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Electronic and Steric Tuning of a Prototypical Piano Stool Complex: Rh(III) Catalysis for C-H Functionalization

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CONSPECTUS

The history of transition metal catalysis is heavily steeped in ligand design, clearly demonstrating the importance of this approach. The intimate relationship between metal and ligand can profoundly affect the outcome of a reaction, often impacting selectivity, physical properties and the life-time of a catalyst. Importantly, this metal-ligand relationship can provide near limitless opportunities for reaction discovery. Over the past several years, transition metal-catalyzed C-H bond functionalization reactions have been established as a critical foundation in organic chemistry that provides new bond forming strategies. Among the d-block elements, palladium is arguably one of the most popular metals to accomplish such transformations. One possible explanation for this achievement could be the broad set of phosphine and amine based ligands available in the chemist's toolbox compatible with palladium. In parallel, other metals have been investigated for C-H bond functionalization. Among them, pentamethylcyclopentadienyl (Cp*) Rh(III) complexes have emerged as a powerful mode of catalysis for such transformations providing a broad spectrum of reactivity. This approach possesses the advantage of often very low catalyst loading, and reactions are typically performed under mild conditions allowing broad functional group tolerance. Cp*Rh(III) is considered as a privileged catalyst and a plethora of reactions involving a C-H bond cleavage event have been developed. The search for alternative cyclopentadienyl based ligands has been eclipsed by the tremendous effort devoted to exploring the considerable scope of reactions catalyzed by Cp*Rh(III) complexes, despite the potential of this strategy for enabling reactivity. Thus, ligand modification efforts in Rh(III) catalysis have been an exception and research directed toward new rhodium catalysts has been sparse. Recently, chiral cyclopentadienyl ligands have appeared allowing enantioselective Rh(III)-catalyzed C-H functionalization reactions to be performed. Alongside chiral ligands, an equally important collection of achiral cyclopentadienyl-derived ligands have also emerged. The design of this new set of ligands for rhodium has already translated to significant success in solving inherent problems of reactivity and selectivity encountered throughout the development of new Rh(III)-catalyzed transformations. This account describes the evolution of cyclopentadienyl ligand skeletons in Rh(III)-catalysis since the introduction of pentamethylcyclopentadienyl ligands to the present. Specific emphasis is placed on reactivity and synthetic applications achieved with the new ligands with the introduction of achiral mono-, di-, or pentasubstituted cyclopentadienyl ligands

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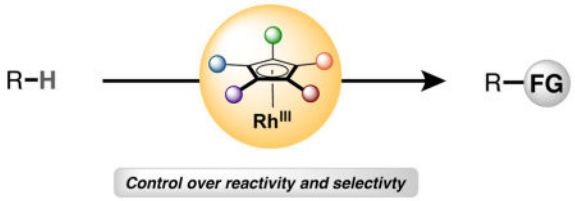
exhibiting a stunning effect on reactivity and selectivity. Furthermore, an underlying question when dealing with ligand modification strategies is to explain the reason one ligand outperforms another. Conjecture and speculation abound, but extensive characterization of their steric and electronic properties has been carried out and information about electronic and steric properties of the ligands all contribute to our understanding and give crucial pieces to solve the puzzle.

Graphical Abstract



Introduction

The development of protocols that enable the expedient synthesis of functionally complex nitrogen containing molecules from readily available starting materials has been an ongoing target of our research. The methods that we have initially developed en route involve Rh(I)-catalyzed alkenyl isocyanate cycloadditions with alkynes (Figure 1).[1] Notably, we have demonstrated a two-component strategy where interception of rhodacyclic intermediates in a [2 + 2 + 2] cycloaddition provides access to indolizidines, quinolizidines, and dihydropyrimidines. The emphasis throughout is on accessibility of starting materials and utility of products. Although this methodology tolerates a wide range of substrates, it relies on a tethering strategy. Furthermore, the requisite isocyanates are a far less common nitrogenous functional group than amines or amides.

In an attempt to render the process more general and convenient, we thus pursued a strategy relying on C-H activation. Pioneering work of Satoh and Miura revealed that benzoic acid is capable of directing C-H activation in the presence of catalytic amount of Cp*Rh(III) (where Cp* is pentamethylcyclopentadienyl), delivering isocoumarins.[2] Miura and Satoh elaborated on this finding by using mildly acidic NH directing groups which deliver N-heterocycles when coupled with alkynes.[3] In a tour de force of this approach, Fagnou revealed an indole synthesis utilizing simple *N*-aryl acetamides and alkynes under cationic Cp*Rh(III) conditions.[4] Independently and concurrently with the Fagnou,[5] Miura[6] and Li[7] groups and stimulated by the mechanistic similarity between the Rh(III) metallacycles accessible by alkenyl isocyanate cycloaddition and C-H activation (Figure 1), we described isoquinolone syntheses based on the directed C-H bond cleavage of benzamides followed by coupling with an alkyne π-component.[8]

Since these initial reports, extensive studies by various groups[9] have been carried out to extend coupling partners to include different directing groups, arene substrates, olefins[10] and alkynes, as well as other functional groups such as diazo compounds,[11] CO,[12] imines,[13] amine derivatives,[14] or borane.[15] Although still rare, a few examples dealing with the cleavage of sp^3 C-H bonds were also reported.[16] However, little attention has been devoted

toward altering the core structure of the cyclopentadienyl ligand. Indeed, among these transformations, Cp*Rh(III) and its cationic forms[17] are nearly universally employed as rhodium source and are considered as privileged catalysts for such reactions. This situation is somewhat in contradiction with the typical course of reaction development in transition metal catalysis where the discovery of novel reactivity is often interrelated with ligand development. Several reasons may account for this situation - Cp*Rh(III) catalyst: a. exhibits a large M-ligand dissociation energy due to the electron-donating ability of the five methyl substituents conferring robustness to enable reactions that sometimes require high temperatures; b. is soluble in most organic solvents whereas CpRh(III) possesses poor solubility; and c. is commercially available making it inherently enabling. Nevertheless, early on we recognized that the exploration of the immense chemical space available between the Cp* and Cp structure could be an opportunity for reaction discovery and therefore deserved our attention. Finally, despite a large core of inorganic chemistry literature dedicated to the synthesis of cyclopentadienyl derivatives, the myth that these procedures are only reserved to a handful of specialists is persistent. Herein, we describe our efforts toward this goal.

The present review shows the progression of our research path that led us to design new cyclopentadienyl ligand from our first steps in the field until now. We hope to depict the issues that we encountered over the years and how we overcame them by tuning the cyclopentadienyl ligand. Moreover, this review also describes our attempts to rationalize the ligand effect in reactions through the analysis of electronic and steric properties of ligands. As with all areas of science, our efforts in this field have not been conducted in a vacuum. Aside from specific precedent from other laboratories that have impacted various studies discussed below, several reports have emerged dealing with tailored cyclopentadienyl ligands on Rh(III) and their impact on C-H activation. Miura described polyarylated Cp ligands and observed a positive effect in some transformations.[18] Tanaka and co-workers advanced an ethoxycarbonyl-substituted cyclopentadienyl (Cp^E)[19] as ligand for Rh(III) that exhibits an increase of reactivity and allows milder reaction conditions than when employing Cp*Rh(III) in several transformations.[20] Cramer has reported a cyclohexyl-fused Cp ligand (Cp^{Cy}) and its impact on several reactions.[21] Chang and coworkers reported a chemodivergent effect induced by the ligand in one reaction, noting a switch between two annulation pathways by modifying substitutions in the Cp ligand.[22] Reactions dealing with chiral cyclopentadienyl ligands have been summarized previously and are outside the scope of the present manuscript.[23,24]

Synthesis of Isoquinolones, Pyridones, and their Derivatives

As mentioned above, our initial efforts were focused on isoquinolone synthesis from benzamides and alkynes. In the context of that work, a broad range of isoquinolones with different substitution patterns are obtained in excellent yield (Figure 2). Importantly, in the case of unsymmetrical alkynes high regioselectivities are achieved (>10:1). When the substituents are electronically equivalent but sterically different, the larger group is preferentially placed β- to the nitrogen atom, presumably to avoid repulsive steric interactions with the Rh catalyst during the migratory insertion step. When the polarization

of the alkyne is significant, the most electron donating group prefers being α- to the nitrogen atom, possibly to stabilize the high-valent Rh(III) metal before reductive elimination.

In contrast, expanding this transformation to activate alkenyl C-H bonds to access pyridones by coupling with an alkyne, results in low regioselectivities with Cp*Rh(III) catalyst (Figure 3).[25] We speculated that altering the isotropic character of the ligand should increase the selectivity of the alkyne insertion. To this end, we prepared a Rh(III) precatalyst bearing a 1,3-di-*tert*-butylcyclopentadienyl group (Cp^t). The use of this catalyst results in a notable improvement in regioselectivity (14:1). Additionally, extensive substitution on the acrylamide is tolerated and the pyridone rings are formed in high yields and regioselectivities. Further investigation revealed that unsymmetrical alkynes containing an alkyl and an aryl substituent give higher regioselectivity with the Cp^t ligand than when the Cp* ligand is used, presumably due to strong steric interactions between the ligand and alkyne in the insertion event. However, the Cp^tRh catalyst gives no reactivity with relatively hindered di-alkyl alkynes, but reactivity can be restored with Cp*Rh(III) catalyst affording the desired product with high regioselectivity in cases where the two groups on the alkyne are sterically different enough.

