enough selective stabilization for such a structure to be a minimum on the potential energy surface. This is indeed the case, although only low barriers for subsequent ring-closure have been

Scheme 1. Rh_2L_2-Promoted C−H Insertion Reaction with a Discrete Intermediate. [Rh] = $Rh_2(OAc)_4$

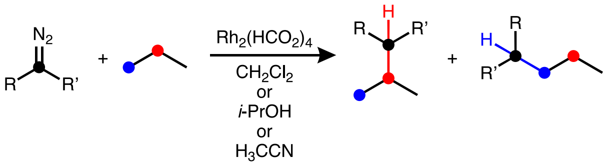


observed to date. An example is shown in Scheme 1, computed by Dmitrenko, Fox and co-workers.[14] In this system, the carbocation center in the zwitterionic intermediate bears both an oxygen with a lone pair ripe for donation and an electron-rich aryl group. Despite the presence of these capable donors, the barrier for ring closure was predicted to be only a few kcal/mol (in terms of both enthalpy and free energy), providing a significant impediment to stereochemical scrambling. Note that the second (ring-closing) step of this reaction is akin to an intramolecular S_E2 reaction in which [Rh] is displaced by an electrophilic carbon.[15] Other related intermediates have been characterized computationally and shown to be relevant to stereocontrol.[15]

HOW UNCOORDINATED?

In general, computational models of Rh_2L_4 catalysts do not include apical ligands, i.e., solvent or other molecules bound to the Rh that is not bound to the carbene carbon (or nitrene nitrogen). But is this a reasonable approach? In some experimental investigations, solvent effects have been observed that could be associated with apical bonding.[16] To address this issue at a fundamental level, we carried out a systematic study on C−H insertion into propane using $Rh_2(HCO_2)_4$ with several different explicit solvent molecules (Scheme 2) based on the mechanistic scenario depicted in Figure 4.[2] The effects of apical coordination on barriers for N_2 loss and C−H insertion were computed for [Rh] carbenes with different combinations of donor and acceptor groups, as was the regioselectivity for C−H insertion. While predicted effects of coordination were not large, they also were not always negligible. Differences in $\Delta\Delta G^{\ddagger}$ for insertion into propane's methyl and methylene groups varied with complexation by as much as ∼1 kcal/mol, with more donating apical ligands decreasing selectivity for our acceptor/acceptor carbene model but not showing a clear trend for the other carbenes examined. In any case, this work indicates that one should proceed with caution if not modeling apical ligands, especially if theory and experiment (without apical ligands modeled) fail to correspond.

Scheme 2. Model C−H Insertion Reactions Examined to Predict the Effects of Apical Coordination by Solvent Molecules[a]



[a] Various combinations of R/R′ donor (Ph) and acceptor (CO_2CH_3) groups were examined.

Rh_2L_4 promoted reactions with ligands bearing groups that can participate in apical coordination (e.g., Figure 5) also display distinctive reactivity in some cases.[17] We are now examining such cases in collaboration with the Darko group.

SHOULD I STAY OR SHOULD I GO NOW?

Generally, when one teaches organometallic chemistry,[18] a transition metal catalyst is shown to first bind a substrate, then undergo multiple steps to form a catalyst-bound product, then dissociate. Experimental and computational evidence has indicated, however, that this scenario is often not the case for Rh_2L_4 catalyzed reactions.[19] Instead, a [Rh] carbene (or nitrene) undergoes a reaction that generates a species to which the binding of [Rh] is relatively weak, allowing the catalyst to dissociate before a key step along the path to product formation. Several examples of this type of reaction are discussed below, along with some simple principles useful for predicting whether or not one should expect [Rh] to dissociate before a product formation step.

Our first encounter with this type of scenario occurred during an examination of an indole-forming reaction in collaboration with the Driver group.[20] Part of the relevant mechanism is shown in Scheme 3. After formation of a [Rh] nitrene, cyclization occurs, which is followed by the migration of one of two groups (MG^1 or MG^2). Migration with and without [Rh] was modeled and for most MG^1/MG^2 combinations the same group was predicted to migrate preferentially in both cases. However, with MG^1/MG^2 = H/CO_2CH_3 the migration of CO_2CH_3 was predicted to dominate with [Rh] bound, but migration of H was predicted to dominate with no metal present. Several reactions for which we made predictions were tested experimentally, and when an ester-bearing substrate was used (MG^1/MG^2 = H/CO_2*i*-Pr for practical reasons) only H migration was observed, suggesting that [Rh] had indeed departed before rearrangement.[21]

Later, we undertook a systematic study of Rh_2L_2 catalyzed [2,3] sigmatropic shifts (Scheme 4),[1] in part because stereochemical scrambling and crossover had been observed in some experiments suggesting again that the [Rh] may not be present during rearrangement.[19] We examined carbenes with various donor/acceptor substituents and various allyl ethers, thioethers, and selenoethers. First, we focused on experimentally studied systems. Of those, [Rh]-bound rearrangement was found to be preferred for the one oxonium ylide examined, but [Rh]-unbound rearrangements were preferred for sulfonium, and selenonium ylides. It makes sense that [Rh] binding can hinder rearrangement, since the electrons of the "$C:^-$" to which it is bound are needed for the rearrangement. Studies on additional systems also demonstrated that steric crowding in the transition

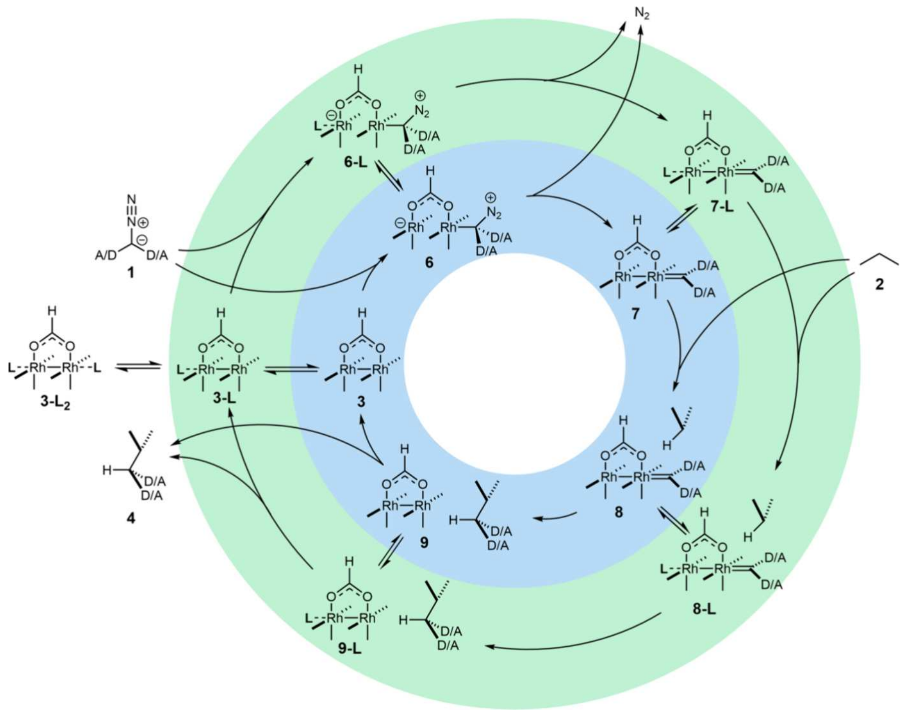


Figure 4. Mechanism postulated for the insertion of a diazo compound into propane catalyzed by $Rh_2(HCO_2)$ (only one formate is drawn explicitly). Blue inner ring: no axial ligand; green outer ring: one axial ligand bound. Reproduced from ref 2. Copyright 2021 American Chemical Society.

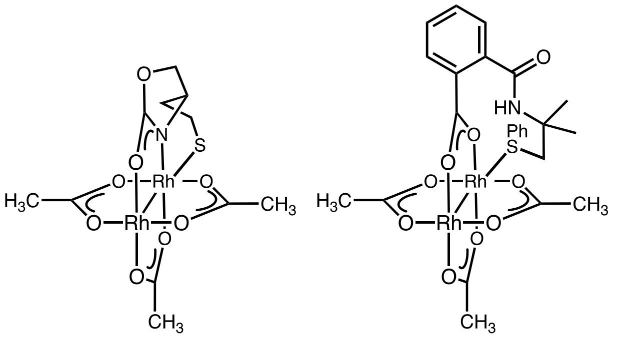
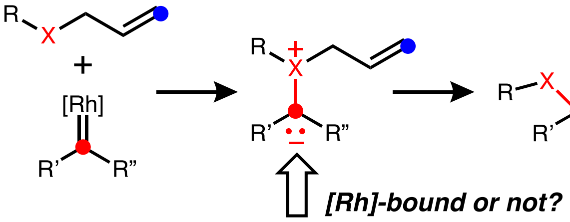


Figure 5. Catalysts studied by Darko and co-workers with ligands expected to bind to the rhodium atom distal to the carbene.[17d−g]

Scheme 4. [2,3]-Sigmatropic Shifts Examined Computationally[a]



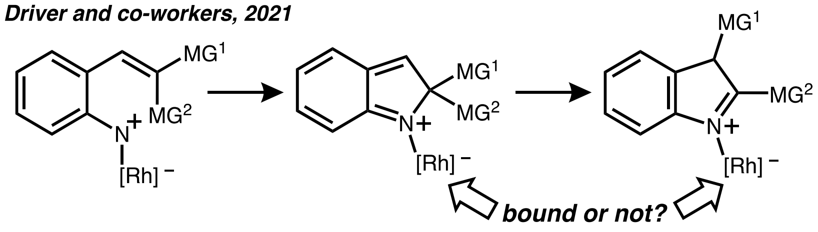
X = O, S, Se
R = Ar, CF_3
R'/R" = combinations of H, Ph, CO_2CH_3, CN

[a] $[Rh] = Rh_2(OAc)_4$.

structure plays a key role. Figure 6 shows an example of a [2,3]-shift transition structure where [Rh] detached from the "C:$^-$" during optimization; note the crowdedness.

