# Metal-Catalyzed Nitrogen-Atom Transfer Methods for the Oxidation of Aliphatic C−H Bonds
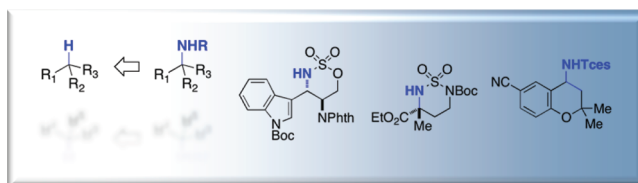
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## CONSPECTUS

For more than a century, chemists have endeavored to discover and develop reaction processes that enable the selective oxidation of hydrocarbons. In the 1970s, Abramovitch and Yamada described the synthesis and electrophilic reactivity of sulfonyliminoiodinanes (RSO₂N=IPh), demonstrating the utility of this new class of reagents to function as nitrene equivalents. Subsequent investigations by Breslow, Mansuy, and Müller would show such oxidants to be competent for alkene and saturated hydrocarbon functionalization when combined with transition metal salts or metal complexes, namely those of Mn, Fe, and Rh. Here, we trace our own studies to develop N-atom transfer technologies for C−H and $\pi$-bond oxidation. This Account discusses advances in both intra- and intermolecular amination processes mediated by dirhodium and diruthenium complexes, as well as the mechanistic foundations of catalyst reactivity and arrest. Explicit reference is given to questions that remain unanswered and to problem areas that are rich for discovery.

A fundamental advance in amination technology has been the recognition that iminoiodinane oxidants can be generated in situ in the presence of a metal catalyst that elicits subsequent N-atom transfer. Under these conditions, both dirhodium and diruthenium lantern complexes function as competent catalysts for C−H bond oxidation with a range of nitrogen sources (e.g., carbamates, sulfamates, sulfamides, etc.), many of which will not form isolable iminoiodinane equivalents. Practical synthetic methods and applications thereof have evolved in parallel with inquiries into the operative reaction mechanism(s). For the intramolecular dirhodium-catalyzed process, the body of experimental and computational data is consistent with a concerted asynchronous C−H insertion pathway, analogous to the consensus mechanism for Rh-carbene transfer. Other studies reveal that the bridging tetracarboxylate ligand groups, which shroud the dirhodium core, are labile to exchange under standard reaction conditions. This information has led to the generation of chelating dicarboxylate dinuclear rhodium complexes, exemplified by Rh₂(esp)₂. The performance of this catalyst system is unmatched by other dirhodium complexes in both intra- and intermolecular C−H amination reactions.

Tetra-bridged, mixed-valent diruthenium complexes function as effective promoters of sulfamate ester oxidative cyclization. These catalysts can be crafted with ligand sets other than carboxylates and are more resistant to oxidation than their dirhodium counterparts. A range of experimental and computational mechanistic data amassed with the tetra-2-oxypyridinate diruthenium chloride complex, [Ru₂(hp)₄Cl], has established the insertion event as a stepwise pathway involving a discrete radical intermediate. These data contrast dirhodium-catalyzed C−H amination and offer a cogent model for understanding the divergent chemoselectivity trends observed between the two catalyst types. This work constitutes an important step toward the ultimate goal of achieving predictable, reagent-level control over product selectivity.

## Introduction

Significant advances in reaction technology over the past two decades have rendered the C−H bond a functional synthon for polar amine and alcohol groups.[1] In many cases, these methods operate at a level of efficiency suitable for application in complex molecule synthesis. The continued development of C−H oxidation reactions necessitates a deeper understanding of the elements that
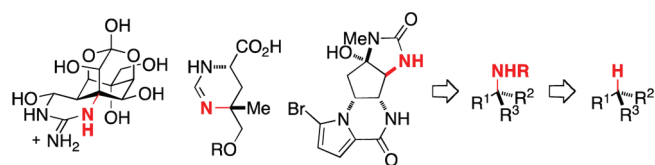
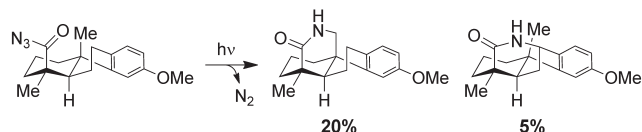**FIGURE 1.** Selective C—H oxidation as a general method for C—N bond formation.



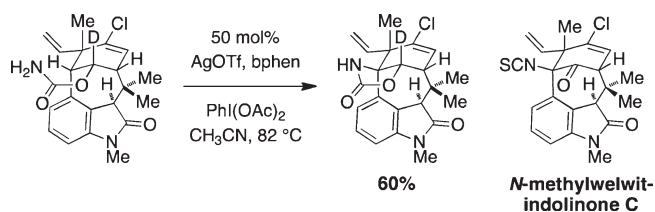**FIGURE 2.** C—H amination through photolytic azide decomposition.



**FIGURE 3.** Intramolecular C—H amination en route to (−)-*N*-methyl-welwitindolinone C isothiocyanate.[16]



**FIGURE 4.** Oxidative cyclization of carbamate and sulfamate esters.

influence chemoselectivity in substrates possessing multiple, differentially substituted C—H centers. Evaluation of catalyst stability and the off-pathway reactions that lead to catalyst arrest is also warranted. Ultimately, such knowledge should give way to the invention of high performance catalyst systems that offer superior reagent-level control over product selectivity. These research efforts are stimulated by the manifold challenges associated with the development of catalytic redox processes that enable selective functionalization of inert chemical bonds and the potential of such methods to transform strategic approaches to chemical synthesis.

For some time, our lab has been invested in the development of heteroatom-transfer methods for C—H bond oxidation, with an emphasis on technologies for the facile amination and hydroxylation of hydrocarbons (Figure 1).[2,3] In this Account, we discuss our investigations of both intra- and intermolecular catalytic C—H and π-bond amination, focusing on our efforts to develop chemoselective and diastereoselective insertion reactions and to understand operative mechanisms for N-atom transfer and catalyst inhibition. An exhaustive overview of the historical traces of this technology and the salient contributions from many others who work in this field has been presented elsewhere and will be largely omitted from this text.[1,4]

## C—H Amination in Synthesis

The potential for C—H amination in synthesis had been recognized by the 1960s in the work of Edwards, Meyer, and Masamune (Figure 2).[5] These early investigations highlight the unique capabilities of such a method as well as the challenges associated with achieving efficient, site-selective C—H bond functionalization using hyper-reactive N-based oxidants. To this latter point, the recognition that sulfonamide-derived aryliodinanes (ArSO$_2$N=IPh) could function as nitrene
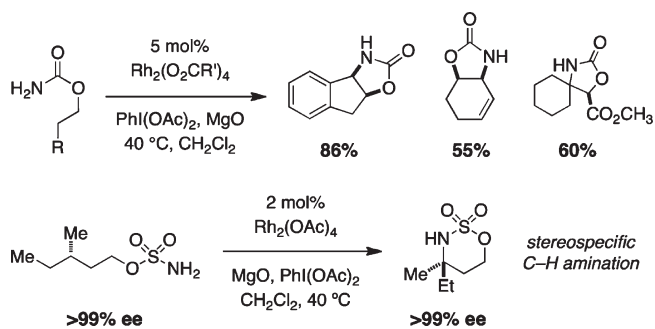
precursors is among the most important advances in the development of N-atom transfer technologies.[6,7] Such oxidants, when combined with metal catalysts, will react with saturated and unsaturated hydrocarbons to give sulfonamide products. A singular example by Breslow and more extensive studies by Müller on the reactivity of ArSO$_2$N=IPh established dirhodium tetracarboxylate complexes as highly effective catalysts for promoting selective C—H bond functionalization.[7a,8]