The use of alkenes as coupling partners in C-H activation of benzhydroxamate to form dihydroisoquinolones has been demonstrated previously.[10] Nevertheless, in most cases acceptable regioselectivities are obtained only with styrenes and acrylates (5:1 to >20:1) whereas alkyl alkenes perform poorly (1:1 to 2:1). We undertook an initial comprehensive study involving simple alkenes tethered to the benzamide and benzoic acid systems at the *meta* position.[26,27] While this has the clear disadvantage of being a tethering strategy, we gained insights into the reaction and examined the reactivity of more complex stereochemically defined internal alkenes.

Elaborating on this study, we challenge the intermolecular coupling of alkenes with arylhydroxamate esters. As mentioned previously, while acrylates and styrenes prove high selectivity, simple aliphatic alkenes are more problematic, and with the isotropic Cp*Rh(III) catalyst deliver the product with poor regioselectivity (Figure 4). We hypothesized that an anisotropic, hindered cyclopentadienyl ligand on the rhodium could enable higher regioselectivity. Notably, $[Cp^tRhCl_2]_2$ delivers the 4-substituted isomer in exquisite regioselectivities.[28] Furthermore, systematic comparative studies between $[Cp^*RhCl_2]_2$ and $[Cp^tRhCl_2]_2$ complexes demonstrate that the Cp^t ligand furnishes synthetically useful regioselectivities for a variety of aliphatic alkenes with the 3-substituted regioisomer being the major product.

Continuing our study, we explored the reactivity of other coupling partners that can be utilized with benzamide derivatives. In this context, we studied the reactivity of cyclopropene rings under Rh(III) reaction conditions (Figure 5). Our group initially reported a Rh(III)-mediated coupling of O-pivaloyl benzhydroxamate with 3,3-diester substituted cyclopropenes to afford 4-substituted isoquinolones after ring opening of the three-membered ring.[29] Throughout this study, when using the methyl 1-phenylcycloprop-2-ene-1-carboxylate as a substrate the Cp*Rh(III) catalyst gives the [4.1.0] bicyclic product in low diastereoselectivity (1.4:1 *dr*). We believe the diastereoselectivity stems from the poor

facial selectivity during the coordination of the cyclopropene unit to the Rh metal preceding the migratory insertion step. Ligand screening with 1-methyl-phenylcycloprop-2-ene reveals that increasing the steric hindrance around the Rh metal center is beneficial for the diastereoselectivity of the reaction.[30]

While Cp^t and Cp^{*CF3} ligands deliver promising diastereoselectivity, heptamethylindenyl ligand (Ind*) proves to be the ligand of choice providing the bicyclic product in 90% yield and 15.2:1 dr. In contrast with the parent indenyl ligand (Ind), Ind* is known to adopt an η^5 coordination mode on the Rhodium metal in the ground state such as Cp* with little to no tilting of the ligand towards η^3.[31] We observed that variation at the *para* and *meta* positions of the cyclopropene units furnish the product in good yields and excellent diastereoselectivities, regardless of the electronic nature of the substituents. The observed major diastereoisomer can be rationalized through the size of the substituents on the cyclopropane ring. Thus, the phenyl group is larger than the carboxylate ester (A-values for -Ph and $–CO_2Me$ are 3.0 and 1.25, respectively) leading to higher diastereoselectivity than our initial result (1.4:1 vs. 8.7:1 *dr*). However, poor facial selectivity is observed (2.3:1 dr) when the substituents are similar in size, such as in the case of a benzyl and a methyl group (A-values for -Bn and –Me are 1.75 and 1.70, respectively).

Synthesis of Pyridine and Pyridine Derivatives

Seminal work by Cheng[32] shows that α,β-unsaturated oxime can be coupled with an alkyne to form pyridine rings using Rh(I) protocol.[33,34] Although showcasing an elegant route for the synthesis of pyridine rings, under these conditions unsymmetrical alkynes give low regioselectivities while requiring high temperatures (130 °C). Inspired by the initial work of Guimond and Fagnou,[5] we recognized that the N-O bond in an oxime can also be used as internal oxidant under Rh(III)-catalysis conditions (Figure 6).[35] We envisioned that Rh(III) catalysis could be exploited for a more convenient pyridine synthesis with milder reaction conditions and a broader substrate scope. During our first attempts, we were pleased to find that the Cp*-containing catalyst delivers the expected pyridine, albeit with low regioselectivity (2:1 *rr*). We then interrogated the effect of Cp^tRh(III) catalyst under these reaction conditions. Notably, in several cases Cp^tRh(III) appeared to increase regioselectivities or alter the intrinsic selectivities to favor the opposite isomer. Despite these advances, inconsistent regioselectivities and restricted terminal alkyne scope limit this methodology. While these results validated our approach for the synthesis of pyridine rings, we recognized that more synthetically useful regioselectivities would render this route more palatable.

To this end, we thought that the insertion of an electron deficient alkene in place of the alkyne, with an external oxidant in addition to the N-O bond internal oxidant, could potentially address the regioselectivity issue and provide a complementary method for pyridine synthesis (Figure 7).[36] An extensive screen of reaction conditions revealed $[Cp^*RhCl_2]_2$ precatalyst in conjunction with an excess of silver(I) acetate as an oxidant in a mixture of dichloromethane/acetic acid as optimal, providing the pyridine ring in 65% yield. Importantly, the reaction proceeds with complete regiocontrol during the insertion of the ethyl acrylate, affording exclusively the 6-substituted pyridine.

We aimed to broaden the scope of pyridine synthesis by interrogating the reactivity of more challenging alkene coupling partners. During our study, we found that substituted acrylic acids provide the complementary regioisomers of the pyridine products, where the carboxylic acid residue acts as traceless directing group (Figure 7).[37] Preliminary results revealed that when using a catalytic amount of $[Cp^*RhCl_2]_2$, the titled 5-substituted pyridine is formed exclusively in 50% yield with extrusion of the carboxylic acid functional group. Further investigations of the reaction conditions lead us to advance the electron deficient $[Cp^{*CF3}RhCl_2]_2$ as catalyst for the transformation. Under these conditions, the yield is substantially higher with the product isolated in 70% yield. The strategy to install a carboxylic acid into the alkene to control the migratory-insertion step proves to be effective for a variety of alkyl- to aryl-substituted acrylic acids forming selectively 5-substituted pyridines. Of mechanistic relevance, we obtained an X-ray crystal structure of a rhodium carboxylate species that presumably correspond to an intermediate of the reaction prior to the decarboxylation step.

In the latter reactions, we never observed the presumed 2,3-dihydropyridine intermediate even in the absence of external oxidants. We speculated that the instability of the 2,3-dihydropyridine was responsible and that *in situ* oxidation to the pyridine ring was more rapid than the initial annulation.[38] We envisioned that the use of 1,1-disubstituted alkenes would prevent oxidation and deliver 2,3-dihydropyridine products (Figure 8). The insertion of such hindered alkenes without reliance on a tethering strategy constituted a major challenge for realizing this transformation. During initial attempts, we found that the insertion of the 1,1-disubstituted alkene occurs selectively with the most hindered site of the alkene placed away from the bulky metal center to deliver the desired 2,3-dihydropyridine in 74% conversion, when using cationic Cp*Rh(III) as the catalyst. However, we observed that after 10 h the reaction stalls, presumably due to catalyst inhibition. When replacing the Cp* ligand with the electron poor $Cp^{*CF3,}$ full conversion is achieved after only 2 h of reaction and the 2,3-dihydropyridine is isolated in 84% yield. The positive impact of Cp^{*CF3} ligand was revealed to be general, enabling access to diversely substituted 2,3-dihydropyridine rings. We further developed a one pot procedure to reduce the 2,3-dihydropyridines to their corresponding piperidine rings. Employing this protocol, a variety of piperidines containing an all carbon-quaternary center at 3-position is obtained in high yields and good diastereoselectivities. Outside the apparent synthetic utility of these transformations, we have shown that a tuned electron poor Cp^{*CF3} ligand on the Rh can impact reactivity and broaden the scope of given transformations.

Cyclopropanation Reaction

Our group has a long-standing interest in investigating new directing groups for Rh(III)-catalyzed C-H activation reactions in order to access greater molecular diversity.