We have observed similar behavior in a variety of other Rh_2L_2 catalyzed reactions with pericyclic product-forming steps (Scheme 5). In work with the Shaw group,[22] the results of our calculations indicated that [Rh] dissociated from the ammonium ylide shown before Stevens rearrangement occurred (concerted in this case, even though formally forbidden based on orbital symmetry, likely due to the presence of the ester);[23] in that case, we were unable to locate a [Rh]-bound transition structure. In a study with the Tambar group involving the

Scheme 3. Cyclization/[1,5]-Sigmatropic Shift Studied with the Driver Group[a]



[a] $[Rh] = Rh_2(esp)_2$ for experiments, $[Rh] = Rh_2(HCO_2)_4$ for calculations.

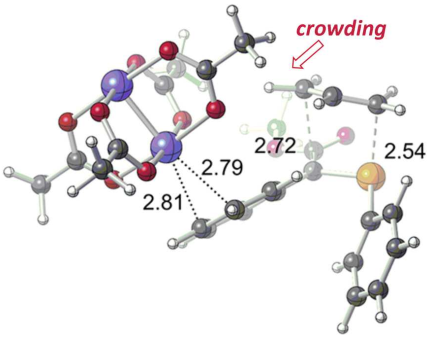
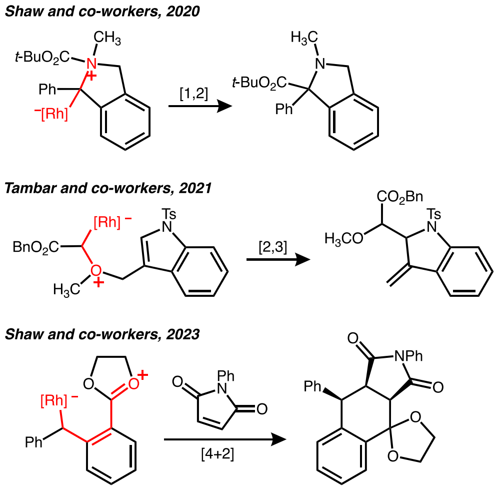


Figure 6. Computed TS for the [2,3]-sigmatropic shift of a selenonium ylide. Distances shown in Å. Adapted from ref 1. Copyright 2021 American Chemical Society.

Scheme 5. Additional Rh_2L_2 Catalyzed Reactions for Which We Predict [Rh] Dissociation before a Key Product-Forming Step



oxonium ylide shown,[24] we again predicted a preference for [Rh]-free rearrangement, and again no competing [Rh]-bound transition structure was found. Finally, in another study with the Shaw group,[25] we predicted [Rh]-free [4 + 2] cycloaddition. Note that the ylide in this case can also be formulated as an *ortho*-quinodimethide. In all of these cases, as for the other [Rh] carbene cases above (Scheme 4), the electrons used to bind [Rh] are needed for the subsequent product-forming reaction, allowing [Rh] dissociation to help the product-forming reaction proceed.[26]

■ DYNAMICAL DISTRACTIONS?

Reactions that do not conform to the doctrines of transition state theory (i.e., they exhibit nonstatistical dynamic behavior) continue to be identified at a seemingly growing pace,[27] and these include reactions of complex organic molecules with large catalysts. Rh_2L_4 catalyzed reactions comprise a class of reactions where nonstatistical dynamic effects have been shown to play important roles in controlling reactivity and selectivity. Prime among these are a variety of Rh_2L_4 catalyzed reactions that involve post-transition state bifurcations (PTSBs), i.e., for which a key transition structure is followed on the potential energy surface by a path downhill in energy that splits toward two products without involving a minimum (intermediate).[27,28] Since one transition structure (saddle point on the potential energy surface) or state (which reflects the highest state along the reaction in terms of free energy) leads to two products, the relative rates of formation of products cannot be determined by barriers for competing reactions, and classic transition state theory is not applicable. Instead, the relative amount of each of the two products is determined by a combination of the curvature of the potential energy surface (i.e., the forces acting on the reacting molecule) and the momentum the reacting molecule possesses as it passes by the transition state (called "ambimodal" when it precedes a PTSB[29]). The effects of this momentum can be characterized by using ab initio molecular dynamics (AIMD, also called direct or on-the-fly dynamics) calculations.[30] Types of Rh_2L_4 catalyzed reactions involving PTSBs that have been examined with AIMD calculations are shown in Figure 7.

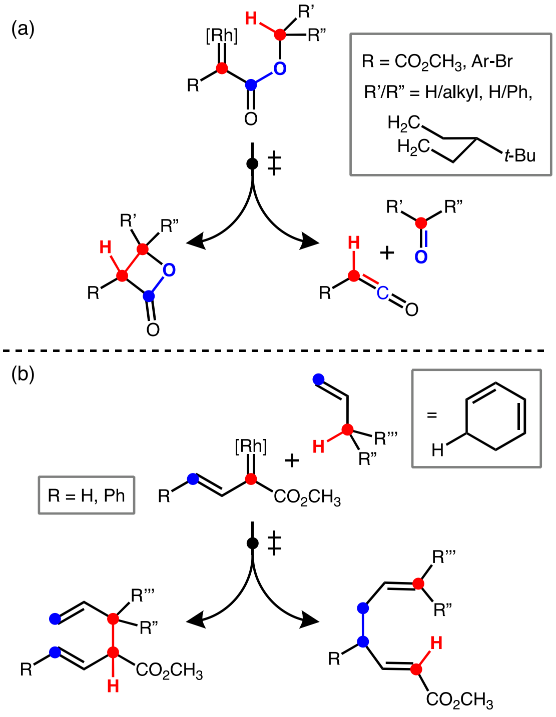


Figure 7. Types of Rh_2L_4 catalyzed reactions for which PTSBs have been proposed and nonstatistical dynamic behavior has been characterized using AIMD calculations. Definitions of [Rh] are included in the main text.

The first such example for which AIMD calculations were employed (not the first for which a PTSB was proposed, *vide infra*) is shown in Figure 7a (R = CO_2CH_3, R/R′ = $(CH_2)_2CHt$-$Bu(CH_2)_2$, [Rh] = $Rh_2(OAc)_4$).[3] In the context of testing computational methods for C−H insertion reactions, we discovered that this reaction, examined originally by Lee and co-workers in the context of developing a process for the synthesis of β-lactones,[31] possessed a PTSB leading to both β-lactone product and products of fragmentation: a ketone and a ketene. Our AIMD calculations (on the exact experimental substrate and catalyst) showed that both β-lactone and fragmentation products can form from a single transition state, with fragmentation dominating. At first we thought that our calculations were unreliable due to the large amount of fragmentation observed, but then a careful rereading of Lee et al.'s paper revealed that *t*-Bu-cyclohexanone was actually the major product of the reaction; this fact was in a footnote on an

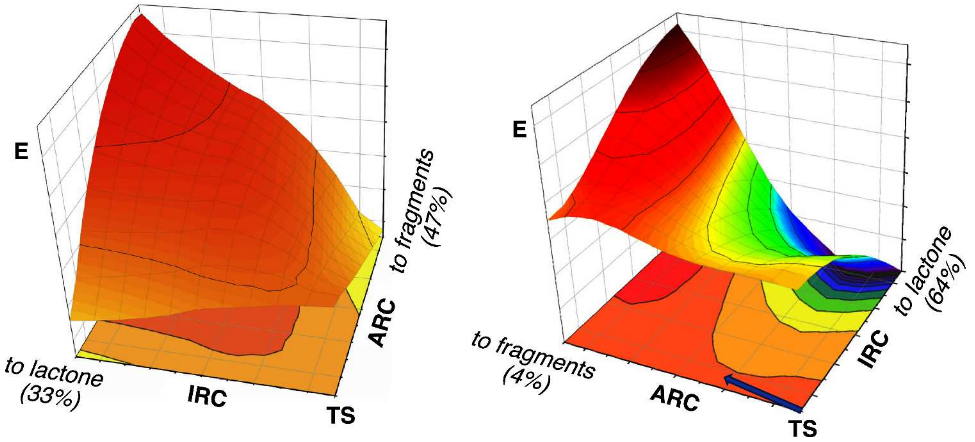


Figure 8. Two potential energy surfaces for reactions with PTSBs. The left-hand surface is for a reaction that leads to significant amounts of both β-lactone product and fragmentation products in AIMD calculations (percentages shown with product labels at plot corners), while the right-hand surface is for a reaction that leads mostly to β-lactone product. ARC = Artificial Reaction Coordinate.[4]

optimization table, since the paper was focused on β-lactone products, so we had missed it (we should have noticed). Luckily for us, this information was actually reported, validating our "retrospective prediction" (a prediction made without knowledge of pre-existing results). Of particular importance to us was the fact that our calculations had demonstrated that an unwanted side-product, the major observed product for this specific system, was the direct result of a PTSB. Therefore, if one wanted to rationally discourage formation of that side-product, it would seem that nonstatistical dynamic effects should be considered. Sometimes your side-product comes from a bifurcation...