Both Che's group and ours recognized the limitations of iminoiodinane preparation (i.e., scope, stability) and found that the isolation of these species could be superseded by simply mixing an appropriate amine derivative with PhI(OAc)$_2$.[9−11] This advance has led to the development of a number of amination methods using nitrogen sources for which there is no known iodoimine equivalent. Amination technologies have also found a place in total synthesis, examples of which include the preparation of (−)-tetrodotoxin,[12] manzacidins A and C,[13] (−)-agelastatin A,[14] and amino-sugars,[15] among others. Garg and co-workers have recently featured an intramolecular C—H amination reaction to install a critical bridgehead amino moiety in an elegant synthesis of (−)-*N*-methylwelwitindolinone C isothiocyanate (Figure 3).[16] These works underscore the power of selective C—H oxidation reactions for streamlining total synthesis.

## Initial Reaction Development

In our earliest efforts to develop a versatile rhodium-catalyzed C—H amination process, we identified both primary
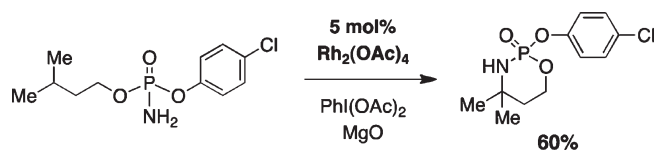
**FIGURE 5.** Oxazaphosphinane synthesis through rhodium-catalyzed amination.



| | | |
|---|---|---|
| S–N: 1.58 Å | 1.61 Å | 1.61 Å |
| S–O: 1.58 Å | 1.60 Å | 1.57 Å |
| ∠N-S-O: 103° | 104° | 95° |

**FIGURE 6.** Metrical parameters for alkoxysulfonamide derivatives.

carbamate and sulfamate ester derivatives as viable substrates (Figure 4).[2] The combination of either carbamate or sulfamate with PhI(OAc)$_2$ and a commercial dirhodium catalyst, Rh$_2$(OAc)$_4$ or Rh$_2$(oct)$_4$ (typically 2−5 mol %), results in oxazolidin-2-one or [1,2,3]-oxathiazinane-2,2-dioxide formation, respectively. In certain instances, reaction performance is enhanced using the Ikegami/Hashimoto complex Rh$_2$(O$_2$CCPh$_3$)$_4$, which is easily prepared from Rh$_2$(OAc)$_4$.[10,17] Moderate to high catalyst turnover numbers are achieved with the inclusion of MgO, which serves as a basic additive to scavenge the carboxylic acid byproduct generated from PhI-(OAc)$_2$. Product yields are usually in excess of 70% for substrates possessing either a tertiary or benzylic C−H center. Reactions with chiral sulfamate esters often give high levels of diastereoinduction (≥10:1); substrate-based stereochemical control can be rationalized by invoking an energy-minimized chairlike transition structure in the bond-forming event.[18,19] Levels of diastereocontrol in reactions with acyclic carbamate esters are considerably more modest.[10,20] Heterocyclic products furnished through these oxidative cyclization processes function as useful surrogates for 1,2-amino alcohols and 1,3-difunctionalized amine derivatives.[21]

Dirhodium-catalyzed amination can be performed on carbamate and sulfamate substrates possessing a number of common functional groups (alkynes, acetals, silyl ethers, esters, 2° and 3° amides). Alternative N-derivatives, including ureas, guanidines, sulfonamides, hydroxylamine sulfamates, sulfamides, and phosphoramidates, will also engage in intramolecular oxidation reactions (Figure 5).[2,20,22,23] Among these nitrogen sources, only a small subset of sulfonyliminoiodinanes have been prepared and characterized; all other functional equivalents are generated in situ and are postulated as transient intermediates in the catalytic cycle.

## Five- versus Six-Membered Ring Formation

The geometrical parameters of the tethered nitrogen-bearing functional group appear to dictate the ring size of the corresponding heterocycle. With carbamates as starting materials, five-membered oxazolidinones form preferentially over the six-membered homologues. Reactions with
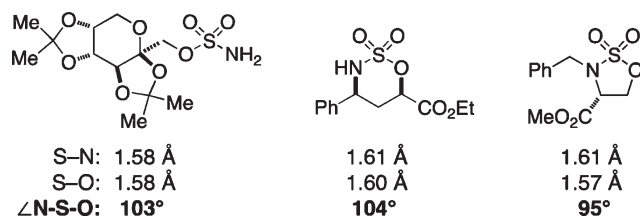
sulfamates and phosphoramidates are predisposed toward the generation of six-membered ring oxathiazinanes and oxazaphosphinanes, respectively, and are complementary to carbamate oxidation in this regard. For sulfamate cyclization, the strong bias for oxathiazinane formation can be rationalized by comparing metrical parameters (in particular, the N−S−O bond angle) between the starting sulfamate and product heterocycle (Figure 6).[20] This preference for oxathiazinane production can be overridden by designing substrates that preclude six-membered ring formation, in which case five- or seven-membered ring products are furnished. Che et al. have demonstrated that a Ru(II)-porphyrin catalyst will engage phenethyl alcohol-derived sulfamates to furnish five-membered heterocycles in modest yields (31−61%).[24] In our hands, dirhodium tetracarboxylate catalysts have typically underperformed with these same substrates.