In this context, we sought to develop a protocol to activate vinyl C-H bonds and considered enoxyphthalimide as potential precursor (Figure 9).[39] Conceptually, we thought that the directing group would bear the ubiquitous amide carbonyl that can direct the C-H bond cleavage and the N-O cleavage/Rh reoxidation step would result in release of a formal enol species. We chose to test this reactivity with an alkene coupling partner. To our surprise,

when ethyl acrylate was used as the coupling partner in initial screens, we observed the formation of a 1,2-disubstituted *trans*-cyclopropane. However, with the Cp*Rh(III) catalyst low diastereoselectivity is observed (2:1 *dr*). Deviations from the initial reaction conditions by changing the base or the solvent have little to no effect on the diastereoselectivity of the transformation. After an extensive screen of ligands, we were pleased to find that the monosubstituted isopropylcyclopentadienyl ligand (Cp^{iPr}) drastically increases the diastereoselectivity, furnishing the *trans*-cyclopropane in 12:1 *dr* and 79% yield. The reaction conditions allow the cyclization to proceed with electron deficient alkenes such as acrylates, acrylamides, acrylonitrile, and vinyl ketones delivering the *trans*-cyclopropane adducts in good to excellent diastereoselectivities. A plausible mechanism for this transformation is illustrated in Figure 10. After C-H bond activation by the Rh(III) catalyst, alkene coordination precedes migratory insertion to form an alkyl Rh(III) intermediate bearing a tethered enoxyphthalimide intact. Carborhodation across the tethered alkene generates the cyclopropane and forms an intermediate that presumably undergoes rapid N-O bond cleavage to turn the catalyst over.

Initial work of Fagnou and Glorius shown that the nature of the directing group can change the coordination sphere of the Rh catalyst and therefore impact the outcome of a reaction.[5,10a] We found that in presence of methanol under slightly basic conditions, the enoxyphthalimide opens *in situ*, liberating the amine functionality forming concomitantly a bidentate directing group.[40] In presence of Cp*Rh(III) catalyst, cesium acetate as base, and dimethylfumarate as coupling partner we observed the formation of the carboamination product, the addition of the enol and phthalimide across the alkene. Furthermore, we established that the carboamination adduct is formed as a single diastereoisomer with the relative configuration assigned being consistent with a *syn*-addition process. To our knowledge, this constitutes the first report of a stereoselective intermolecular carboamination reaction of alkenes. However, along with the formation of the product of interest, the reaction also produces the cyclopropane adduct (3.5:1 chemoselectivity). To overcome the chemoselectivity issues observed in the transformation, we performed a ligand screen, and found the carboamination product is favored when increasing the effective size of the cyclopentadienyl ligand. Notably, the *tert*-butyl-tetramethyl-cyclopentadienyl ligand ($Cp^{*t\text{-}Bu}$) delivers the best result (8.4:1). Finally, replacing the base cesium acetate with cesium adamantylcarboxylate significantly improves the chemoselectivity (14.8:1), producing the desired product in 82% yield. When probing the stereochemical outcome of the reaction with dimethylmaleate, only one isomer is formed that is different from the one obtained with the fumarate ester. This result suggests that the insertion event is a stereospecific *syn* addition across the alkene. Moreover, the reaction enables addition across unsymmetrically substituted alkenes in excellent chemoselectivities and good regiocontrol. In all cases, the bulkiest substituent is placed away from the phthalimide group. The reaction proceeds with many electron-deficient alkenes, but also tolerates more electron-rich substrates such as 1,2-dihydrofuran.

Our mechanistic investigations as well as our experimental observations led us to postulate that the origin of the chemodivergence between the cyclopropanation and the carboamination reaction stems from the nature of the directing group. In the cyclopropanation process, we propose that a coordinatively Rh species is formed after

carborhodation with the alkene partner where the Rh atom is ligated with the enol fragment favoring therefore the cyclopropanation reaction. Whereas in the carboamination reaction, the saturation of the Rh atom could conceivably occur by intramolecular coordination to a bidentate directing group. Such coordination environment around the Rh metal disfavors the ligation onto the enol moiety and instead drives the reaction toward the carboamination path by favoring reductive elimination to form the C-N bond.

Study of Electronic and Steric Properties of Cp^X Ligands

Over the years our research group has invested tremendous effort into synthetizing new cyclopentadienyl-type ligands for Rh(III) to solve inherent issues of selectivity and reactivity that we encountered. This synthetic effort has led to the construction of a broad library of structurally diverse Rh(III) catalysts. We recently undertook a systematic study of their electronic and steric properties to achieve a finer understanding of ligand effects and ultimately accelerate our research.[41] One of the challenges in this study was to define universal steric and electronic parameters for Cp^XRh(III) catalysts that encompass the most structural diversity as possible.

We first selected a panel of 22 Cp^XRh(III) catalysts among our “in-house” available complexes and studied their electronic and steric properties (Figures 11).

To probe the electronic density of the Rh metal, we utilized several different experimental approaches such as IR spectroscopy (Tolman Electronic Parameter) and ^{31}P NMR. However, these methods involve an indirect probe of the electronics on the Rh metal that require the installation of ancillary ligands such as CO and $P(OEt)_3$ on the Rh complex. Indeed, the nature of the technique employed imposes an additional steric perturbation that may influence the measurement and thus introduce inconsistencies. Therefore, we complemented our study by determining the redox potential of the Rh complexes which allows to evaluate the electronics without chemically modifying the metal complex. To complete our analysis, we also calculated the Rh chemical shift and the NBO charge of the Rh complexes by DFT. The collected data allows us to build electronegativity scales of the Rh(III) complexes. A scale based on the half-potentials (Rh[III/II] couple) of the 22 complexes is presented in Figure 12.

Likewise, we also investigated methods to quantify the steric properties of Cp^XRh(III) complexes. Inspired by unsymmetrical phosphine ligands, we established a convention to determine Tolman Cone Angles (TCA) of the corresponding piano stool Rh catalysts. However, TCA gives a rudimentary analysis of the steric environment of the Rh complexes overlooking anisotropic character of these entities. Thus, to assess the steric environment of the Rh catalyst more accurately, we also determined their sterimol parameters.[42] The value B_5-B_1 constitutes a simplified representation of anisotropy of the Cp^X ligand in the plane of the ring. B_5-B_1 values for all the 22 Rh complexes are presented in a scale in Figure 14. Small B_5-B_1 values correspond to disc-shaped like Cp^X ligand (little anisotropy), whereas larger B_5-B_1 values are characteristic of ligands with a more elliptical shape (pronounced anisotropy).

We ultimately hope that such studies will assist in the growth of cyclopentadienyl ligands for metal catalysis in the tool-box of organic chemists.

Multivariate Regression Based on Cp^{x}Rh(III) Properties

Although the development of new cyclopentadienyl ligands for Rh(III)-catalysis undeniably has the potential to impact the field, several questions remain. We have observed throughout our investigations that subtle variation on the structure of the cyclopentadienyl core can lead to dramatic difference in terms of reactivity and selectivity. Attempts to rationalize ligand effects in catalysis remain a challenge and often lead to a speculative analysis. Recently, Sigman and co-workers elegantly displayed multivariate linear regression analysis to quantitatively describe the interplay between the catalyst structure and selectivity.[43] Importantly, this approach possesses a predictive power allowing the extrapolation of catalyst performance in a transformation. Thus, we utilized multivariate regression approach to correlate the structure of Cp^{X}Rh(III) catalysts to their reactivity in model reactions.

To demonstrate the proof of concept, we selected two Cp^{X}Rh(III)-catalyzed reactions previously developed in our group. As previously discussed, the regioselectivity of Rh(III)-catalyzed insertion of alkyl alkenes such as 1-decene into C-H bond of O-pivaloyl benzhydroxamic acid is strongly dependent on the nature of the Cp^{X} ligand on Rh leading to a mixture of regioisomers (Figure 4). With the library of Cp^{X}Rh(III) catalyst in hand, the regioselectivity data sets of the reaction were used to produce correlations between experimental values and catalyst-based molecular descriptors (Figure 13). Applying this approach with a defined training set (denoted by grey circles in Figure 13), we built a statistically robust regression model. The model displays an overall good agreement between the predicted regioselectivity values and the experimental data (represented as $\Delta\Delta G^{\neq}$). The predictive capability of the regression model was confirmed through external validation with four complexes (denoted with red triangles in Figure 13).

In an attempt to test the generality of multivariate regression approach in Rh(III) catalysis, we also searched for correlations between the diastereoselectivity of cyclopropene insertion and the molecular descriptors of Cp^{X}Rh(III) catalysts (Figure 14). While a regression model was found where the predicted diastereoselectivities closely matched the experimental values, the model was unable to predict the performance of the two best catalysts in the reaction, namely Ind*Rh(III) and Cp*^{Ph2}Rh(III). Classically, breaks in univariate correlations such as those in a Hammett plot are indicative of a change in mechanism. In the case of a multivariate correlation, this change can be identified through the presence of obvious outliers. Based on this, we postulated that the high diastereoselectivities exhibited by Ind*Rh(III) and Cp*^{Ph2}Rh(III) might arise from a change in structure of the transition state. Competing transition structures for the selectivity-determining migratory insertion step were investigated computationally. We found that the stereoselectivity enhancement comes from structural differences in the metal π-coordination for Ind*Rh(III) and Cp*^{Ph2}Rh(III) showing larger variation than Cp*Rh(III). The anomalously high diastereoselectivities observed with Ind* and Cp*^{Ph2} ligands result from greater slippage towards a (η^3 + η^2) in the favored insertion TS. This effect increases the diastereoselectivity by accommodating the methyl group of the cyclopropene in the TS leading to the major diastereoisomer. We

anticipate that this feature of the Ind* and Cp*^{Ph2} ligands can be the key element for future ligands design for related reactions.