Curious as to whether PTSBs would be found in other Rh_2L_4 catalyzed β-lactone-forming reactions, we examined additional cases for which experimental results had been reported by the Bach and Davies groups (Figure 7a; for Bach: R = 2-Br-Ph, R′/R″ = H/CH_2*i*-Pr, [Rh] = $Rh_2(OAc)_4$; for Davies: R = 2-Br,5-OCH_3−Ph, R′/R″ = H/Ph, [Rh] = Rh_2(*s*-TCPTTL$)_4$).[4] For the Bach system (modeled with the exact experimental substrate and catalyst),[32] our computations reproduced the experimentally observed diastereoselectivity (*cis* v. *trans* substituents on the β-lactone product) when the lowest energy conformations of transition structures leading to each product were compared (24:1 for *trans* experimentally, and ∼20:1 for *trans* computationally). But were these transition structures/states followed by PTSBs? Our AIMD calculations indicated that they were. For the lowest energy transition state leading to the *trans* product, we observed β-lactone formation in 33% of trajectories and fragmentation in 47%. The experimental yield for this substrate was reported to be 43%,[32] so we again suspect that significant mass was lost to post-transition state fragmentation. A potential energy surface for this reaction is shown in Figure 8 (left; constructing such a surface was difficult, and technical details can be found in ref 4 and its Supporting Information). The bottom righthand corner of this surface corresponds to the transition structure. Moving toward the bottom left-hand corner leads to β-lactone, while moving toward the back righthand corner leads to fragmentation products. There does not appear to be a large energetic preference for either, and both are formed in significant amounts in the AIMD calculations. In contrast, Figure 8 (right) shows an analogous surface for a different transition structure for which there appears to be a strong preference for β-lactone formation based on the curvature of the surface. AIMD calculations for the associated transition state do indeed predict predominantly β-lactone formation (64% compared to only 4% fragmentation). The small arrow from the transition structure in this figure indicates, roughly, the direction expected for the momentum.[33] In this case, the momentum is toward fragmentation, but that momentum is not enough to overcome the effect of the potential energy surface curvature. The transition structure associated with this surface actually leads to the disfavored *cis* β-lactone product, while that for Figure 8 (left) leads to the preferred *trans* product, so diastereoselectivity comes at the cost of PTSB-associated yield reduction in this case.

Reactions studied by the Davies group were then examined.[34] First, calculations using $Rh_2(OAc)_4$ as catalyst were carried out, but these predicted perfectly incorrect diastereoselectivity.[4] We then resorted to including the whole Rh_2(*s*-TCPTTL$)_4$ catalyst (Figure 9)[35] in our calculations (e.g., Figure 10). Doing so led to a match between experimental and predicted diastereoselectivity (>19:1 for *cis* for the experiment and a >4 kcal/mol preference from computations). In addition, the predicted sense of enantioinduction (*s*-TCPTTL is chiral) for experiment and computations also matched. However, AIMD calculations for this system predicted complete selectivity for fragmentation over β-lactone formation! How could this be? It turns out that in this system, conversion of the fragmentation products to the β-lactone product with the correct configuration can occur within the catalyst binding pocket via a ketone-ketene [2 + 2]

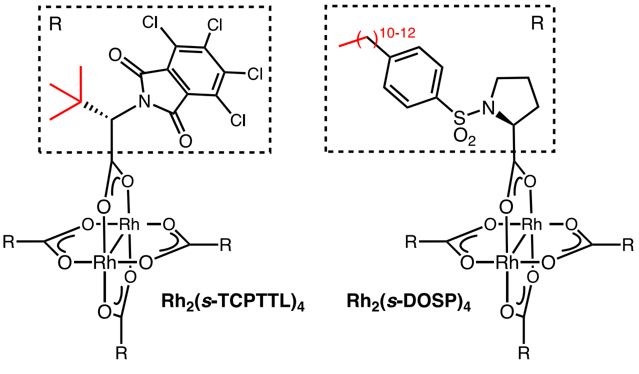


Figure 9. Representative Rh_2L_4 catalysts with large ligands.

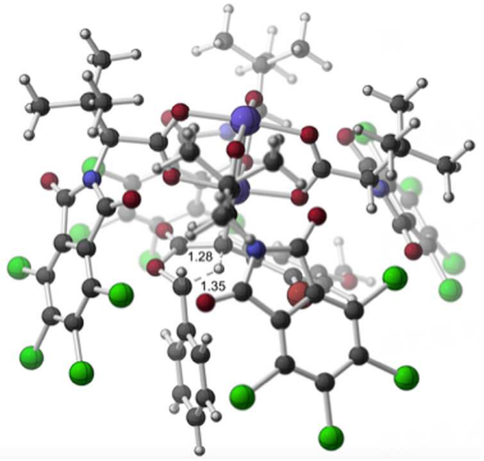


Figure 10. Preferred C−H insertion transition structure with Rh_2(*s*-TCPTTL)$_4$ catalyst.[4] For an X-ray crystal structure of a chiral [Rh] carbene related to Rh_2(*s*-TCPTTL)$_4$, see ref 35.

cycloaddition; the *β*-lactone product was predicted to be thermodynamically preferred and the barrier for cycloaddition was predicted to be low enough for this system (but not for the others discussed above). So we are left with a model of reactivity/selectivity for the Rh_2(*s*-TCPTTL)$_4$ catalyzed system that involves (Figure 11): (1) stereo- (both diastereo- and enantio-) selectivity by way of competing transition states followed by (2) an apparent PTSB for the preferred transition state that is so unsymmetrical that it is essentially not a bifurcation, but rather a direct path to fragmentation products, and (3) recombination of the undesired products in the catalyst binding site. While this course of events was not part of the original reaction design, computations of the type described here could allow such complex scenarios to be faced head-on when developing reactions.

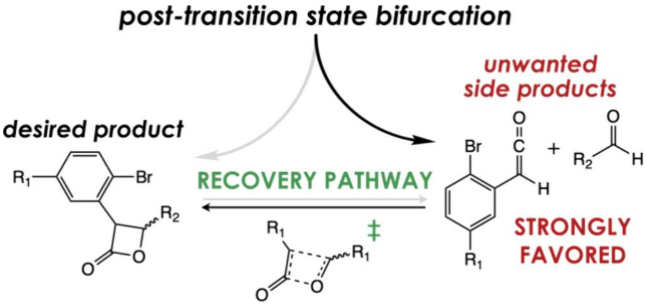


Figure 11. Model for reactivity/selectivity derived from the results of AIMD calculations.

Recently, another family of Rh_2L_4 catalyzed reactions with PTSBs was subjected to AIMD calculations. These include the first Rh_2L_4 catalyzed reaction for which a PTSB was proposed: Davies and co-workers′ combined C−H insertion/Cope Rearrangement (CHCR) reaction (Figure 7b).[36] On the basis of calculations on the reaction coordinate for this reaction, Davies, Autschbach and-co-workers invoked the presence of a PTSB.[36b] Many years later, we set out to examine the dynamics at play in this reaction.[37] We found that the networks of transformations originating from CHCR transition states were quite complex, with that complexity varying with the substrate. The most complex network explored is shown in Figure 12. Other systems explored have slightly simpler networks but share many of the features of the one shown. Among the key features are (1) Products of the PTSB proposed by Davies, Autschbach and-co-workers are indeed found to arise in MD trajectories initiated at the CHCR transition state (Figure 12, left, products **CH** and **trans-CHCR**). (2) A very shallow ion pair intermediate ($\mathbf{IM_{H\text{-}trans\text{-}in\text{-}2}}$) was found to follow the CHCR transition structure. For some systems, this type of structure is not a minimum on the potential energy surface, but appears instead to be an entropic intermediate (a minimum in free energy because of its favorable entropy).[38] (3) The time it takes for trajectories to leave the vicinity of this intermediate varies from system to system and is lengthened by "dynamic mismatching" − momentum possessed by trajectories leaving the region of the CHCR transition state that diverts them away from exit channels from the intermediate region. A similar analysis and conclusions appeared in an excellent, closely related studied carried out simultaneously by Schaefer and Ess, who also proposed an ion pair entropic intermediate and described the "vibrational synchronization" responsible for its selective formation of CH/CR products.[39] (4) This intermediate allows for the facile formation of side products resulting from cyclohexadienyl deprotonation to form benzene−a possible source of low yields in some systems. While it is difficult to imagine how such a complex system could be manipulated through rational catalyst design, characterization of its dynamic behavior at least opens the door to doing so, e.g., one can imagine constructing catalyst binding sites that hinder certain vibrations. For example, for Davies and co-workers′ CHCR reactions promoted by Rh_2(s-DOSP)$_4$ (Figure 9), which favor CHCR products over others and do so with high stereoselectivity,[36] we suspect that the shape of the catalyst binding site preferentially accommodates a [Rh] carbene conformation that has dynamical tendencies that favor formation of the desired products over formation of the putative competing intermediate.[37]

What do these systems have in common that might point to the presence of a PTSB or entropic intermediate? For all of them, one could write an arrow-pushing mechanism with an intermediate for which barriers for conversion to multiple products would be expected to be very low. In the case where those barriers are zero in terms of potential energy, then the "intermediate" would not be a minimum on the potential energy surface. Instead, it might turn out to be an entropic intermediate or a point along a bifurcating reaction coordinate. We sometimes draw such structures to facilitate arrow-pushing but are careful to label them as "not an intermediate" (Figure 13) to emphasize that they are not minima on potential energy surfaces. For the [Rh] carbene reactions discussed here, these "not an intermediate" structures involve carbocation character, and it is well-known that carbocation rearrangements are prone to involving concerted reactions with multiple events combined so as to avoid potential intermediates and also PTSBs.[40]

■ WHY CARE?