## Mechanistic Investigations

Intramolecular C−H insertion technologies have evolved in tandem with inquiries into operative reaction mechanisms. These studies have focused primarily on sulfamate ester oxidation, as this process does not require MgO to achieve reasonable catalyst turnover numbers.[25] As such, homogeneous reaction mixtures can be analyzed by spectroscopic methods. Our collective studies provide insight into the interaction between sulfamate and hypervalent iodine oxidant, the influence of catalyst architecture on product selectivity, the transition structure at the C−N bond forming event, and catalyst decomposition pathways. Relevant mechanisms using other nitrogen sources (e.g., carbamates, ureas, sulfonamides, sulfamides) are drawn by analogy in the absence, to date, of any direct experimental data. Che, Phillips, and co-workers have disclosed a theoretical investigation of carbamate-based C−H amination, the findings from which accord with experimental mechanistic data obtained for sulfamate oxidation.[26]

The amination reaction purportedly initiates with the formation of iminoiodinane ROSO$_2$N=IPh (Figure 7).[25] NMR studies in which sulfamate is combined with either

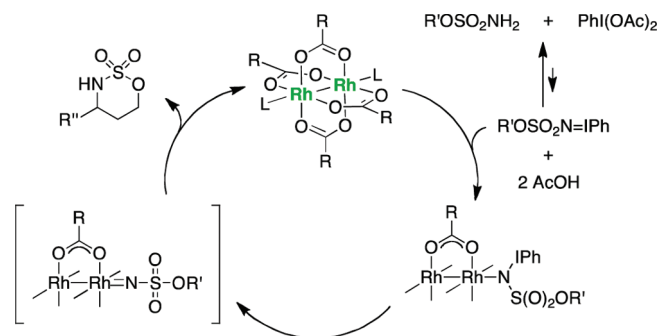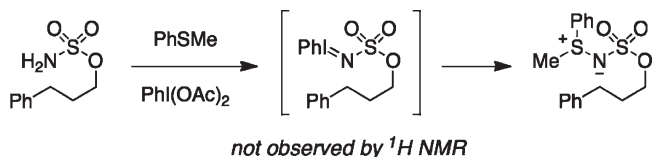**FIGURE 7.** Proposed mechanism for dirhodium-catalyzed C—H amination.



*not observed by $^1$H NMR*

**FIGURE 8.** Sulfilimine formation supports intermediacy of iminoiodinane oxidant.

PhI(OAc)$_2$ or PhI(O$_2$C$^t$Bu)$_2$ give no evidence for the generation of this intermediate, except when Cl$_3$CCH$_2$OSO$_2$NH$_2$ is used as the nitrogen source. Compelling indirect evidence for the formation of ROSO$_2$N=IPh follows from reactions with a PhSMe additive, which is oxidized by the transient iminoiodinane to give the corresponding sulfilimine (Figure 8). In the C—H amination pathway, coordination of the iminoiodinane to the dirhodium catalyst facilitates the extrusion of PhI and generates the active nitrenoid.[20,25,27] C—H bond oxidation proceeds through a direct insertion event to afford the heterocyclic product and to regenerate the catalyst. Kinetic data from NMR experiments show no variance in product formation rates within the first 100 s of oxidant addition across 0.5–5.0 mol % catalyst loadings, implying that the initial reaction rate is limited by the production of ROSO$_2$N=IPh. Our efforts to identify the rate-determining step in the proposed reaction pathway have not reached a definitive conclusion. Given the rapid rate of product formation, low-temperature kinetic data is needed to obtain a higher resolution understanding of the earliest mechanistic time points. Initial rate investigations with sulfonylated N-hydroxycarbamate derivatives, which do not require added oxidant, could provide greater insight into the nitrenoid-forming step in this process.[27b]

A substantial body of mechanistic data on the rhodium-catalyzed amination process shapes our understanding of the product-determining C—H insertion event. For studies with Rh$_2$(OAc)$_4$, an intramolecular cyclopropane clock having an estimated fragmentation rate constant of $10^{11}$ s$^{-1}$ fails to provide any indication of ring-opened products.[25]
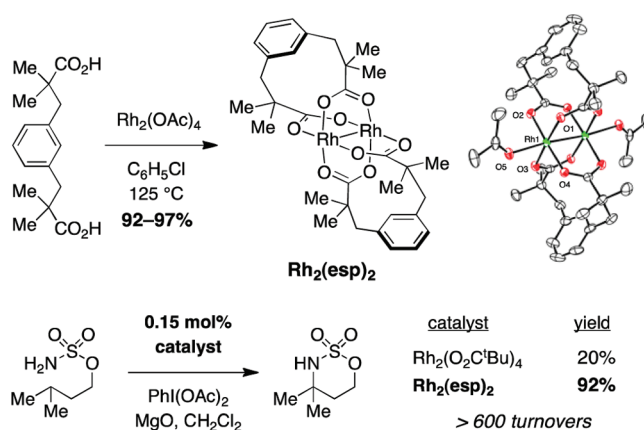


**FIGURE 9.** Efficient preparation and high performance of Rh$_2$(esp)$_2$.

Evidence for a concerted asynchronous C—H oxidation transition state is supported by a measured kinetic isotope value of 2.6 and a Hammett $\rho$ value of $-0.55$.[25,28] Additionally, stereochemical retention in the amination of optically active tertiary C—H bonds has been noted for both carbamate and sulfamate esters.[10,13] While these collective findings appear consistent with a singlet-type nitrene C—H insertion, recent studies on the *inter*molecular C—H amination reaction suggest that a stepwise C—H abstraction/radical rebound pathway may be operative.[29]

For some time, we have endeavored to understand the fate of the dirhodium catalyst in reactions that underperform. Kinetic experiments show a clear difference in rate data following the first 100 s of the reaction, evidencing a change in catalyst order. These observations indicate a possible change in reaction mechanism and/or in situ modification of catalyst structure. We have found that simple dirhodium tetracarboxylate complexes (i.e., Rh$_2$(OAc)$_4$, Rh$_2$-(O$_2$C$^t$Bu)$_4$) undergo facile ligand exchange reactions: within 60 s of diacetoxyiodobenzene addition, the isotopically labeled complex Rh$_2$(O$_2$$^{13}$CMe)$_4$ liberates Me$^{13}$CO$_2$H. Coordination of PhI(OAc)$_2$ to one of the two axial sites on the dirhodium catalyst is believed to initiate this ligand exchange process. Although ligand metathesis between PhI(OAc)$_2$ and Rh$_2$(O$_2$$^{13}$CMe)$_4$ should be degenerate, we hypothesize that the exchange process renders the dirhodium(II) centers susceptible to oxidative degradation.