Summary and Outlook

Over the past decade, Rh(III)-catalyzed C-H activation protocol has proven to be an attractive methodology to construct N-heterocycles. Our efforts in this area have centered on expanding the suitable partners for this reaction but also controlling the outcome of the transformation. With respect to the latter, we have found that modification of the cyclopentadienyl ring sometimes leads to significant improvements in:

- chemoselectivity – enoxyphthalimides lead to alkene cyclopropanation with Cp$^{i\text{-}Pr}$ but carboamination with Cp*$^{t\text{-}Bu}$;
- regioselectivity – aliphatic alkenes provide poor regioselectivity in dihydroisoquinolone synthesis with Cp*, but high selectivities with Cp^{t};
- diastereoselectivity – permethylated indenyl (Ind*) is optimal for cyclopropene insertion;
- reactivity – drastic reduction in reaction time when using Cp*^{CF3} for dihydropyridine synthesis; and
- reaction yield – many examples, with reasons difficult to conclusively determine, but may involve acceleration of slow steps or avoidance of catalyst decomposition pathways.

Of course, enantioselectivity is also a significant challenge in Rh(III) catalysis that has been addressed by ligand modification with the introduction of chiral Cp ligands on Rh or by embedding the Rh catalyst inside a protein to achieve an artificial metalloenzyme.[44]

The interplay of electronics and sterics on the cyclopentadienyl ring and its communication to the metal center is not always easy to interpret. To that end, we have assembled a panel of Cp^{X}Rh(III) catalysts and assessed their properties using a combined experimental and computational approach. This dataset allows an interpretation of reaction outcome using a multi-variate analysis. While the technique and the experimental approach are at an early stage, the results can be quite surprising and may lead to new mechanistic insight. Importantly, many of the underlying concepts in cyclopentadienyl ligand properties are not restricted to Rh(III) catalysis. It is likely that these findings translate well to other metals, and that the ligands described here will lead to breakthroughs in other fields.

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Biographies

Tiffany Piou obtained her M. Sc. Degree at University of Paris-Orsay. After graduation, she joined Jieping Zhu's group at ICSN at Gif-Sur-Yvette (France), and then moved with his group to EPFL (Lausanne, Switzerland) to complete her doctoral studies. Tiffany pursued her training in the group of Tomislav Rovis starting in 2013 at Colorado State University before moving with the group to Columbia University. In 2017, she joined Merck's process team in Rahway (NJ).

Tomislav Rovis was born in Zagreb, Croatia but raised in Southern Ontario, Canada. He conducted his undergraduate and graduate studies at the University of Toronto, and received his Ph.D. in 1998, working with Mark Lautens. Following postdoctoral studies with David Evans at Harvard, he began his independent career at Colorado State University in 2000. In 2016, he assumed his current position as Professor of Chemistry at Columbia University.

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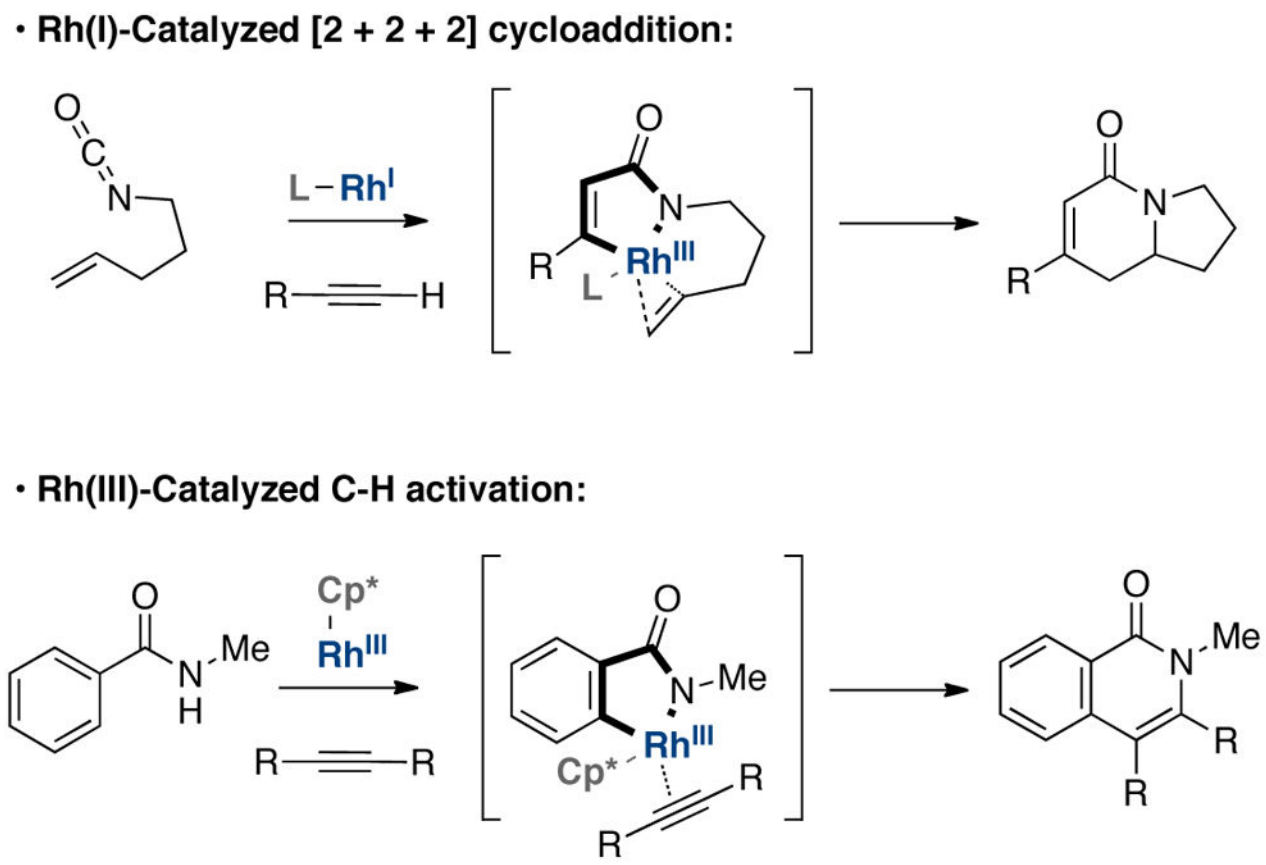

Figure 1.
Rh-Catalyzed N-Heterocycle Synthesis.

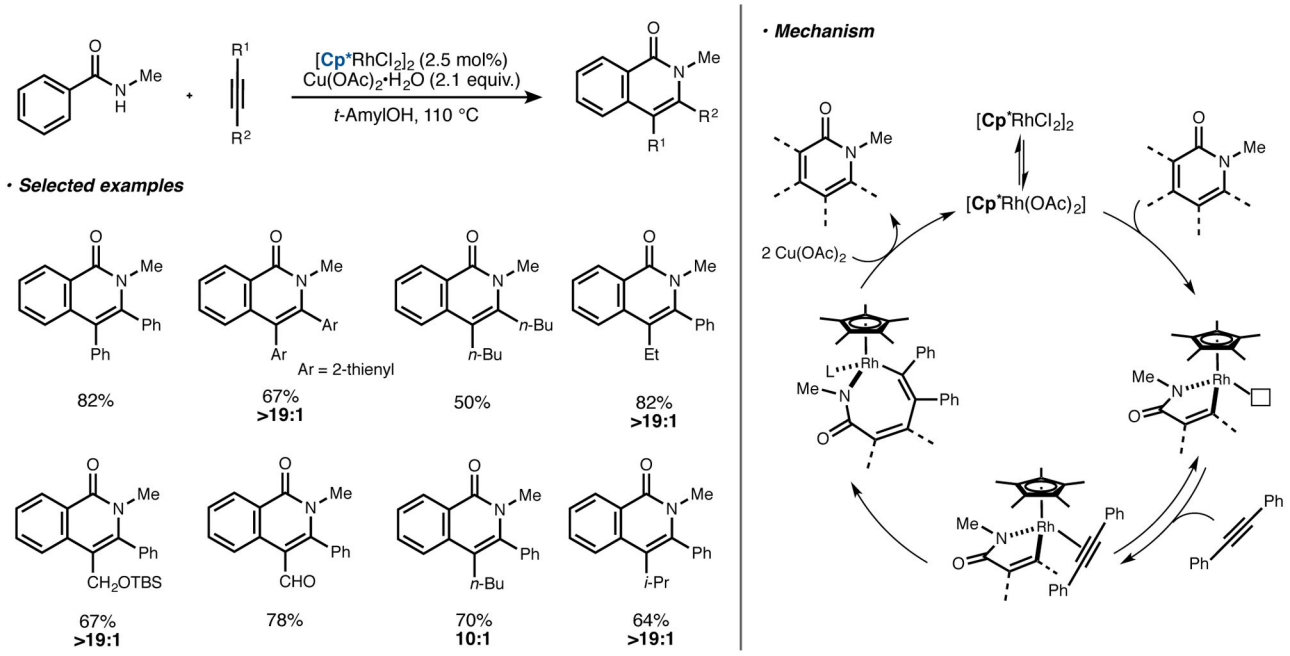

Figure 2.
Initial Discovery and Mechanism.