Why should one care about these computational results? Some specifics: (1) If a discrete zwitterionic intermediate is formed and has a sufficient lifetime, stereochemical scrambling and formation of undesired side-products could occur. (2) Neglecting explicit solvent complexation when modeling Rh_2L_4 catalyzed reactions can be dangerous. (3) Rh_2L_4 catalysts may fall off before one wants them to exert their influence on substrates. (4) Sometimes side-products result from non-statistical dynamic effects, especially for reactions with PTSBs. Hopefully, these considerations will be incorporated into design

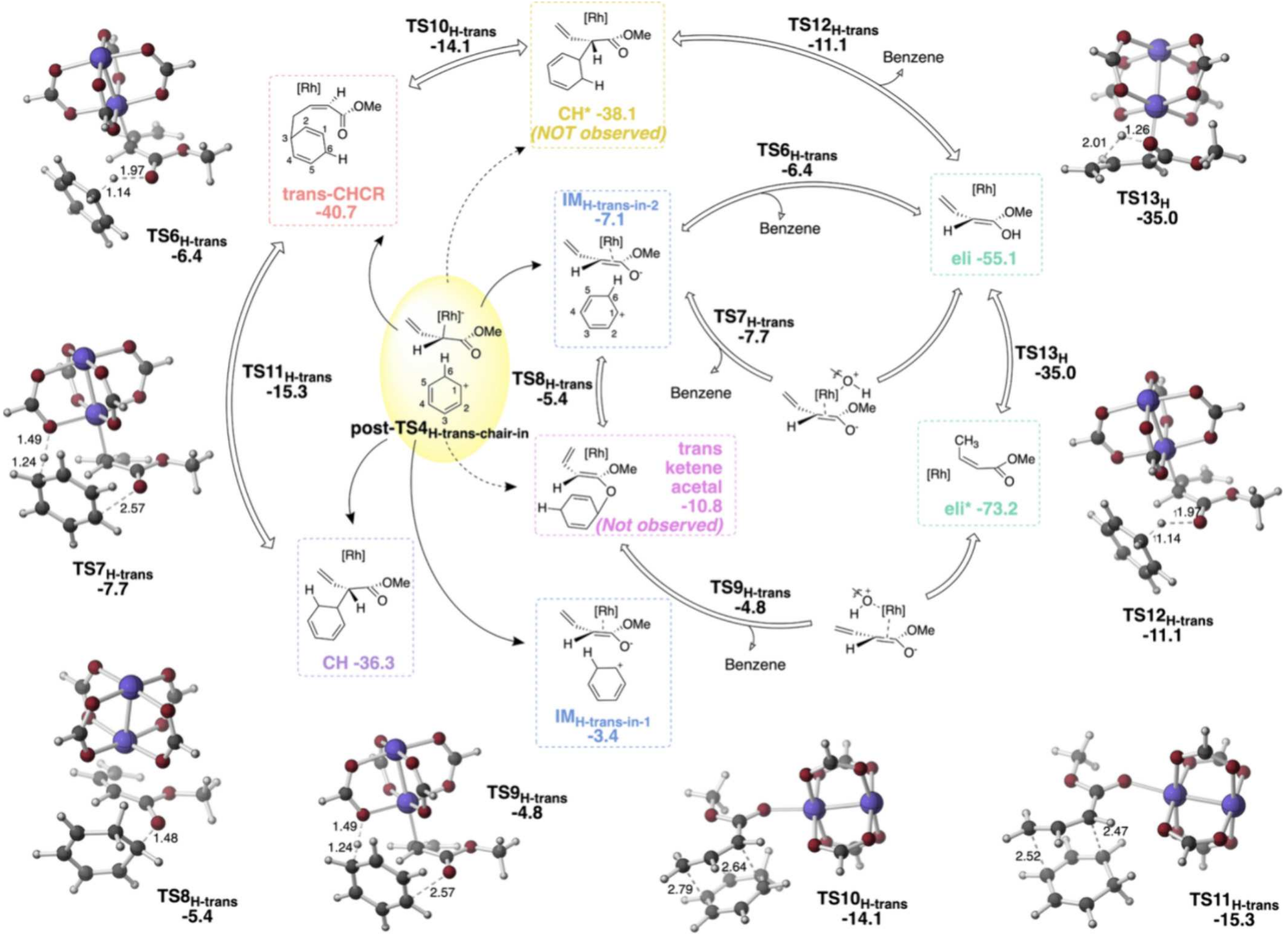


Figure 12. Example of a reaction network discovered by examining the potential energy surface and the results of AIMD calculations starting with a CHCR transition structure/state. Computed free energies relative to the best [Rh] carbene/1,3-cyclohexadiene complex are shown (kcal/mol; B3LYP-D3(0)/6-311+G(d,p)+LANL2DZ//B3LYP-D3(0)/6-31G(d)+LANL2DZ). Dotted arrows correspond to pathways that might be expected but were not observed in AIMD trajectories (B3LYP-D3(0)/6-31G(d)+LANL2DZ). Solid arrows correspond to pathways that were observed in AIMD trajectories. Wide hollow arrows correspond to pathways for which transition structures were located. Reproduced from ref 37. Copyright 2024 American Chemical Society.

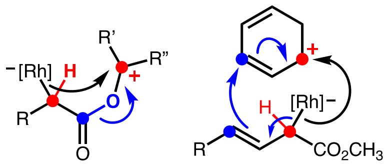


Figure 13. "Not an intermediate" structures for the reactions described here with differently colored curved arrows indicating how they can be transformed into different products.

efforts moving forward—including ligand design for asymmetric reactions and other types of Rh_2L_4 catalyzed reactions—and their generality and associated subtleties will become clearer as more computations (in particular, AIMD studies) on larger and more flexible systems are performed.

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Notes

The author declares no competing financial interest.

Biography

Dean Tantillo was born and raised in Quincy, Massachusetts, USA. He received an A.B. degree in Chemistry in 1995 from Harvard and a Ph.D. in 2000 from UCLA (with Ken Houk) and then moved to Cornell where he did postdoctoral research with Roald Hoffmann. Dean joined the faculty at UC Davis in 2003. Research in Dean's group is driven by puzzling mechanistic questions in the areas of biosynthesis, organometallic chemistry, and stereoselective synthetic reactions. These days, he is particularly interested in nonstatistical dynamic effects, entropy, and organic photochemistry (none of which are mutually exclusive).

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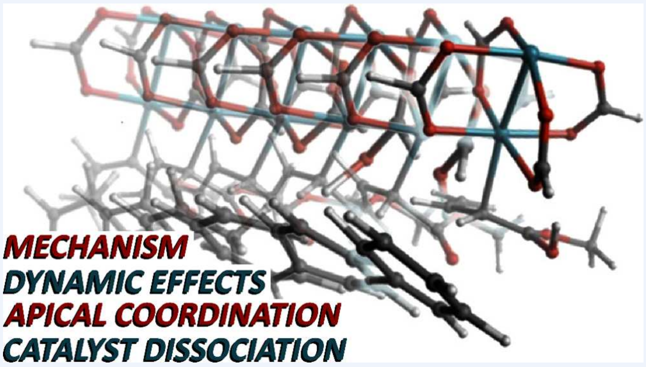

CONSPECTUS: Rh_2L_4 catalysts have risen in popularity in the world of organic synthesis, being used to accomplish a variety of reactions, including C−H insertion and cyclopropanation, and often doing so with high levels of stereocontrol. While the mechanisms and origins of selectivity for such reactions have been examined with computational quantum chemistry for decades, only recently have detailed pictures of the dynamic behavior of reacting Rh_2L_4-complexed molecules become accessible. Our computational studies on Rh_2L_4 catalyzed reactions are described here, with a focus on C−H insertion reactions of Rh_2L_4-carbenes. Several issues complicate the modeling of these reactions, each providing an opportunity for greater understanding and each revealing issues that should be incorporated into future rational design efforts. First, the fundamental mechanism of C−H insertion is discussed. While early quantum chemical studies pointed to transition structures with 3-center [C−H−C] substructures and asynchronous hydride transfer/C−C bond formation, recent examples of reactions with particularly flat potential energy surfaces and even discrete zwitterionic intermediates have been found. These reactions are associated with systems bearing π-donating groups at the site of hydride transfer, allowing for an intermediate with a carbocation substructure at that site to be selectively stabilized. Second, the possible importance of solvent coordination at the Rh atom distal to the carbene is discussed. While effects on reactivity and selectivity were found to be small, they turn out not to be negligible in some cases. Third, it is shown that, in contrast to many other transition metal promoted reactions, many Rh_2L_4 catalyzed reactions likely involve dissociation of the Rh_2L_4 catalyst before key chemical steps leading to products. When to expect dissociation is associated with specific features of substrates and the product-forming reactions in question. Often, dissociation precedes transition structures for pericyclic reactions that involve electrons that would otherwise bind to Rh_2L_4. Finally, the importance of nonstatistical dynamic effects, characterized through ab initio molecular dynamics studies, in some Rh_2L_4 catalyzed reactions is discussed. These are reactions where transition structures are shown to be followed by flat regions, very shallow minima, and/or pathways that bifurcate, all allowing for trajectories from a single transition state to form multiple different products. The likelihood of encountering such a situation is shown to be associated again with the likelihood of formation of zwitterionic structures along reaction paths, but ones for which pathways to *multiple* products are expected to be associated with very low or no barriers. The connection between these features and reduced yields of desired products are highlighted, as are the means by which some Rh_2L_4 catalysts modulate dynamic behavior to produce particular products in high yield.

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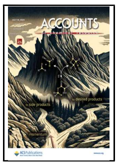

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interpretation of solvent effects, the effects of additives, and the use of ligands with additional Lewis basic groups.

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■ SETTING THE STAGE

Mechanisms of Rh_2L_4 catalyzed reactions have been subjected to scrutiny using computational chemistry for approximately three decades,[5] with the most attention being paid to C−H insertion reactions.[6] In the seminal work of Taber and co-workers, molecular mechanics calculations were shown to be capable of reproducing the sense of diastereoselectivity for several $Rh_2(OAc)_4$ catalyzed intramolecular C−H insertion reactions.[7] These computations made use of constrained distances and angles to capture the geometry of the $Rh_2(OAc)_4$ substructure optimized independently with ZINDO[8] and to constrain forming/breaking bonds to a 4-center transition structure geometry (Figure 1). The agreement between experimentally observed diastereoselectivities and the computational results provided support for the reasonability of a 4-center transition structure.

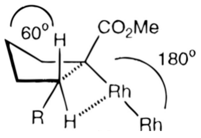


Figure 1. Taber's 4-center transition structure model. Reproduced from ref 7. Copyright 1996 American Chemical Society.

The 4-center model has not been borne out in studies using density functional theory (DFT), however. Nakamura and co-workers' early work using the B3LYP/6-31G(d)-LANL2DZ method (with some benchmarking against MP2(FC)) to model C−H insertion into simple alkanes by the catalyst model $Rh_2(HCO_2)_4$ indicated that a 3-center model (Figure 2) is more likely (in addition to mapping out the pathway for [Rh] carbene formation from a diazo compound and showing that N_2 loss can be rate-limiting).[9] This study also pointed out that the C−H insertion reaction coordinate involved asynchronous events—initial hydride transfer to the carbene carbon followed by C−C bond formation—even though the process was concerted.[10] This study was followed up by calculations on larger systems making use of the PM3(tm) semiempirical method with constraints based on DFT results on small models,[11] including some overlap with the systems studied previously by Taber. Later studies (as described below) have shown the generality of the concerted 3-center transition structure model associated with asynchronous hydride transfer and C−C bond forming events.