The evident lability of Rh$_2$(OAc)$_4$ and related tetracarboxylate complexes under the reaction conditions has encouraged the design of alternative, chelating dicarboxylate-based architectures.[30] The complex Rh$_2$(esp)$_2$, born from these studies and inspired by work of Taber and Davies, has demonstrated exemplary performance in a wide variety of amination reactions (Figure 9).[31] Critical design elements include both a
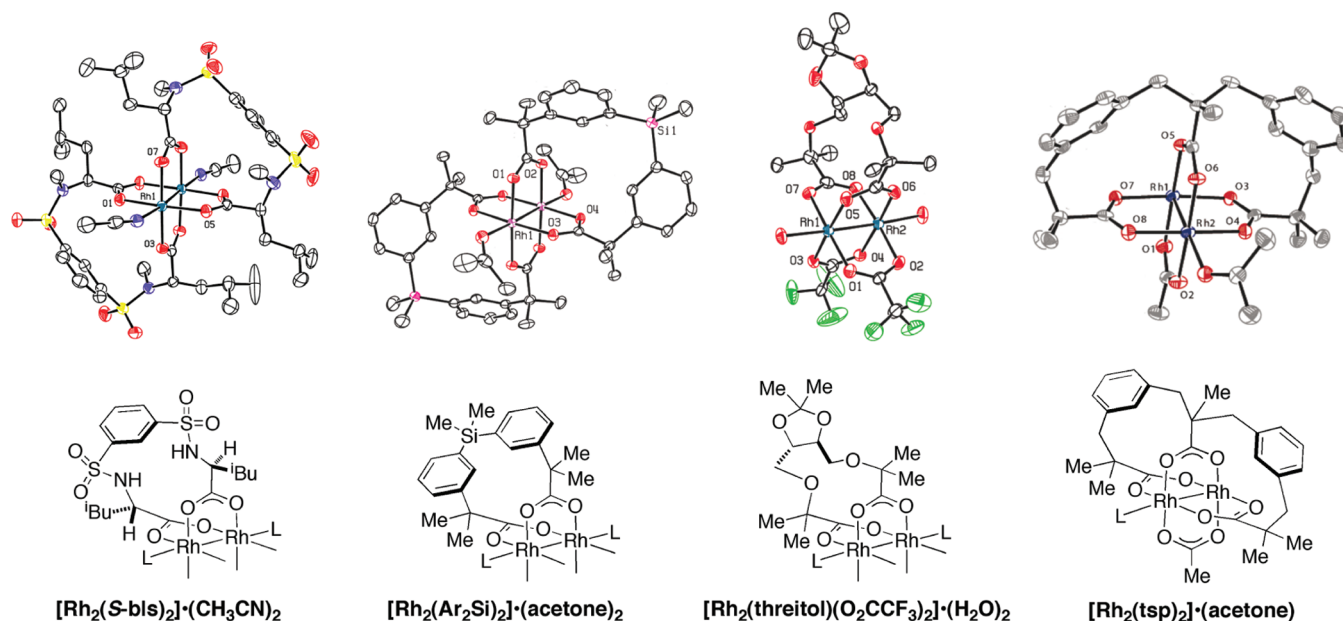
**FIGURE 10.** Novel dirhodium strapped carboxylate catalysts.

strapped four-point binding motif and *gem*-dimethylated α-carbon centers, which confer a more conformationally rigid catalyst structure. In the presence of PhI(OAc)$_2$, no ligand exchange takes place with Rh$_2$(esp)$_2$ over a period of hours to days.[32] This catalyst offers unmatched performance relative to the more common tetradic carboxylate systems. In select examples, intramolecular sulfamate ester insertion reactions have been effected in high yield with catalyst loadings as low as 0.15 mol % (Figure 9).[30]

Rh$_2$(esp)$_2$ is only one of a number of strapped dicarboxylate catalyst designs that we have explored, several of which are pictured in Figure 10. While preparation of these complexes is straightforward, no other chelated dicarboxylate system has surpassed the performance and scope of Rh$_2$(esp)$_2$ for mediating C–H amination reactions.[33] Crystallographic analysis of these structures gives insight into the underlying reasons for their modest performance and poor stability under the reaction conditions. In the preferred arrangement, four bridging carboxylate groups coordinate the dirhodium core at right angle connections.[34] For most strapped complexes, the ligand design does not precisely conform to this geometry, forcing a degree of twisting and torsional strain that presumably results in greater lability toward exchange. The esp ligand appears to have an optimal geometry and chelate size for spanning the two rhodium centers. To this point, it is interesting to note that one of the most effective strapped dicarboxylate catalysts for Rh-carbene reactions, Rh$_2$(bi-TBSP)$_2$, is particularly poor at promoting amination reactions.[31b]

In addition to demonstrating improved stability and catalyst turnover numbers, Rh$_2$(esp)$_2$ has proven effective in facilitating nitrogen-transfer reactions from a broad range of nitrogen sources, including ureas, guanidines, sulfamides, and hydroxylamine-derived sulfamates.[19,22,23] For many of these substrate types, other dirhodium complexes either fail to catalyze the reaction or severely underperform. To our knowledge, oxidative cyclization reactions with urea and guanidine substrates have not been demonstrated with other, non-dirhodium metal catalysts.

Despite the evident advantages afforded by Rh$_2$(esp)$_2$, several of these oxidation methods require additional development. With a few notable exceptions, the formation of five-membered ring products using carbamate, urea, and guanidine substrates is generally limited to insertion at tertiary and benzylic C–H centers.[35] In addition, secondary alcohol-derived carbamates typically afford ketone products when subjected to the amination conditions.[16,20] Some improvement in the overall performance of the carbamate oxidation, however, has been witnessed with the use of a silver(I) catalyst, findings that should encourage future efforts in reaction development.[16,36]

## Chemoselectivity in Intramolecular Reactions

Our desire to perform oxidation reactions on substrates bearing multiple C–H bonds has motivated studies to assess the influence of substrate and catalyst structure on chemoselectivity. In intramolecular reactions of sulfamate substrates with Rh$_2$(OAc)$_4$, relative rate data for C–H insertion
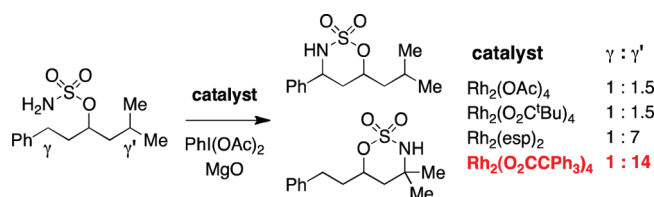
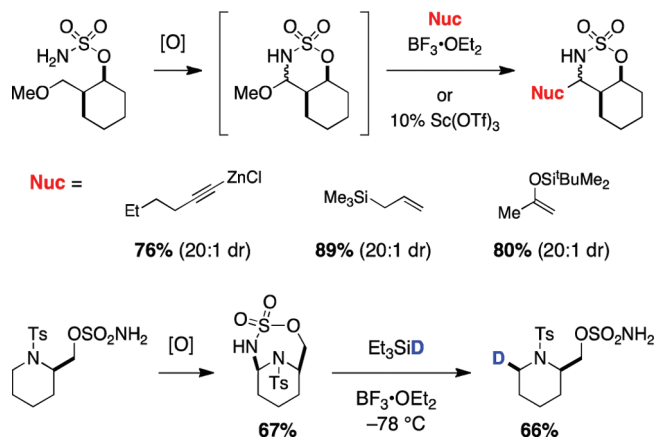**FIGURE 11.** Catalyst choice influences positional selectivity.



**FIGURE 12.** Heterocyclic acetals available through α-ethereal and α-aminal C−H insertion.

follow the trend: 3° > α-ethereal, α-aminal, benzylic > 2° ≫ 1° (Figure 11).[25] The choice of catalyst structure and the nature of the protecting groups, however, can significantly influence positional selectivity. Looking forward, a grand challenge for C−H amination reaction development is to better appreciate the nuanced details of the noncovalent interactions between substrate and catalyst that influence product ratios, information that should lead to greater predictive power with respect to both substrate design and catalyst selection.