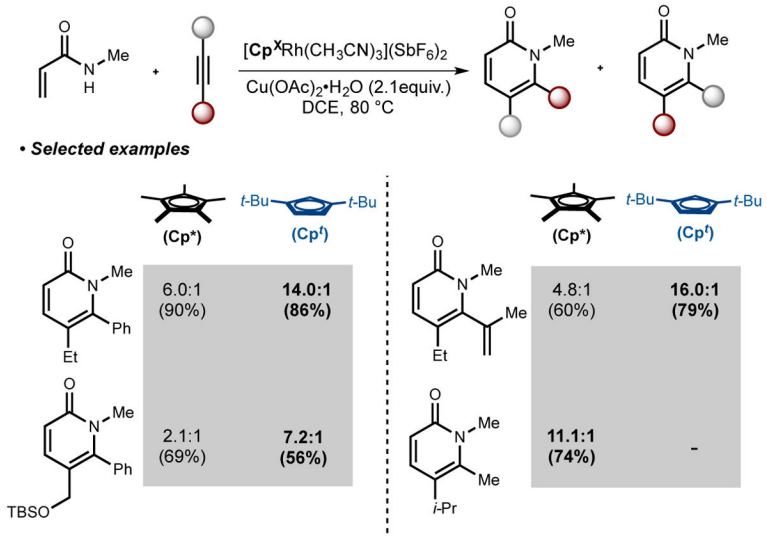

Figure 3.
Regioselectivity in the Coupling of Acrylamides with Alkynes

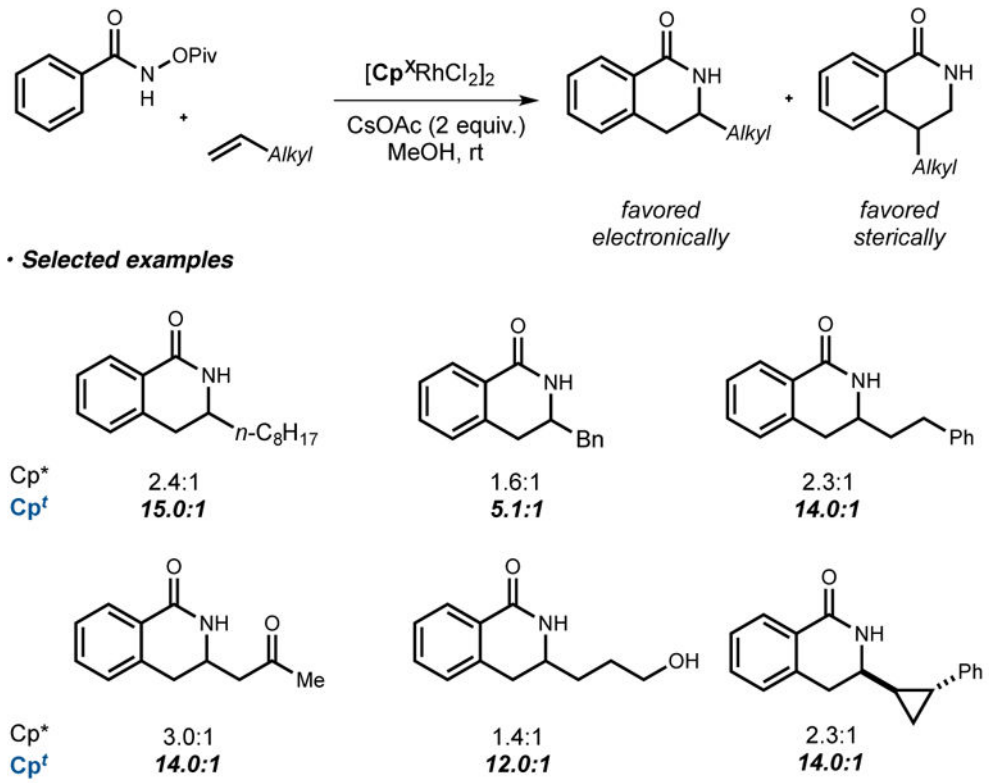

Figure 4.
Regioselectivity in the Coupling of Arylhydroxamate Esters with Alkyl Alkenes.

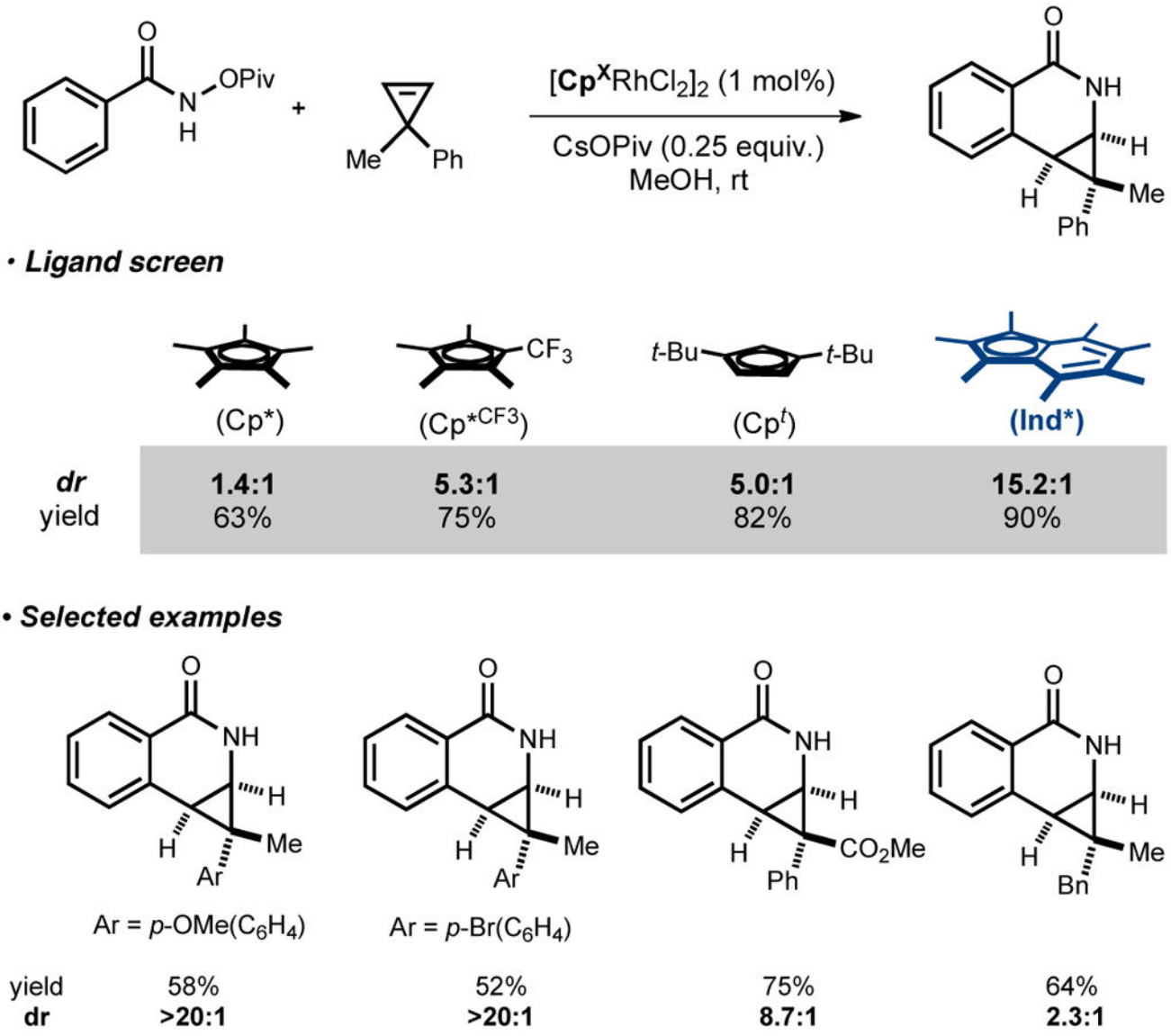

Figure 5.
Diastereoselectivity in the Coupling of Arylhydroxamate Esters with Cyclopropenes