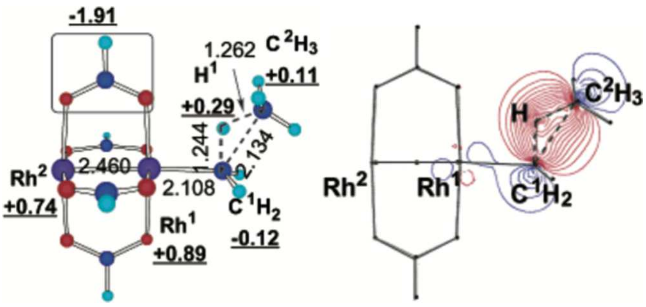


Figure 2. Left: Computed transition structure for C−H insertion into methane (selected bond lengths shown in Å and natural charges shown underlined). Right: Key orbital showing 3-center delocalization in the C−H insertion transition structure. Both images reproduced from ref 9. Copyright 2002 American Chemical Society. Similar geometries and orbitals were found for other systems examined in ref 9.

Transition structures for other Rh_2L_4 catalyzed reactions such as *β*-hydride migration, cyclopropanation, ylide formation, epoxide formation, cycloaddition, and [2,3] sigmatropic shifts also have been computed with DFT (e.g., Figure 3).[12] Many of these processes also were found to be concerted with asynchronous events. Related examples are discussed below.

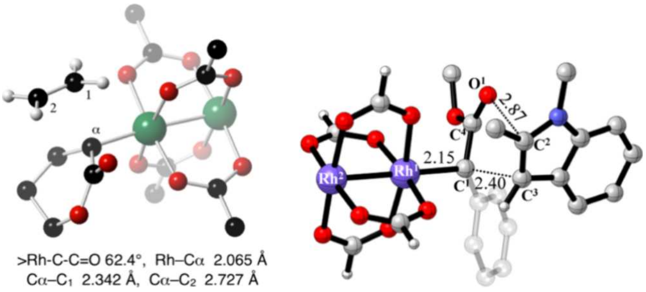


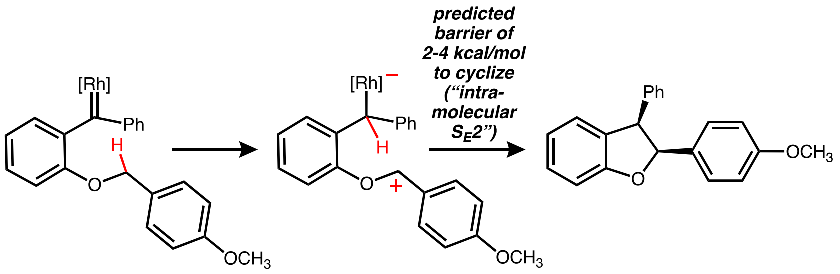
Figure 3. Representative transition structures for other Rh_2L_4 promoted reactions. Reproduced from ref 12a,e. Copyright 2011 and 2015 American Chemical Society.

In contrast, computational studies on Rh_2L_4 catalyzed reactions involving nitrenes have confirmed that they are generally electronically more complex than those involving carbenes. In particular, triplet states can be involved, allowing radical reactivity to be expressed,[13] while this type of reactivity generally is not observed for [Rh] carbenes.

■ DOING A TWO-STEP?

As described above, Rh_2L_4-promoted C−H insertion generally follows a concerted mechanism, but H transfer and C−C bond formation events can, however, occur quite asynchronously. Can the extreme of this scenario occur where these two events are actually separated by a barrier, i.e., there is a zwitterionic intermediate? Since initial hydride transfer to the carbene carbon would leave a carbocation center behind, *π*-donor substituents at this position could potentially provide enough selective stabilization for such a structure to be a minimum on the potential energy surface. This is indeed the case, although only low barriers for subsequent ring-closure have been

Scheme 1. Rh_2L_2-Promoted C−H Insertion Reaction with a Discrete Intermediate. [Rh] = $Rh_2(OAc)_4$

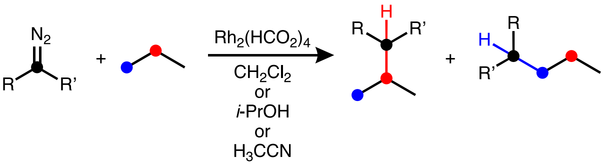


observed to date. An example is shown in Scheme 1, computed by Dmitrenko, Fox and co-workers.[14] In this system, the carbocation center in the zwitterionic intermediate bears both an oxygen with a lone pair ripe for donation and an electron-rich aryl group. Despite the presence of these capable donors, the barrier for ring closure was predicted to be only a few kcal/mol (in terms of both enthalpy and free energy), providing a significant impediment to stereochemical scrambling. Note that the second (ring-closing) step of this reaction is akin to an intramolecular S_E2 reaction in which [Rh] is displaced by an electrophilic carbon.[15] Other related intermediates have been characterized computationally and shown to be relevant to stereocontrol.[15]

HOW UNCOORDINATED?

In general, computational models of Rh_2L_4 catalysts do not include apical ligands, i.e., solvent or other molecules bound to the Rh that is not bound to the carbene carbon (or nitrene nitrogen). But is this a reasonable approach? In some experimental investigations, solvent effects have been observed that could be associated with apical bonding.[16] To address this issue at a fundamental level, we carried out a systematic study on C−H insertion into propane using $Rh_2(HCO_2)_4$ with several different explicit solvent molecules (Scheme 2) based on the mechanistic scenario depicted in Figure 4.[2] The effects of apical coordination on barriers for N_2 loss and C−H insertion were computed for [Rh] carbenes with different combinations of donor and acceptor groups, as was the regioselectivity for C−H insertion. While predicted effects of coordination were not large, they also were not always negligible. Differences in $\Delta\Delta G^{\ddagger}$ for insertion into propane's methyl and methylene groups varied with complexation by as much as ∼1 kcal/mol, with more donating apical ligands decreasing selectivity for our acceptor/acceptor carbene model but not showing a clear trend for the other carbenes examined. In any case, this work indicates that one should proceed with caution if not modeling apical ligands, especially if theory and experiment (without apical ligands modeled) fail to correspond.

Scheme 2. Model C−H Insertion Reactions Examined to Predict the Effects of Apical Coordination by Solvent Molecules[a]



[a]Various combinations of R/R′ donor (Ph) and acceptor (CO_2CH_3) groups were examined.

Rh_2L_4 promoted reactions with ligands bearing groups that can participate in apical coordination (e.g., Figure 5) also display distinctive reactivity in some cases.[17] We are now examining such cases in collaboration with the Darko group.

SHOULD I STAY OR SHOULD I GO NOW?

Generally, when one teaches organometallic chemistry,[18] a transition metal catalyst is shown to first bind a substrate, then undergo multiple steps to form a catalyst-bound product, then dissociate. Experimental and computational evidence has indicated, however, that this scenario is often not the case for Rh_2L_4 catalyzed reactions.[19] Instead, a [Rh] carbene (or nitrene) undergoes a reaction that generates a species to which the binding of [Rh] is relatively weak, allowing the catalyst to dissociate before a key step along the path to product formation. Several examples of this type of reaction are discussed below, along with some simple principles useful for predicting whether or not one should expect [Rh] to dissociate before a product formation step.

Our first encounter with this type of scenario occurred during an examination of an indole-forming reaction in collaboration with the Driver group.[20] Part of the relevant mechanism is shown in Scheme 3. After formation of a [Rh] nitrene, cyclization occurs, which is followed by the migration of one of two groups (MG^1 or MG^2). Migration with and without [Rh] was modeled and for most MG^1/MG^2 combinations the same group was predicted to migrate preferentially in both cases. However, with MG^1/MG^2 = H/CO_2CH_3 the migration of CO_2CH_3 was predicted to dominate with [Rh] bound, but migration of H was predicted to dominate with no metal present. Several reactions for which we made predictions were tested experimentally, and when an ester-bearing substrate was used (MG^1/MG^2 = H/CO_2*i*-Pr for practical reasons) only H migration was observed, suggesting that [Rh] had indeed departed before rearrangement.[21]

Later, we undertook a systematic study of Rh_2L_2 catalyzed [2,3] sigmatropic shifts (Scheme 4),[1] in part because stereochemical scrambling and crossover had been observed in some experiments suggesting again that the [Rh] may not be present during rearrangement.[19] We examined carbenes with various donor/acceptor substituents and various allyl ethers, thioethers, and selenoethers. First, we focused on experimentally studied systems. Of those, [Rh]-bound rearrangement was found to be preferred for the one oxonium ylide examined, but [Rh]-unbound rearrangements were preferred for sulfonium, and selenonium ylides. It makes sense that [Rh] binding can hinder rearrangement, since the electrons of the "C:$^-$" to which it is bound are needed for the rearrangement. Studies on additional systems also demonstrated that steric crowding in the transition