The formal products of methylene or methyl oxidation may be accessed in two steps by taking advantage of the facility of α-ethereal (or α-aminal) C−H bond oxidation using sulfamate esters (Figure 12). The resultant N,O- and N,N-acetals can be directly converted (generally without intermediate purification) to cyclic and acyclic products through Lewis acid-mediated addition reactions. A wide range of common nucleophiles (allylsilanes, alkynylzinc reagents, silyl enol ethers, silylhydrides, tethered phenols) will engage in this process.[37,38] Product diastereoselectivity in many instances is exceptional (>20:1), and has been rationalized through a combined Stevens/Felkin-Ahn model.

One of the principle challenges in amination methods development is achieving chemoselectivity that favors C−H insertion products in reactions of unsaturated compounds.[39]
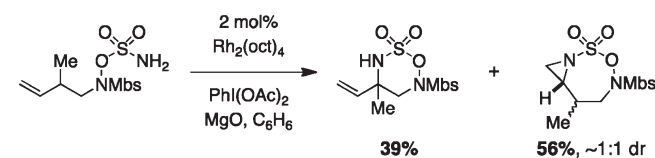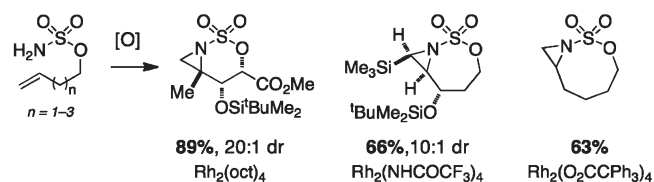


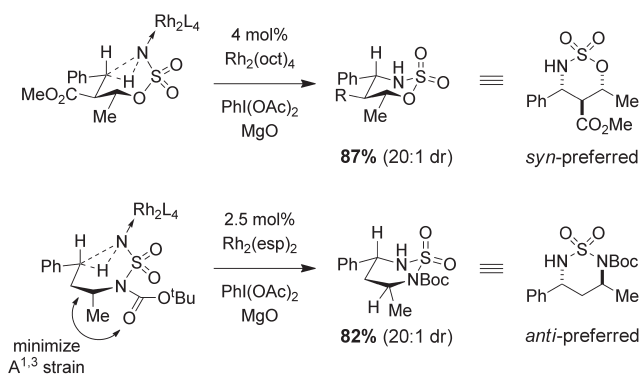**FIGURE 13.** Competitive aziridination and C−H insertion reactions.



**FIGURE 14.** Divergent stereochemical outcomes in sulfamate and sulfamide C−H insertion reactions.

Substituted alkenes are particularly adept substrates for reactions with electrophilic nitrenoids, and the prevailing tendency of unsaturated sulfamates and carbamates is to generate aziridine product(s).[14,23,25,28] Examples include reactions of bis- and tris-homoallylic sulfamate esters, which preferentially furnish the 7- and 8-membered fused bicyclic structures, respectively (Figure 13). For intermolecular amination reactions, alkene aziridination dominates. Motivated by this problem and given the utility of allylic amines in synthesis, we have sought catalyst systems that can override the inherent bias of the nitrenoid toward olefin oxidation (vide infra).

## Diastereoselectivity in Intramolecular Reactions

A predictive model has been put forth to rationalize diastereochemical selectivity in C−H oxidation reactions with chiral sulfamate and sulfamide derivatives (Figure 14). α-Substitution at the sulfamate results in preferential formation of the corresponding 1,3-*syn* oxathiazinane, whereas substitution at the β-carbon favors the 1,2-*anti* isomer.[18] The sense of induction may be rationalized by invoking a putative
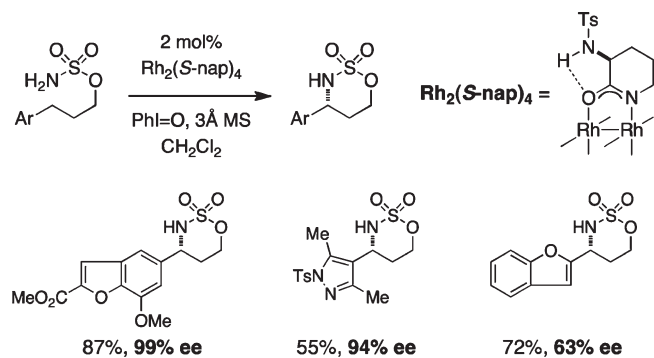
**FIGURE 15.** Asymmetric intramolecular C−H amination of aryl-substituted sulfamate esters.



**FIGURE 16.** Catalyst SAR data highlights the influence of remote steric groups on reaction performance.



| entry | catalyst | R | n | I/A | yield |
|---|---|---|---|---|---|
| 1 | [Rh$_2$(OAc)$_4$] | Ph | 0 | 1:20 | |
| 2 | [Rh$_2$(PTPI)$_4$] | Ph | 0 | 1:3 | |
| 3 | [Rh$_2$(S-nap)$_4$] | Ph | 0 | 2:1 | 48% |
| 4 | [Rh$_2$(OAc)$_4$] | Me | 1 | 2:1 | |
| 5 | [Rh$_2$(S-nap)$_4$] | Me | 1 | >20:1 | 51% |

**FIGURE 17.** Competitive aziridination versus allylic C−H amination. Product ratios were estimated by $^1$H NMR integration.

chairlike transition structure in which substituent groups are disposed in pseudoequatorial arrangements in response to A-strain. Few sulfamate reactions have been identified that do not accord with this stereochemical model. Notably, cyclization reactions of α-branched, *N*-Boc sulfamide derivatives favor formation of the *anti*-isomer with moderate levels of stereocontrol.[19] This preference can be rationalized using the same cyclic transition state model in which A$^{1,3}$-strain between the *N*-Boc group and the α-substituent forces the latter into a pseudoaxial alignment, thereby favoring the *anti*-diastereomer.

The interaction of optically active amination substrates with enantiomeric dirhodium catalysts has not been extensively explored. The design and examination of new catalyst systems that could override substrate-biased stereocontrol could aid efforts to better understand catalyst−substrate interactions and would have considerable utilitarian value in synthesis.

## Asymmetric C−H Amination

Enantioselective C−H amination has been accomplished using the dirhodium carboxamidate complex, Rh$_2$(S-nap)$_4$ (Figure 15).[40] This particular catalyst is unique in its effectiveness at promoting amination, as most other amide-based rhodium dimers (an exception being the electron-withdrawn tetrakis-trifluoroacetamide catalyst) are susceptible to rapid oxidative degradation under the reaction conditions. A ligand-based hydrogen bond interaction in Rh$_2$(S-nap)$_4$ appears to be an important design feature; N-methylation of the α-amino moiety significantly reduces the performance of this catalyst system.