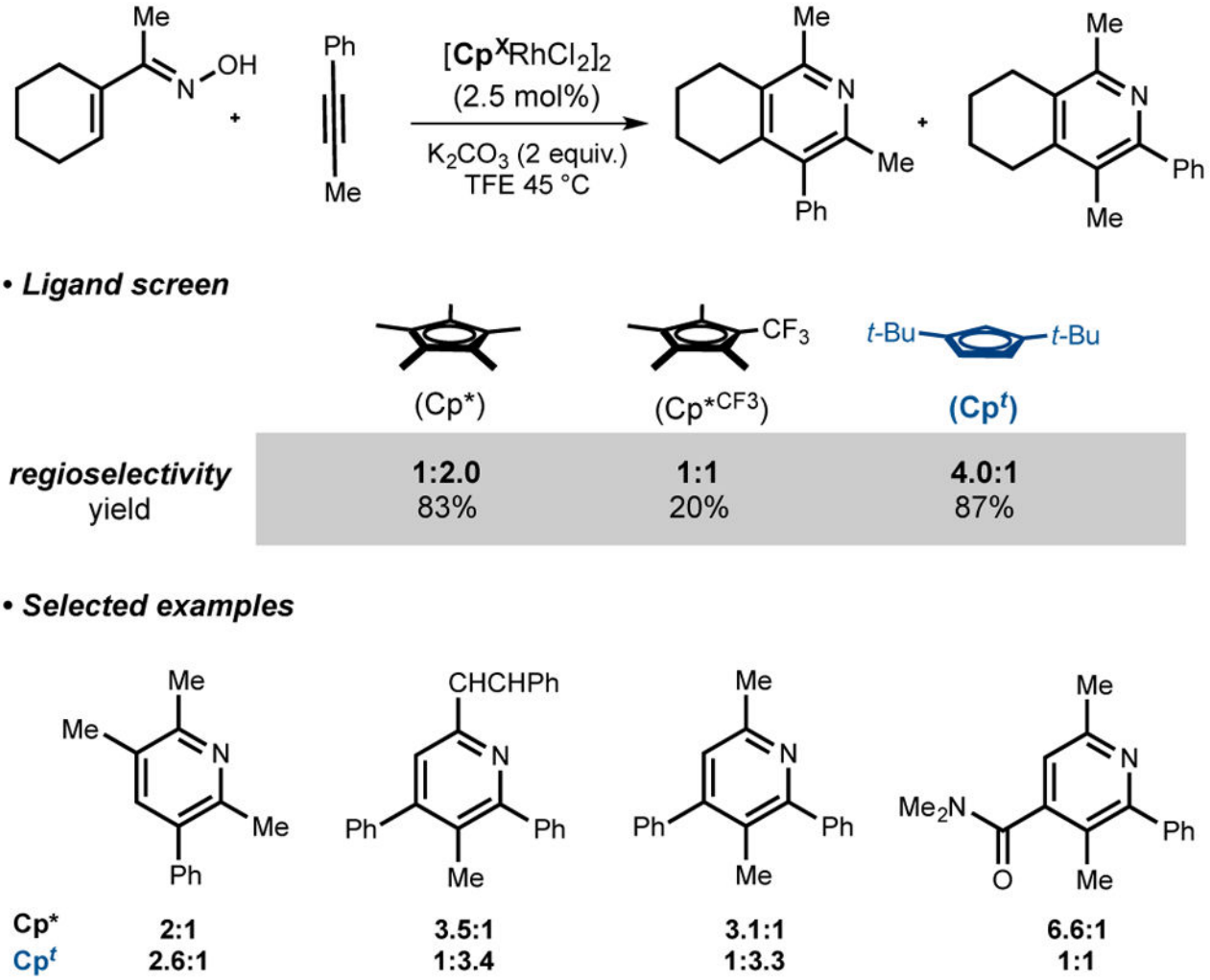

Figure 6.
Regioselectivity in the Coupling of α,β-Unsaturated Oximes and Alkynes

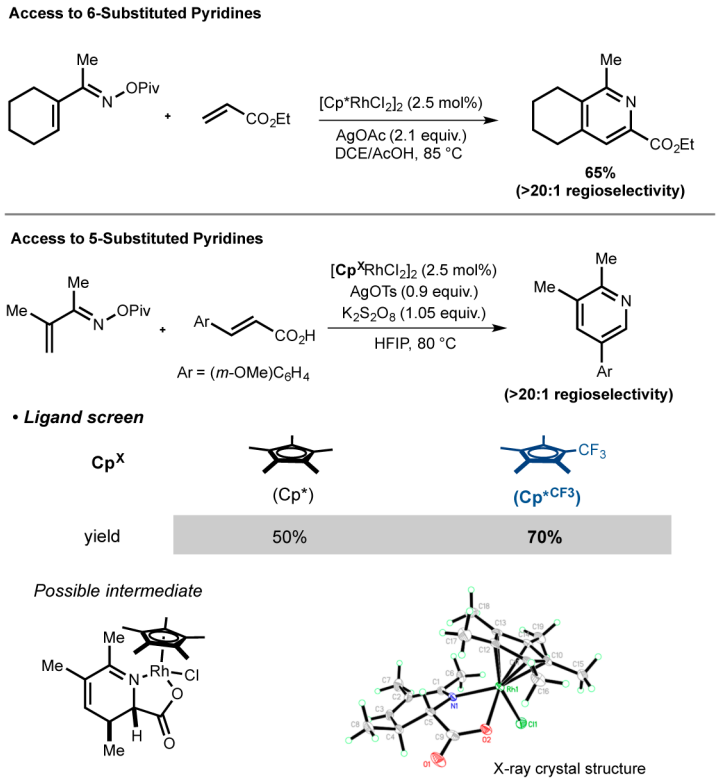

Figure 7.

Coupling of α,β-Unsaturated Oximes with Alkenes for the Selective Synthesis of 6- and 5-Substituted Pyridine Rings

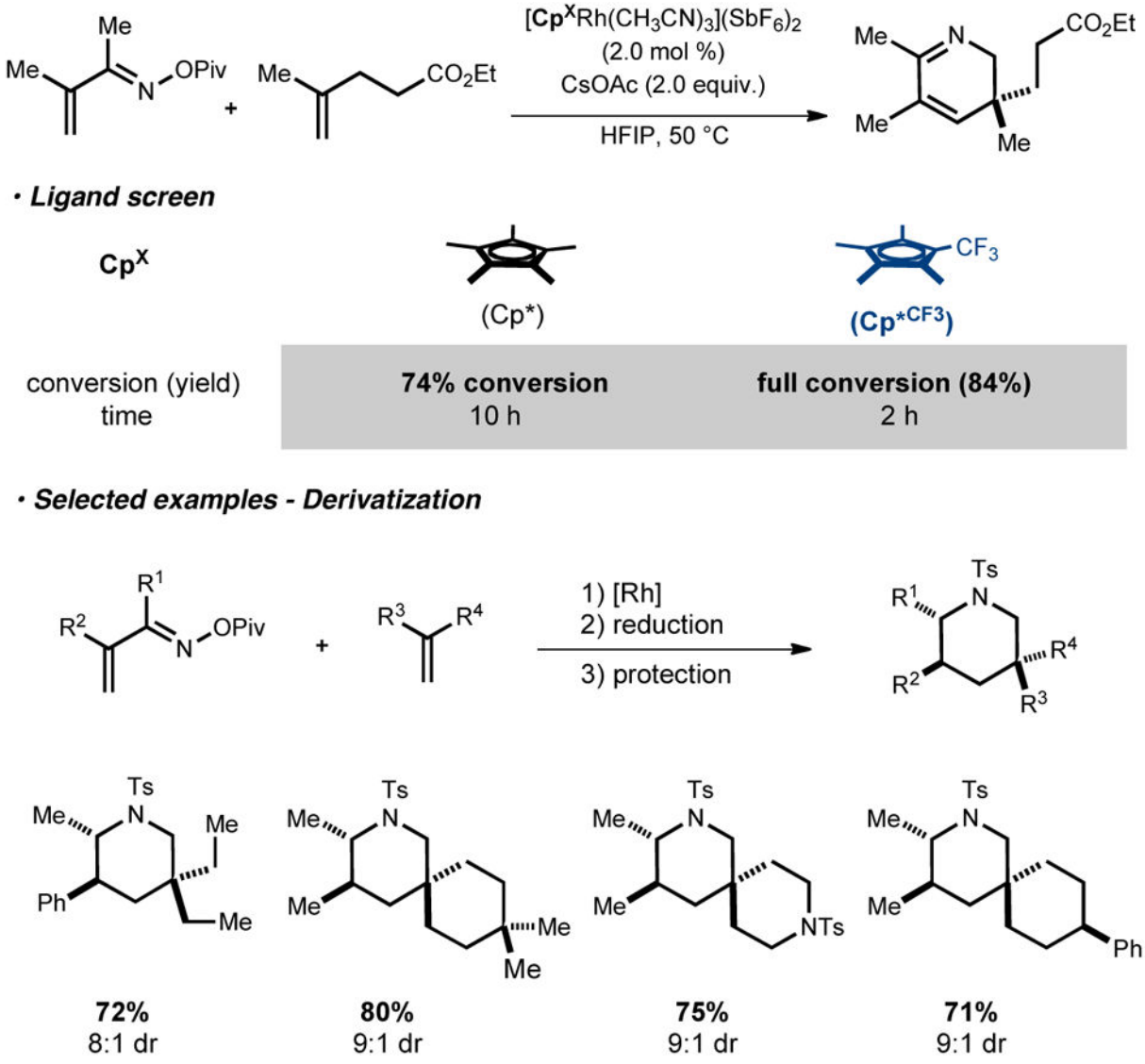

Figure 8.