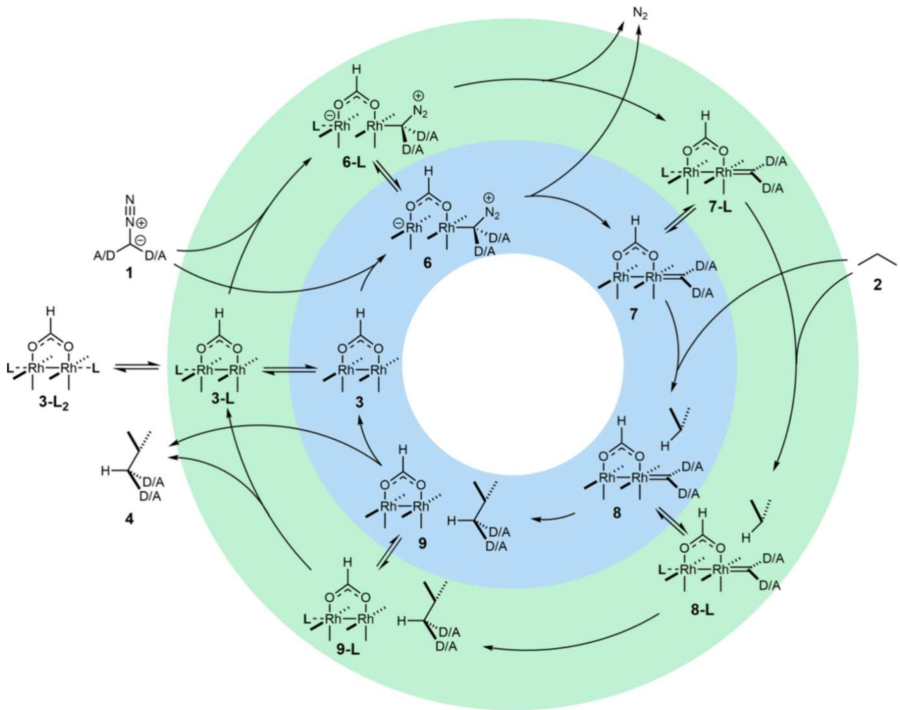


Figure 4. Mechanism postulated for the insertion of a diazo compound into propane catalyzed by $Rh_2(HCO_2)$ (only one formate is drawn explicitly). Blue inner ring: no axial ligand; green outer ring: one axial ligand bound. Reproduced from ref 2. Copyright 2021 American Chemical Society.

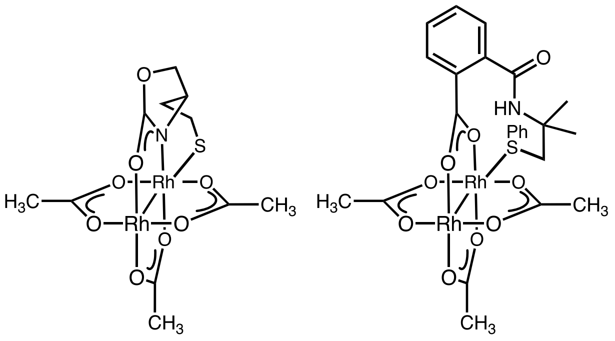
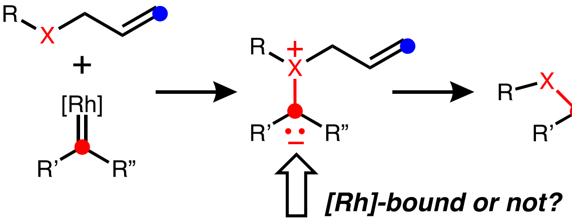


Figure 5. Catalysts studied by Darko and co-workers with ligands expected to bind to the rhodium atom distal to the carbene.[17d−g]

Scheme 4. [2,3]-Sigmatropic Shifts Examined Computationally[a]



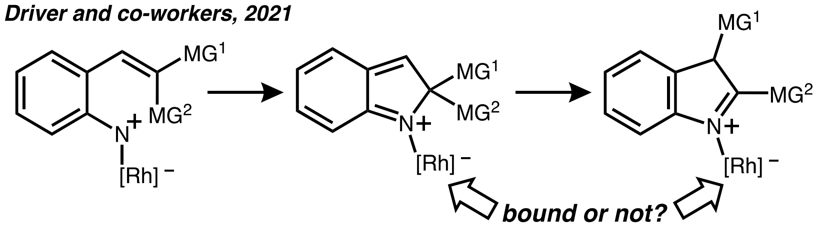
X = O, S, Se
R = Ar, CF_3
R'/R" = combinations of H, Ph, CO_2CH_3, CN

[a] $[Rh] = Rh_2(OAc)_4$.

structure plays a key role. Figure 6 shows an example of a [2,3]-shift transition structure where [Rh] detached from the "C:$^-$" during optimization; note the crowdedness.

We have observed similar behavior in a variety of other Rh_2L_2 catalyzed reactions with pericyclic product-forming steps (Scheme 5). In work with the Shaw group,[22] the results of our calculations indicated that [Rh] dissociated from the ammonium ylide shown before Stevens rearrangement occurred (concerted in this case, even though formally forbidden based on orbital symmetry, likely due to the presence of the ester);[23] in that case, we were unable to locate a [Rh]-bound transition structure. In a study with the Tambar group involving the

Scheme 3. Cyclization/[1,5]-Sigmatropic Shift Studied with the Driver Group[a]



[a] $[Rh] = Rh_2(esp)_2$ for experiments, $[Rh] = Rh_2(HCO_2)_4$ for calculations.

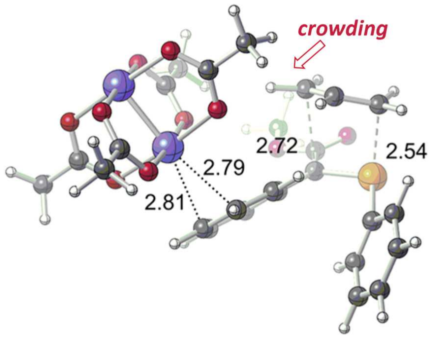
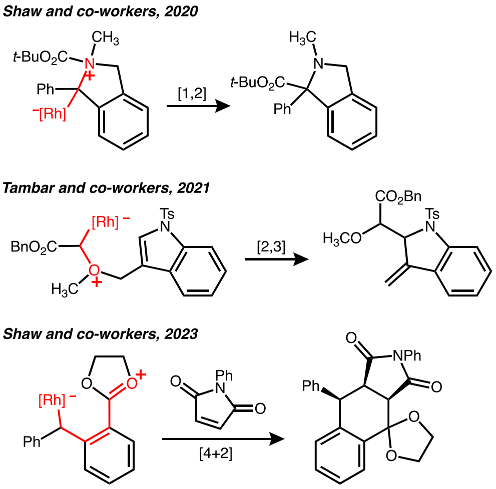


Figure 6. Computed TS for the [2,3]-sigmatropic shift of a selenonium ylide. Distances shown in Å. Adapted from ref 1. Copyright 2021 American Chemical Society.

Scheme 5. Additional Rh_2L_2 Catalyzed Reactions for Which We Predict [Rh] Dissociation before a Key Product-Forming Step



oxonium ylide shown,[24] we again predicted a preference for [Rh]-free rearrangement, and again no competing [Rh]-bound transition structure was found. Finally, in another study with the Shaw group,[25] we predicted [Rh]-free [4 + 2] cycloaddition. Note that the ylide in this case can also be formulated as an *ortho*-quinodimethide. In all of these cases, as for the other [Rh] carbene cases above (Scheme 4), the electrons used to bind [Rh] are needed for the subsequent product-forming reaction, allowing [Rh] dissociation to help the product-forming reaction proceed.[26]

■ DYNAMICAL DISTRACTIONS?

Reactions that do not conform to the doctrines of transition state theory (i.e., they exhibit nonstatistical dynamic behavior) continue to be identified at a seemingly growing pace,[27] and these include reactions of complex organic molecules with large catalysts. Rh_2L_4 catalyzed reactions comprise a class of reactions where nonstatistical dynamic effects have been shown to play important roles in controlling reactivity and selectivity. Prime among these are a variety of Rh_2L_4 catalyzed reactions that involve post-transition state bifurcations (PTSBs), i.e., for which a key transition structure is followed on the potential energy surface by a path downhill in energy that splits toward two products without involving a minimum (intermediate).[27,28] Since one transition structure (saddle point on the potential energy surface) or state (which reflects the highest state along the reaction in terms of free energy) leads to two products, the relative rates of formation of products cannot be determined by barriers for competing reactions, and classic transition state theory is not applicable. Instead, the relative amount of each of the two products is determined by a combination of the curvature of the potential energy surface (i.e., the forces acting on the reacting molecule) and the momentum the reacting molecule possesses as it passes by the transition state (called "ambimodal" when it precedes a PTSB[29]). The effects of this momentum can be characterized by using ab initio molecular dynamics (AIMD, also called direct or on-the-fly dynamics) calculations.[30] Types of Rh_2L_4 catalyzed reactions involving PTSBs that have been examined with AIMD calculations are shown in Figure 7.

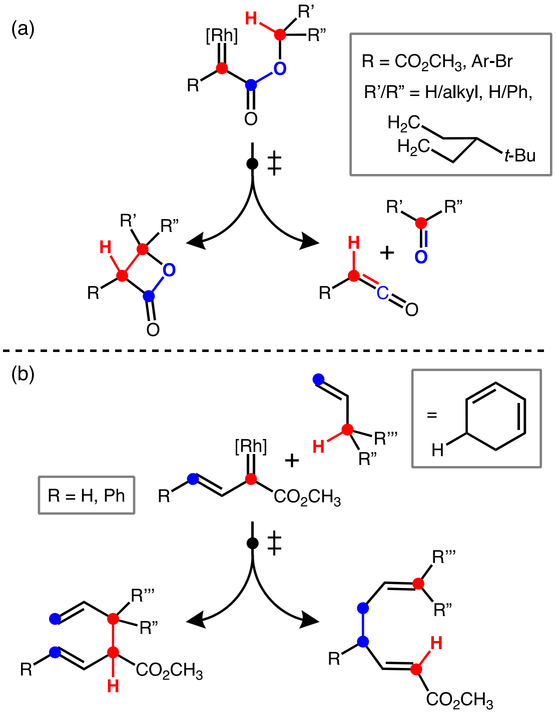


Figure 7. Types of Rh_2L_4 catalyzed reactions for which PTSBs have been proposed and nonstatistical dynamic behavior has been characterized using AIMD calculations. Definitions of [Rh] are included in the main text.