Despite progress in asymmetric C−H amination with the advent of Rh$_2$(S-nap)$_4$, the substrate scope of these reactions remains limited. To date, only benzylic and allylic substrates afford products in acceptable yields (40−90%) and only the former class of substrates can be oxidized with reasonable
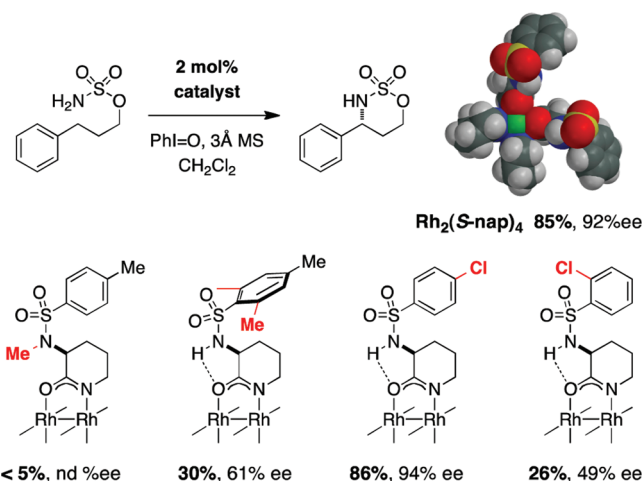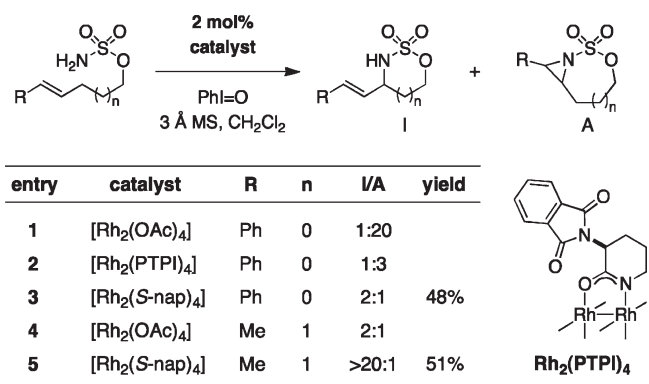
asymmetric control (er ∼ 10:1). An especially curious feature of the *S*-nap ligand system is that changes to the sulfonamide moiety, ostensibly remote to the metal binding site, affect both catalyst performance and product enantiomeric ratios (Figure 16). Findings such as these give a sense as to why the development of new catalysts for enantioselective C−H amination remains an outstanding challenge in this field.

A rather surprising feature of Rh$_2$(S-nap)$_4$ is its predilection to favor formation of C−H insertion products over the isomeric bicyclic aziridines in oxidation reactions of bishomoallylic sulfamates (Figure 17). We are unaware of any other dirhodium system that exhibits such a preference in intramolecular reactions. Other metal complexes, including Mn- and Ru-porphyrin catalysts and Ru(pybox) have been shown to favor allylic insertion pathways.[7b,9,41,42] With Rh$_2$(S-nap)$_4$, the substrate scope is narrowly defined and product yields are moderate; the bias this dirhodium catalyst

has for allylic C−H insertion, however, is rather remarkable such that even 5-membered ring formation is favored with homoallylsulfamate. The unique capabilities of Rh$_2$(S-nap)$_4$ should inspire continued efforts to investigate the mechanism for substrate oxidation by this catalyst system and the influence of the ligand architecture on chemoselectivity.

## Ruthenium Catalysts for Intramolecular Allylic C−H Insertion

Rh$_2$(tfacam)$_4$ and Rh$_2$(S-nap)$_4$ complexes notwithstanding, effective dirhodium systems for C−H amination are largely restricted to a subset of tetracarboxylate designs.[1a,2,4] Dirhodium complexes supported by strongly donating amidate ligands appear to be quickly oxidized under the reaction conditions, while electron-withdrawn carboxylate frameworks (e.g., α-amino acid derivatives, trifluoroacetate) are labile to ligand exchange. We have for some time sought non-rhodium metal complexes that promote competent N-atom transfer. While much of this work has met with limited success, the efforts of Che and Blakey have encouraged further analysis of Ru-based catalyst systems.[41,43]

Initial reports on the synthesis of mixed valent diruthenium(II,III) paddlewheel complexes can be found as early as 1966.[44] Despite intensive studies on the coordination chemistry and spectroscopy of these complexes and their obvious parallels to dirhodium structures, these systems have found almost no utility as catalysts for organic transformations.[45,46] We have investigated the viability of mixed-valent diruthenium(II,III) complexes for catalyzing intra- and intermolecular C−H amination. The higher oxidation potential of the diruthenium core vis-à-vis analogous dirhodium complexes was viewed as a potential advantage that would allow greater flexibility in ligand design by permitting the use of amidate and other strongly donating ligand sets.[28]

We have disclosed the first examples of diruthenium tetracarboxylate- and tetra-2-oxypyridinate-mediated intramolecular sulfamate C−H amination reactions (Figure 18).[28] The strapped dicarboxylate complex, [Ru$_2$(esp)$_2$]SbF$_6$, boasts outstanding catalytic efficiency, and oxidizes isoamyl sulfamate to the corresponding oxathiazinane in excess of 600 turnovers. Empirical examination of a variety of ligand architectures, and their efficacy in promoting useful levels of conversion on a range of functionalized substrates, highlights one particular complex, [Ru$_2$(hp)$_4$Cl]. This tetrakis(2-oxypyridinato) adduct readily promotes sulfamate cyclization, while the dirhodium analogue Rh$_2$(hp)$_4$ expectedly fails, presumably due to its low solubility and rapid oxidative degradation under the reaction
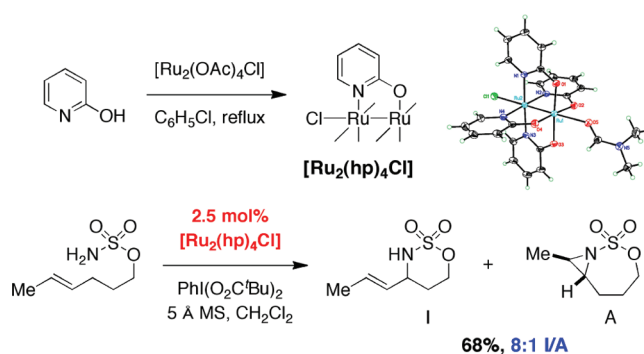


**FIGURE 18.** [Ru$_2$(hp)$_4$Cl] for selective, intramolecular allylic C−H amination.

conditions. For most substrates, low catalyst loadings of [Ru$_2$(hp)$_4$Cl] may be utilized (2.5 mol %); substrates possessing an assortment of different functional groups will engage, and 6-membered ring oxathiazinanes are generally furnished in 60−75% yield. The uniqueness of [Ru$_2$(hp)$_4$Cl] is displayed in reactions of bis-homoallylic sulfamates, which strongly favor products of allylic C−H insertion over the corresponding aziridines. This catalyst complex is superior to Rh$_2$(S-nap)$_4$ for chemoselective allylic amination.