Coupling of α,β-unsaturated Oximes with 1,1-Disubstituted Alkenes: Synthesis of 2,3-Dihydropyridines

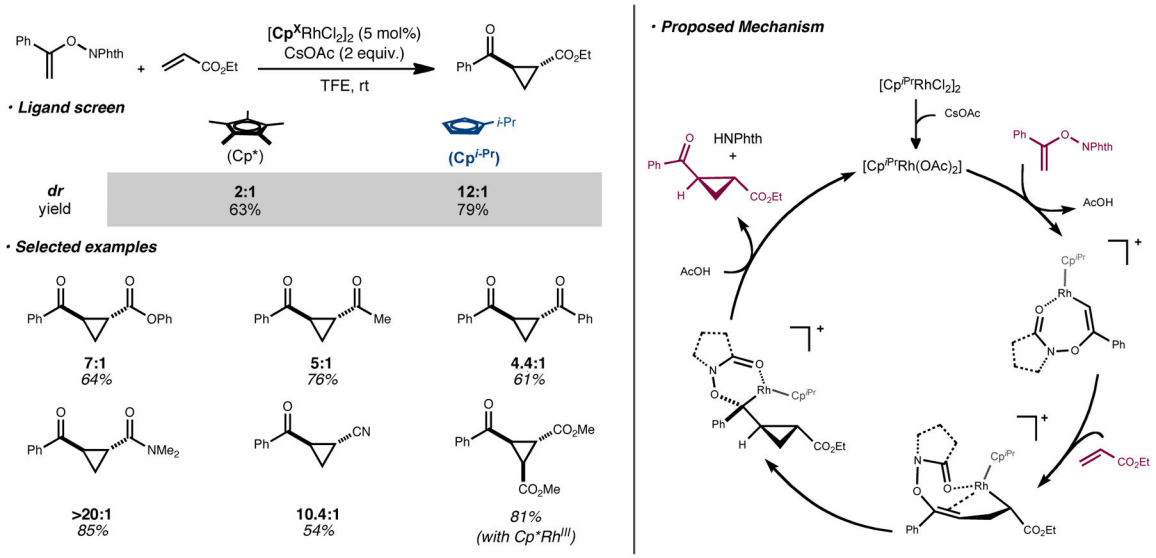

Figure 9.

Diastereoselectivity in Cyclopropanation Reaction: Coupling of N-Enoxyphthalimides with Alkenes

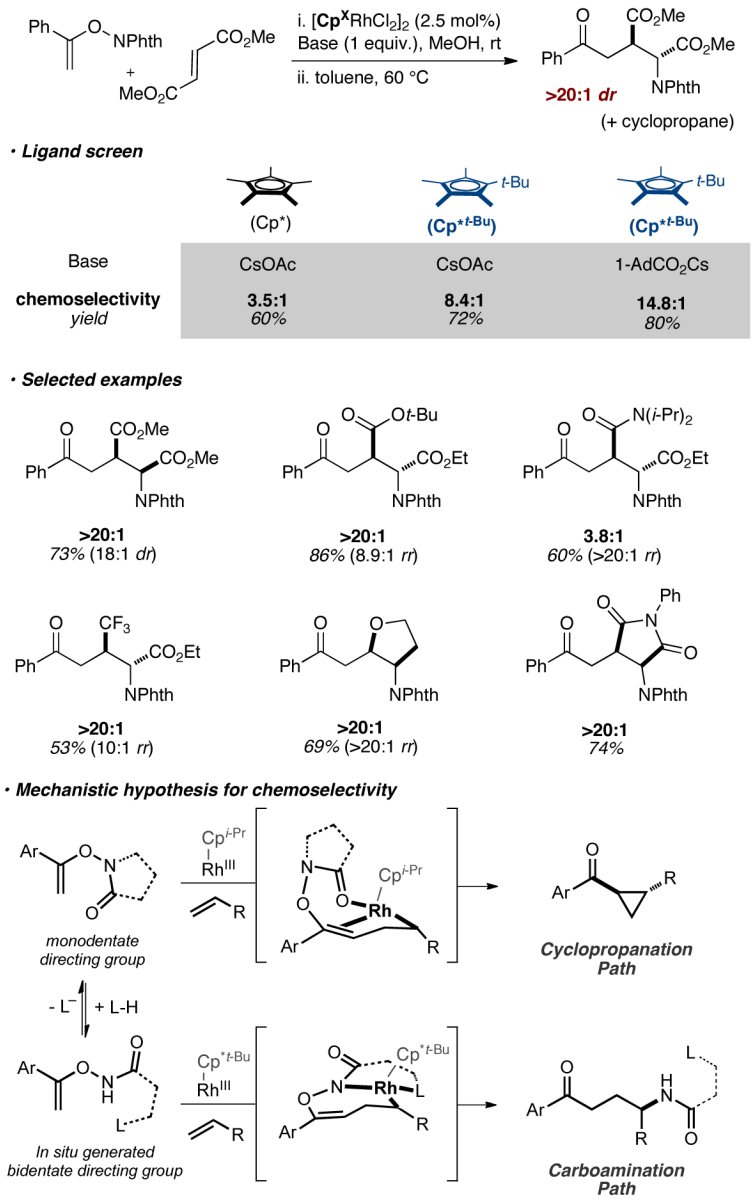

Figure 10.
Controlling Chemoselectivity in Intermolecular Carboamination Reaction

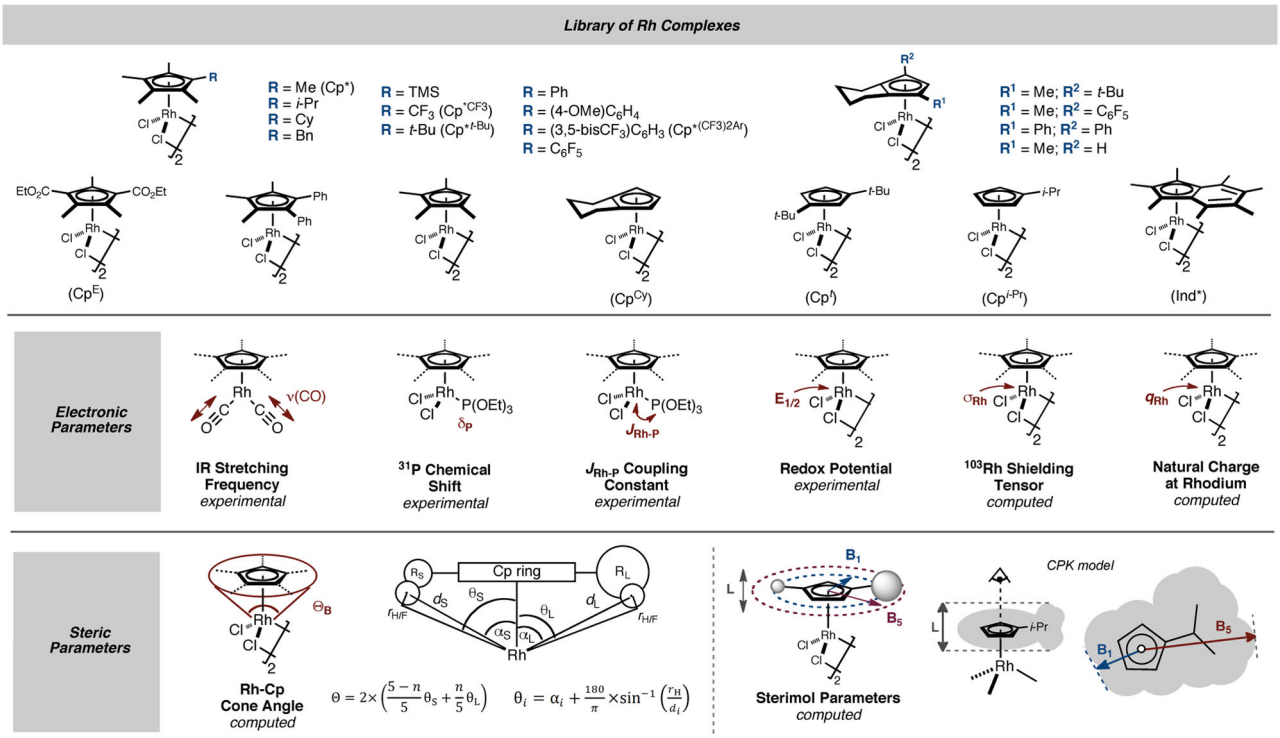

Figure 11.