The first such example for which AIMD calculations were employed (not the first for which a PTSB was proposed, *vide infra*) is shown in Figure 7a (R = CO_2CH_3, R/R′ = $(CH_2)_2CH$*t*-Bu$(CH_2)_2$, [Rh] = $Rh_2(OAc)_4$).[3] In the context of testing computational methods for C−H insertion reactions, we discovered that this reaction, examined originally by Lee and co-workers in the context of developing a process for the synthesis of β-lactones,[31] possessed a PTSB leading to both β-lactone product and products of fragmentation: a ketone and a ketene. Our AIMD calculations (on the exact experimental substrate and catalyst) showed that both β-lactone and fragmentation products can form from a single transition state, with fragmentation dominating. At first we thought that our calculations were unreliable due to the large amount of fragmentation observed, but then a careful rereading of Lee et al.'s paper revealed that *t*-Bu-cyclohexanone was actually the major product of the reaction; this fact was in a footnote on an

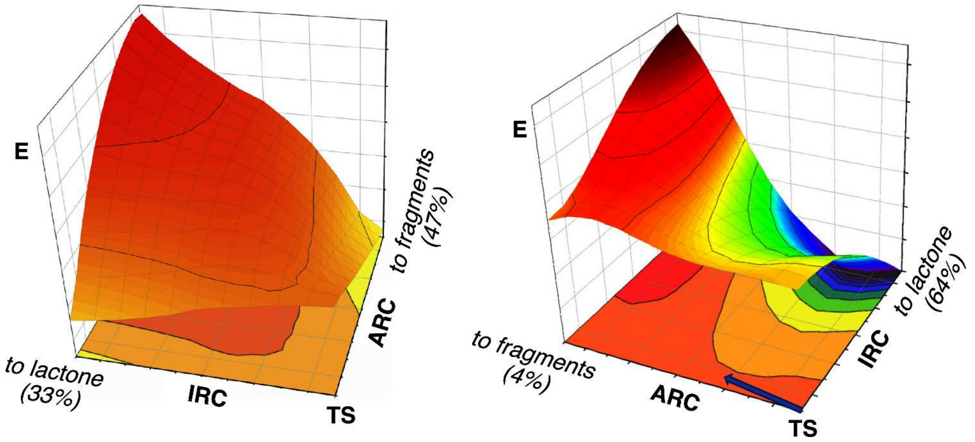


Figure 8. Two potential energy surfaces for reactions with PTSBs. The left-hand surface is for a reaction that leads to significant amounts of both β-lactone product and fragmentation products in AIMD calculations (percentages shown with product labels at plot corners), while the right-hand surface is for a reaction that leads mostly to β-lactone product. ARC = Artificial Reaction Coordinate.[4]

optimization table, since the paper was focused on β-lactone products, so we had missed it (we should have noticed). Luckily for us, this information was actually reported, validating our "retrospective prediction" (a prediction made without knowledge of pre-existing results). Of particular importance to us was the fact that our calculations had demonstrated that an unwanted side-product, the major observed product for this specific system, was the direct result of a PTSB. Therefore, if one wanted to rationally discourage formation of that side-product, it would seem that nonstatistical dynamic effects should be considered. Sometimes your side-product comes from a bifurcation...

Curious as to whether PTSBs would be found in other Rh_2L_4 catalyzed β-lactone-forming reactions, we examined additional cases for which experimental results had been reported by the Bach and Davies groups (Figure 7a; for Bach: R = 2-Br-Ph, R'/R'' = H/CH_2*i*-Pr, [Rh] = $Rh_2(OAc)_4$; for Davies: R = 2-Br,5-OCH_3−Ph, R'/R'' = H/Ph, [Rh] = Rh_2(*s*-TCPTTL)$_4$).[4] For the Bach system (modeled with the exact experimental substrate and catalyst),[32] our computations reproduced the experimentally observed diastereoselectivity (*cis* v. *trans* substituents on the β-lactone product) when the lowest energy conformations of transition structures leading to each product were compared (24:1 for *trans* experimentally, and ∼20:1 for *trans* computationally). But were these transition structures/states followed by PTSBs? Our AIMD calculations indicated that they were. For the lowest energy transition state leading to the *trans* product, we observed β-lactone formation in 33% of trajectories and fragmentation in 47%. The experimental yield for this substrate was reported to be 43%,[32] so we again suspect that significant mass was lost to post-transition state fragmentation. A potential energy surface for this reaction is shown in Figure 8 (left; constructing such a surface was difficult, and technical details can be found in ref 4 and its Supporting Information). The bottom righthand corner of this surface corresponds to the transition structure. Moving toward the bottom left-hand corner leads to β-lactone, while moving toward the back righthand corner leads to fragmentation products. There does not appear to be a large energetic preference for either, and both are formed in significant amounts in the AIMD calculations. In contrast, Figure 8 (right) shows an analogous surface for a different transition structure for which there appears to be a strong preference for β-lactone formation based on the curvature of the surface. AIMD calculations for the associated transition state do indeed predict predominantly β-lactone formation (64% compared to only 4% fragmentation). The small arrow from the transition structure in this figure indicates, roughly, the direction expected for the momentum.[33] In this case, the momentum is toward fragmentation, but that momentum is not enough to overcome the effect of the potential energy surface curvature. The transition structure associated with this surface actually leads to the disfavored *cis* β-lactone product, while that for Figure 8 (left) leads to the preferred *trans* product, so diastereoselectivity comes at the cost of PTSB-associated yield reduction in this case.

Reactions studied by the Davies group were then examined.[34] First, calculations using $Rh_2(OAc)_4$ as catalyst were carried out, but these predicted perfectly incorrect diastereoselectivity.[4] We then resorted to including the whole Rh_2(*s*-TCPTTL)$_4$ catalyst (Figure 9)[35] in our calculations (e.g., Figure 10). Doing so led to a match between experimental and predicted diastereoselectivity (>19:1 for *cis* for the experiment and a >4 kcal/mol preference from computations). In addition, the predicted sense of enantioinduction (*s*-TCPTTL is chiral) for experiment and computations also matched. However, AIMD calculations for this system predicted complete selectivity for fragmentation over β-lactone formation! How could this be? It turns out that in this system, conversion of the fragmentation products to the β-lactone product with the correct configuration can occur within the catalyst binding pocket via a ketone-ketene [2 + 2]

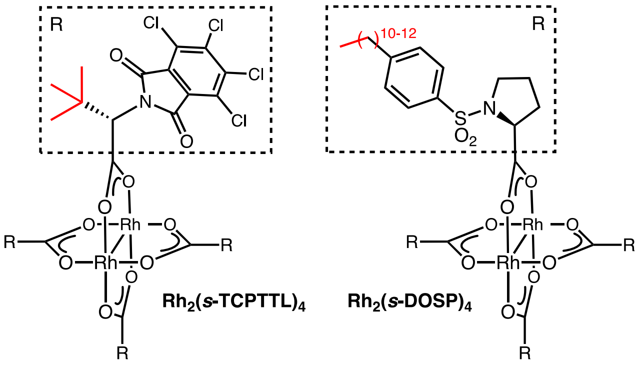


Figure 9. Representative Rh_2L_4 catalysts with large ligands.

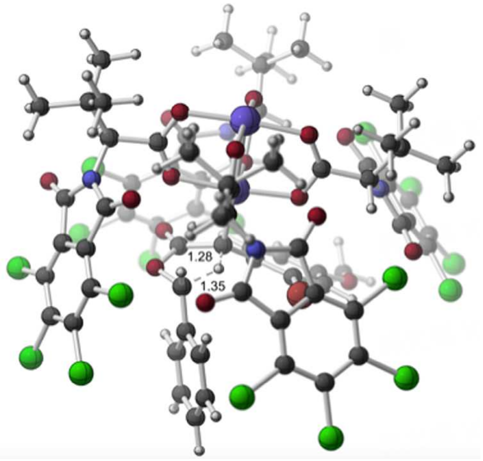


Figure 10. Preferred C−H insertion transition structure with Rh_2(*s*-TCPTTL)$_4$ catalyst.[4] For an X-ray crystal structure of a chiral [Rh] carbene related to Rh_2(*s*-TCPTTL)$_4$, see ref 35.

cycloaddition; the *β*-lactone product was predicted to be thermodynamically preferred and the barrier for cycloaddition was predicted to be low enough for this system (but not for the others discussed above). So we are left with a model of reactivity/selectivity for the Rh_2(*s*-TCPTTL)$_4$ catalyzed system that involves (Figure 11): (1) stereo- (both diastereo- and enantio-) selectivity by way of competing transition states followed by (2) an apparent PTSB for the preferred transition state that is so unsymmetrical that it is essentially not a bifurcation, but rather a direct path to fragmentation products, and (3) recombination of the undesired products in the catalyst binding site. While this course of events was not part of the original reaction design, computations of the type described here could allow such complex scenarios to be faced head-on when developing reactions.

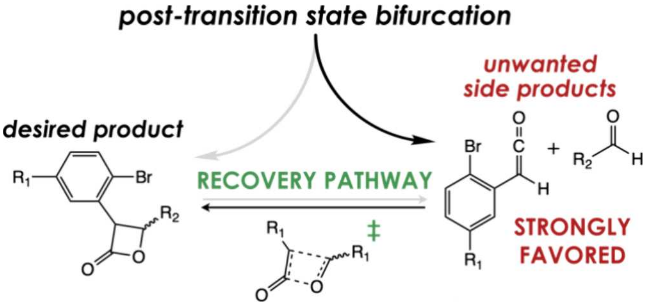


Figure 11. Model for reactivity/selectivity derived from the results of AIMD calculations.