The differential performance of [Ru$_2$(hp)$_4$Cl] for allylic C−H bond oxidation has compelled mechanistic inquiry.[28] A large body of physical organic data on the intramolecular *rhodium*-catalyzed amination reaction intimates a concerted insertion process through an asynchronous transition state. Stereochemical retention in amination reactions of optically active tertiary C−H centers, cyclopropyl clock studies, computational studies, Hammett data, and KIE values collectively support this conclusion. Experiments with [Ru$_2$(hp)$_4$Cl], which include partial isomerization of a *cis*-cyclopropane radical clock and *cis−trans* alkene isomerization, as well as density functional theory (DFT) calculations, however, reveal an alternative oxidation pathway (Figure 19). This catalyst appears to operate through a discrete two-step mechanism involving homolytic C−H bond scission followed by fast radical recombination. Hammett and kinetic isotope data show significant disparities between dirhodium- and diruthenium-mediated amination, the latter displaying a larger Hammett ρ value (−0.55 vs −0.90, respectively) and KIE (2.6 vs 4.9, respectively). The stepwise nature of the [Ru$_2$(hp)$_4$Cl]-catalyzed reaction accounts for preferential allylic C−H bond functionalization over alkene aziridination. Ongoing studies should continue to reveal differences between dirhodium and diruthenium systems as well as the mechanism(s) for [Ru$_2$(hp)$_4$Cl] arrest and/or decomposition. Such information will enable next-generation catalyst
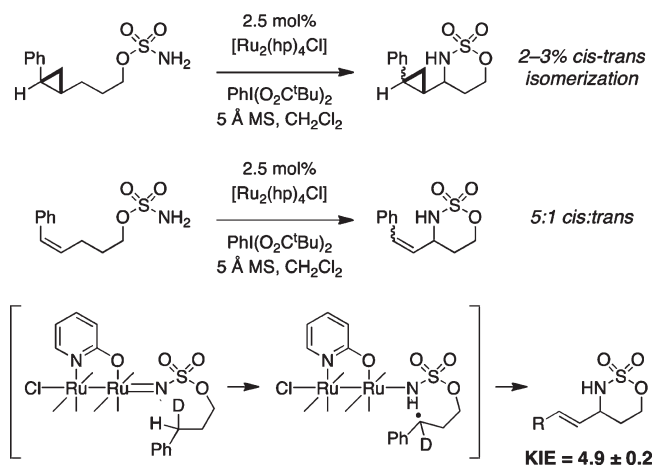
**FIGURE 19.** Results support a stepwise C−H abstraction/radical rebound mechanism for [Ru$_2$(hp)$_4$Cl]-catalyzed amination.

designs that function with other substrates types (e.g., carbamates) and that mediate intermolecular allylic insertion reactions.

## Intermolecular Benzylic C−H Insertion

Chemoselective intermolecular C−H functionalization is an exceptional challenge for oxidative insertion technology. The effectiveness of Rh$_2$(esp)$_2$ as an amination catalyst has made possible an earnest exploration of such a method.[47] With a limiting amount of starting alkane and a simple sulfamate nitrogen source, 2,2,2-trichloroethoxysulfonamide (TcesNH$_2$), moderate to high isolated yields (50−80%) of benzylic amine products are attainable. In combination with TcesNH$_2$, these reactions employ 2 mol % Rh$_2$-(esp)$_2$ and an organic-soluble oxidant, PhI(O$_2$C$^t$Bu)$_2$. A salient feature of this method is that $^{15}$N-labeled TcesNH$_2$ can be prepared and used to generate isotopically enriched amine derivatives (Figure 20).

Conditions for intermolecular amination that employ TcesNH$_2$ favor oxidation of benzylic C−H bonds over tertiary sites (Figure 21). These results contrast intramolecular insertion reactions, which show a clear preference for tertiary C−H functionalization.[25] The mechanism of dirhodium-catalyzed intermolecular C−H amination is under active investigation in an effort to illuminate the underlying reason(s) for the change in chemoselectivity between intra- and intermolecular regimes. The evident disparity between these processes is, admittedly, one of the more perplexing observations that we have been trying to decode.

A small number of reports have outlined protocols for asymmetric intermolecular C−H amination using simple hydrocarbons such as indane and tetralin.[48] Dauban et al.
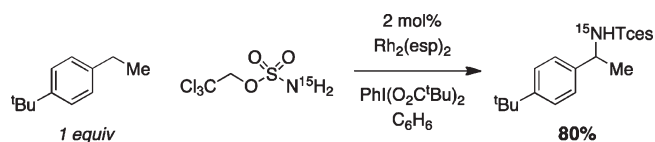


**FIGURE 20.** Generation of $^{15}$N-isotopomers through intermolecular C−H amination.
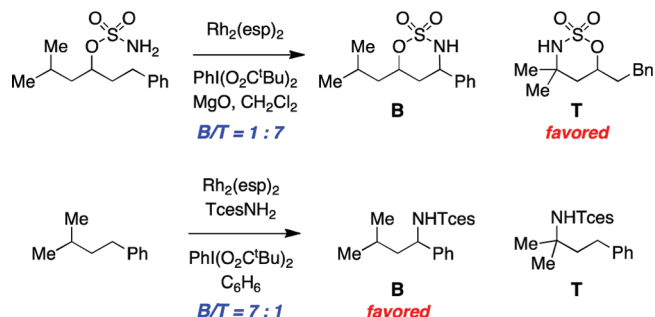


**FIGURE 21.** Intermolecular oxidation with TcesNH$_2$ favors benzylic C−H centers.
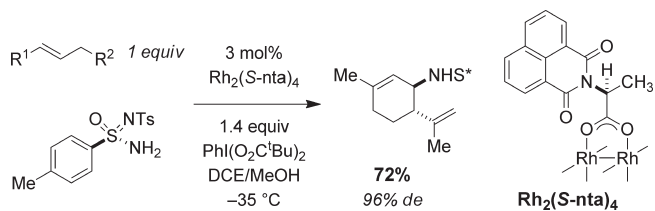


**FIGURE 22.** Chemo- and diastereoselective intermolecular amination of allylic C−H bonds.

have offered an impressive method for diastereoselective C−H amination reactions of benzylic and allylic substrates that relies on a combination of an optically active dirhodium tetracarboxylate catalyst and a chiral sulfonimidamide nitrogen source (Figure 22).[49] Remarkably, the reaction occurs at −35 °C and provides high levels of chemo- and diastereoselectivity for intermolecular allylic insertion. This process is currently unrivaled for both efficiency and stereocontrol.