Methods Employed for the Quantification of Electronic and Steric Properties of $Cp^{X}Rh(III)$ Catalysts

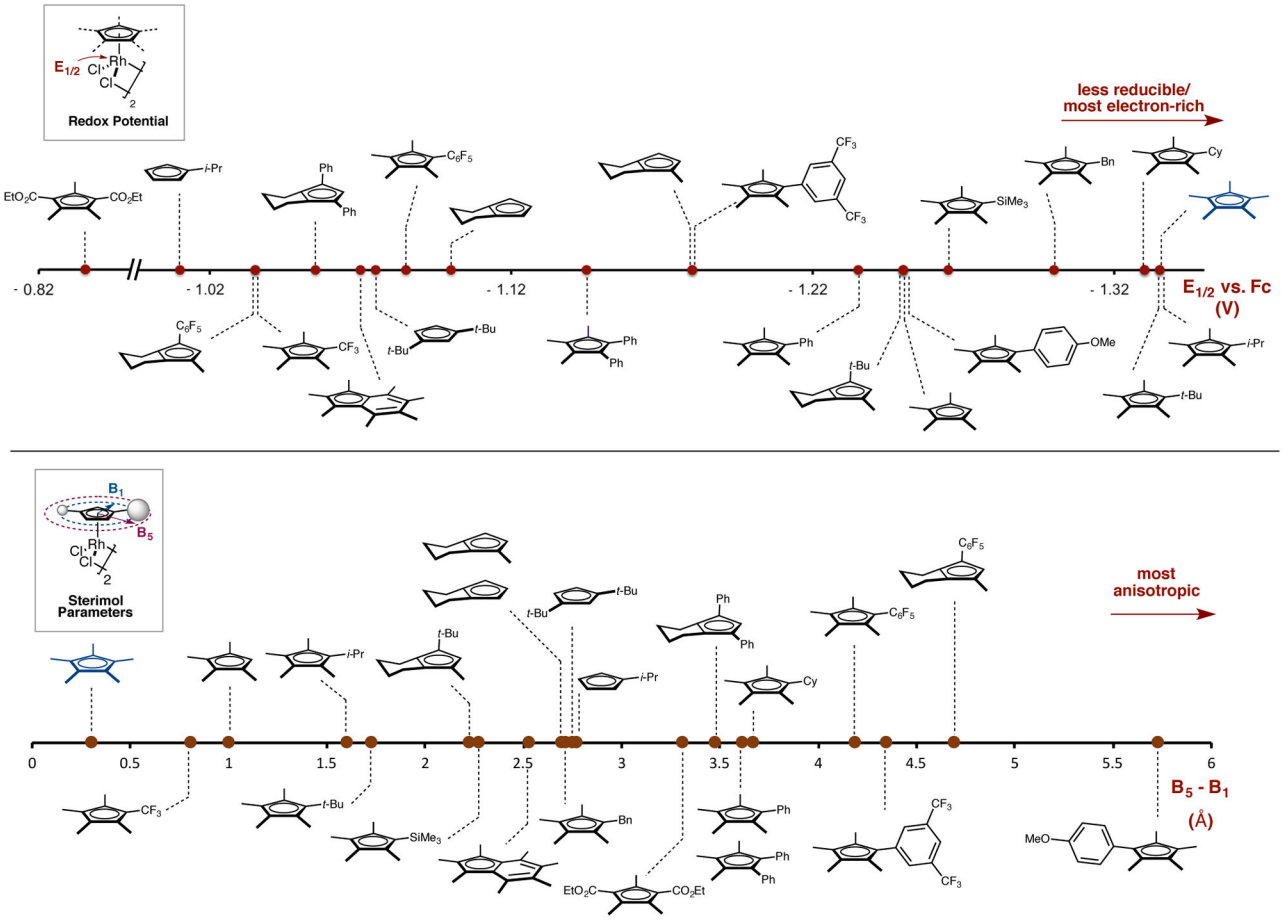

Figure 12.
Steric and Electronic Scales of $Cp^{X}Rh(III)$ Catalysts

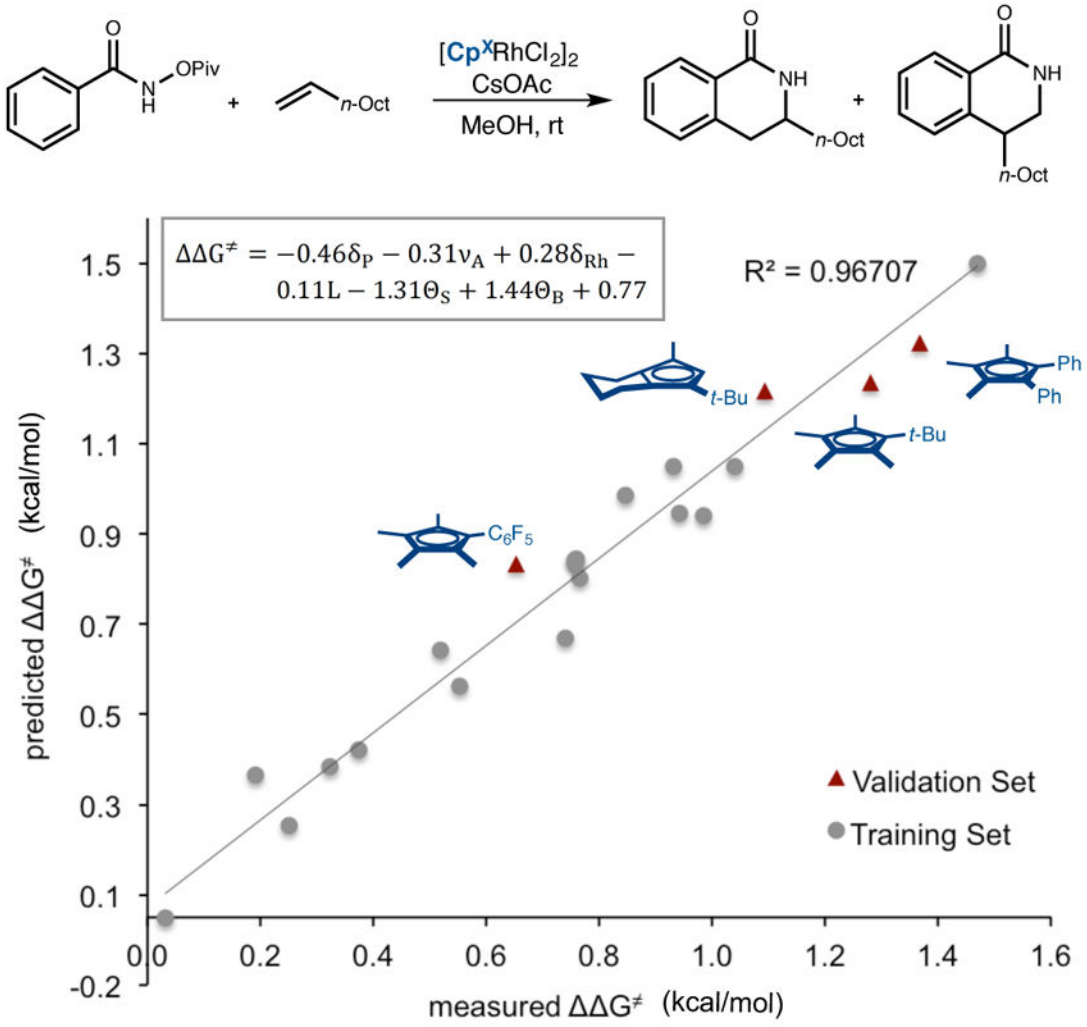

Figure 13.

Multivariate Regression of Regioselectivities in the Coupling of Arylhydroxamate Esters with 1-Decene

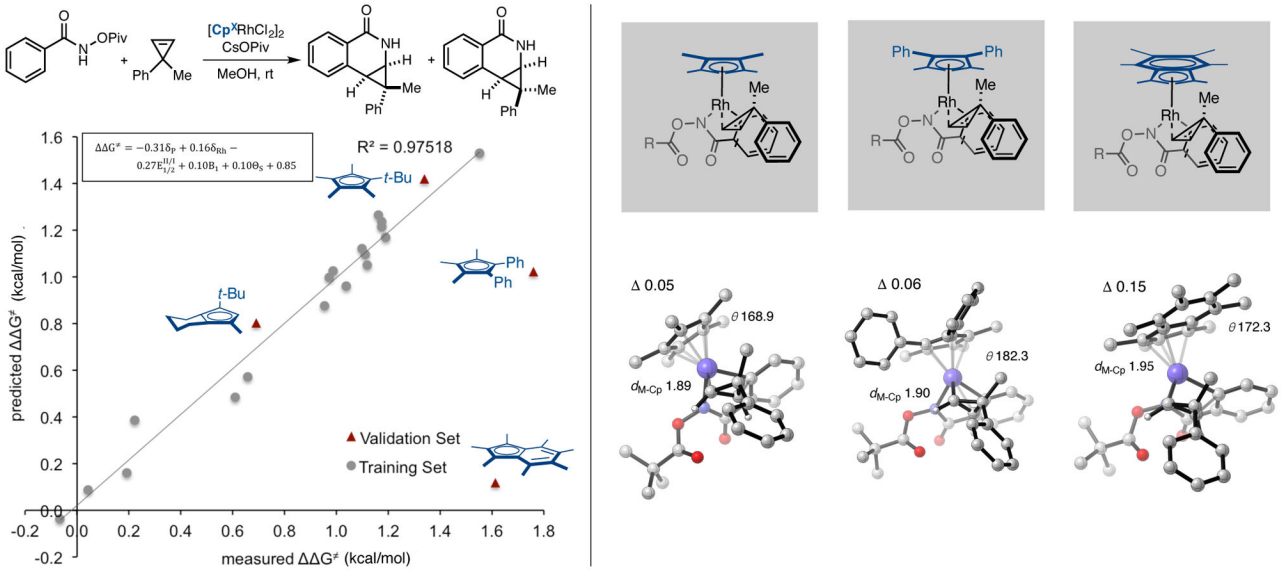

Figure 14.

Multivariate Regression of Diastereoselectivities of in the Coupling of Arylhydroxamate Esters with Cyclopropenes: A Switch in Mechanism