Recently, another family of Rh_2L_4 catalyzed reactions with PTSBs was subjected to AIMD calculations. These include the first Rh_2L_4 catalyzed reaction for which a PTSB was proposed: Davies and co-workers′ combined C−H insertion/Cope Rearrangement (CHCR) reaction (Figure 7b).[36] On the basis of calculations on the reaction coordinate for this reaction, Davies, Autschbach and-co-workers invoked the presence of a PTSB.[36b] Many years later, we set out to examine the dynamics at play in this reaction.[37] We found that the networks of transformations originating from CHCR transition states were quite complex, with that complexity varying with the substrate. The most complex network explored is shown in Figure 12. Other systems explored have slightly simpler networks but share many of the features of the one shown. Among the key features are (1) Products of the PTSB proposed by Davies, Autschbach and-co-workers are indeed found to arise in MD trajectories initiated at the CHCR transition state (Figure 12, left, products **CH** and **trans-CHCR**). (2) A very shallow ion pair intermediate (**IM$_{\text{H-trans-in-2}}$**) was found to follow the CHCR transition structure. For some systems, this type of structure is not a minimum on the potential energy surface, but appears instead to be an entropic intermediate (a minimum in free energy because of its favorable entropy).[38] (3) The time it takes for trajectories to leave the vicinity of this intermediate varies from system to system and is lengthened by "dynamic mismatching" − momentum possessed by trajectories leaving the region of the CHCR transition state that diverts them away from exit channels from the intermediate region. A similar analysis and conclusions appeared in an excellent, closely related studied carried out simultaneously by Schaefer and Ess, who also proposed an ion pair entropic intermediate and described the "vibrational synchronization" responsible for its selective formation of CH/CR products.[39] (4) This intermediate allows for the facile formation of side products resulting from cyclohexadienyl deprotonation to form benzene−a possible source of low yields in some systems. While it is difficult to imagine how such a complex system could be manipulated through rational catalyst design, characterization of its dynamic behavior at least opens the door to doing so, e.g., one can imagine constructing catalyst binding sites that hinder certain vibrations. For example, for Davies and co-workers′ CHCR reactions promoted by Rh_2(s-DOSP)$_4$ (Figure 9), which favor CHCR products over others and do so with high stereoselectivity,[36] we suspect that the shape of the catalyst binding site preferentially accommodates a [Rh] carbene conformation that has dynamical tendencies that favor formation of the desired products over formation of the putative competing intermediate.[37]

What do these systems have in common that might point to the presence of a PTSB or entropic intermediate? For all of them, one could write an arrow-pushing mechanism with an intermediate for which barriers for conversion to multiple products would be expected to be very low. In the case where those barriers are zero in terms of potential energy, then the "intermediate" would not be a minimum on the potential energy surface. Instead, it might turn out to be an entropic intermediate or a point along a bifurcating reaction coordinate. We sometimes draw such structures to facilitate arrow-pushing but are careful to label them as "not an intermediate" (Figure 13) to emphasize that they are not minima on potential energy surfaces. For the [Rh] carbene reactions discussed here, these "not an intermediate" structures involve carbocation character, and it is well-known that carbocation rearrangements are prone to involving concerted reactions with multiple events combined so as to avoid potential intermediates and also PTSBs.[40]

■ WHY CARE?

Why should one care about these computational results? Some specifics: (1) If a discrete zwitterionic intermediate is formed and has a sufficient lifetime, stereochemical scrambling and formation of undesired side-products could occur. (2) Neglecting explicit solvent complexation when modeling Rh_2L_4 catalyzed reactions can be dangerous. (3) Rh_2L_4 catalysts may fall off before one wants them to exert their influence on substrates. (4) Sometimes side-products result from non-statistical dynamic effects, especially for reactions with PTSBs. Hopefully, these considerations will be incorporated into design

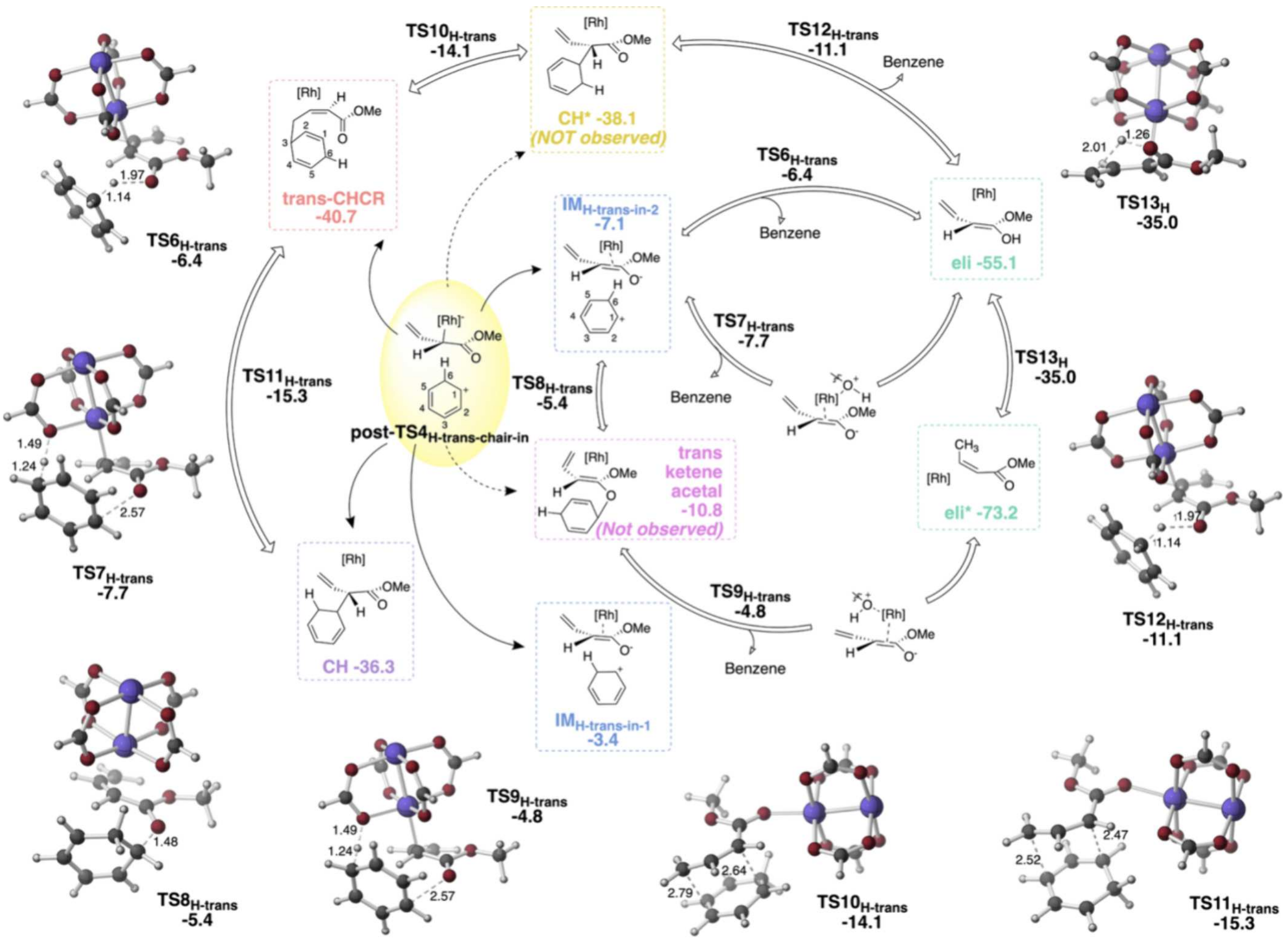


Figure 12. Example of a reaction network discovered by examining the potential energy surface and the results of AIMD calculations starting with a CHCR transition structure/state. Computed free energies relative to the best [Rh] carbene/1,3-cyclohexadiene complex are shown (kcal/mol; B3LYP-D3(0)/6-311+G(d,p)+LANL2DZ//B3LYP-D3(0)/6-31G(d)+LANL2DZ). Dotted arrows correspond to pathways that might be expected but were not observed in AIMD trajectories (B3LYP-D3(0)/6-31G(d)+LANL2DZ). Solid arrows correspond to pathways that were observed in AIMD trajectories. Wide hollow arrows correspond to pathways for which transition structures were located. Reproduced from ref 37. Copyright 2024 American Chemical Society.

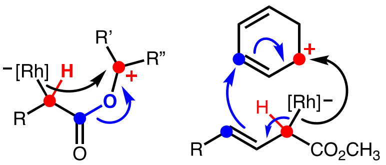


Figure 13. "Not an intermediate" structures for the reactions described here with differently colored curved arrows indicating how they can be transformed into different products.

efforts moving forward—including ligand design for asymmetric reactions and other types of Rh_2L_4 catalyzed reactions—and their generality and associated subtleties will become clearer as more computations (in particular, AIMD studies) on larger and more flexible systems are performed.

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Notes

The author declares no competing financial interest.

Biography

Dean Tantillo was born and raised in Quincy, Massachusetts, USA. He received an A.B. degree in Chemistry in 1995 from Harvard and a Ph.D. in 2000 from UCLA (with Ken Houk) and then moved to Cornell where he did postdoctoral research with Roald Hoffmann. Dean joined the faculty at UC Davis in 2003. Research in Dean's group is driven by puzzling mechanistic questions in the areas of biosynthesis, organometallic chemistry, and stereoselective synthetic reactions. These days, he is particularly interested in nonstatistical dynamic effects, entropy, and organic photochemistry (none of which are mutually exclusive).

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Addition/Correction

Correction to “Quantum Chemical Interrogation of Reactions Promoted by Dirhodium Tetracarboxylate Catalysts—Mechanism, Selectivity, and Nonstatistical Dynamic Effects”

Dean J. Tantillo*

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The following text (in the “Setting the Stage” section) was modified to better represent the work described:

In the seminal work of Taber and co-workers, extended molecular mechanics calculations were shown to be capable of reproducing the sense of diastereoselectivity for several $Rh_2(OAc)_4$ catalyzed intramolecular C−H insertion reactions.[7] These computations made use of constrained distances and angles (to represent a weak bond between the proximal Rh and the target C−H) to capture the geometry at the point of commitment to insertion (Figure 1), with the geometry of the $Rh_2(OAc)_4$ substructure optimized independently with ZINDO.[8] The agreement between experimentally observed diastereoselectivities and the computational results provided support for the reasonability of those constraints.

Later work by Nakamura using density functional theory (DFT) confirmed the importance of the Rh−C−C−H dihedral angle (Figure 2).

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