With the exception of the Dauban and Dodd disclosure, intermolecular amination reactions on alkene-bearing substrates are often complicated by product mixtures arising from indiscriminant π-bond and allylic C−H oxidation. In some cases, it is possible to bias selectivity in favor of aziridine formation; for this purpose, the trifluoroacetamide catalyst Rh$_2$(tfacam)$_4$ and the analogous rhodium perfluorobutyramide have proven indispensible, furnishing azaheterocycles stereospecifically in 65−95% yield (Figure 23).[50] A number of non-dirhodium catalysts have been employed for intermolecular aziridination reactions, but few match the catalytic performance of Rh$_2$(tfacam)$_4$.
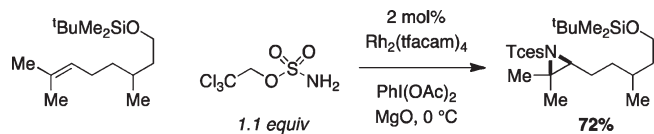
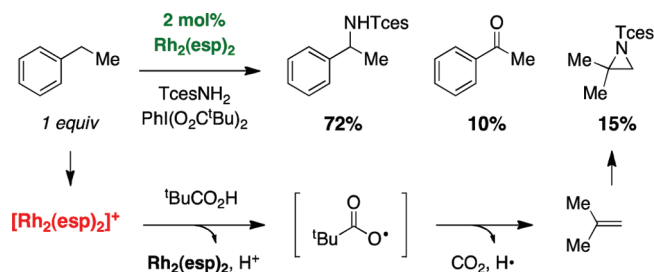**FIGURE 23.** Intermolecular olefin aziridination.



**FIGURE 24.** Ketone and aziridine byproducts identified in intermolecular C–H oxidation.

## Mechanistic Investigations of the Intermolecular Process

Product analysis of intermolecular C–H amination reactions has given way to a number of mechanistic discoveries. Examination of reaction mixtures consisting of ethylbenzene, TcesNH$_2$, PhI(O$_2$C$^t$Bu)$_2$, and catalytic Rh$_2$(esp)$_2$ reveal acetophenone and the aziridine of isobutylene as isolable side products (Figure 24).[33,47] These early observations led to speculation that a one-electron oxidation pathway operates either in parallel with or in lieu of the concerted two-electron amination mechanism. The evident change in solution color from bright green to red suggested a change in the redox state of the dirhodium catalyst. Subsequent spectroscopic and spectrometric experiments have identified this red species as a one-electron oxidized complex, [Rh$_2$(esp)$_2$]$^+$ (Figure 25).[32,51]

We have proposed that [Rh$_2$(esp)$_2$]$^+$ forms through a secondary process during nitrenoid decomposition. Empirically, the onset of the red color appears to correlate with the difficulty associated with oxidizing a particular hydrocarbon substrate. The mixed-valent dimer, [Rh$_2$(esp)$_2$]$^+$, has a prolonged lifetime under the reaction conditions as compared to other, simple dirhodium tetracarboxylates such as [Rh$_2$(O$_2$C$^t$Bu)$_4$]$^+$.[32] A transient red solution of [Rh$_2$(O$_2$C$^t$Bu)$_4$]$^+$ fades rapidly (<60 s) to a pale yellow color, presumably consisting of Rh$^{3+}$ monomeric and/or multimeric species. By contrast, [Rh$_2$(esp)$_2$]$^+$ persists for a much longer duration owing to the chelating nature of the ligand set; this complex can be reduced under the reaction conditions to the corresponding dirhodium(II,II) adduct by the carboxylic acid byproduct, $^t$BuCO$_2$H. These findings have led us to propose that
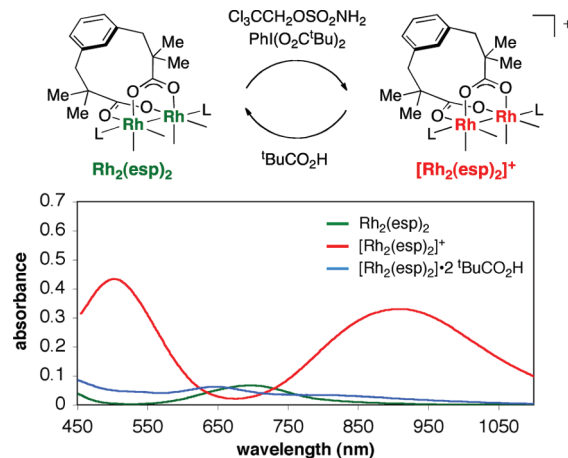


**FIGURE 25.** Spectroscopic characterization of a mixed-valent Rh$_2$(II,III) dimer.
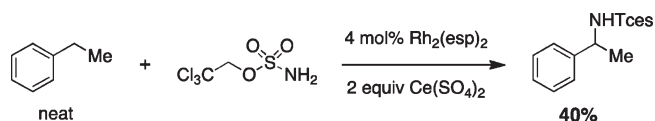


**FIGURE 26.** Intermolecular C–H amination mediated by Ce$^{4+}$ oxidant.

the differential advantage of the esp ligand is its ability to stabilize the mixed-valent dirhodium species, thereby allowing one-electron reduction to take place to return the active (II,II) dimer. Our results also explain the improved performance of PhI(O$_2$C$^t$Bu)$_2$ as a terminal oxidant over PhI(OAc)$_2$. We have found that the use of other carboxylic acids (e.g., dimethylphenylacetic acid), known to be more effective one-electron reducing agents, can improve catalytic turnover numbers in intermolecular amination reactions.[29,33b]

Berry and Kornecki have identified and characterized a red mixed-valent complex as [Rh$_2$(esp)$_2$(HNTces)] and have proposed an alternative amination pathway that operates through proton-coupled one-electron oxidation of the catalyst to give the reactive dirhodium(II,II)-nitrene.[51] Formation of [Rh$_2$(esp)$_2$(HNTces)] is suggested to arise from H-atom loss by the dirhodium TcesNH$_2$ adduct, [Rh$_2$(esp)$_2$]·(H$_2$NTces). This provocative proposal implies a pathway for C–H amination that may be mediated by single-electron oxidants such as Ce$^{4+}$ salts, which Berry and Kornecki have in fact used to effect catalytic turnover (Figure 26). Whether the rate of a sequential proton-coupled electron transfer or H-atom abstraction mechanism is competitive with carboxylic acid-induced [Rh$_2$(esp)$_2$]$^+$ reduction under the normal operating reaction conditions is a question that remains to be answered. The fate of this intermediate mixed-valent dirhodium complex is the subject of active investigations in our laboratory.

## Conclusion

This Account outlines our recent contributions to the advancement of intra- and intermolecular rhodium- and ruthenium-catalyzed amination reactions, specifically highlighting the many unique challenges posed by problems of selectivity (both chemo and stereo) and the complexities of the underlying catalytic reaction mechanism. Despite the progress of other laboratories and ours, absolute reagent control over chemo- and stereoselective C—H bond oxidation remains beyond reach. A deeper understanding of the pathway(s) for catalyst arrest is needed to inform the rational design of next-generation systems that extend the capabilities of current amination technologies. The subtle interplay between catalyst structure and substrate can dramatically influence reaction performance and product distributions, but the molecular details of such interactions remain opaque at this time. Undoubtedly, there is much to learn as we attempt to unravel these mysteries.

### BIOGRAPHICAL INFORMATION

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