Finding Opportunities from Surprises and Failures. Development of Rhodium-Stabilized Donor/Acceptor Carbenes and their Application to Catalyst-Controlled C—H Functionalization.

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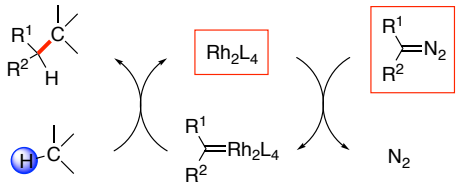
Supporting Information Placeholder

ABSTRACT: Catalyst-controlled C—H functionalization by means of the C—H insertion chemistry of rhodium carbenes has become a powerful synthetic method. The key requirements for the development of this chemistry are donor/acceptor carbenes and the chiral dirhodium tetracarboxylate catalysts. This perspective will describe the stages involved in developing this chemistry and illustrate the scope of the donor/acceptor carbene C—H functionalization.

Introduction

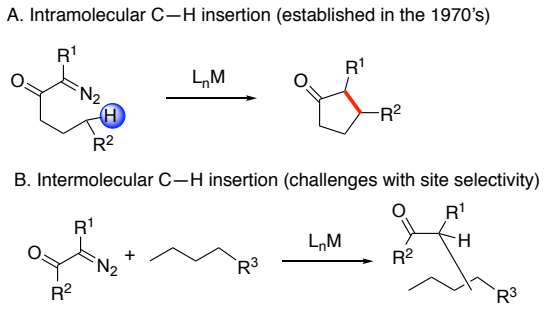
C—H Functionalization has become a very active field of study over the last 25 years because it offers a new logic for organic synthesis.[1] The most well-developed approaches to achieve site-selectivity rely on intramolecular reactions to place a specific C—H bond close to the reagent,[2] using directing groups to coordinate to a metal catalyst and place it in proximity of a specific C—H bond,[1d, 3] or radical chemistry, where specific C—H bonds are inherently more reactive than the other C—H bonds in the substrate.[4] An intriguing alternative approach is to move away from the substrate being the dominant controlling element for the site selectivity and instead rely on catalysts and/or reagents that would select which C—H bond is functionalized.[5] This perspective describes our development of a catalyst-controlled intermolecular C—H alkylation method using rhodium carbenes as the reactive intermediates (Scheme 1). To achieve such a transformation we required a new class of rhodium carbenes, the donor/acceptor carbenes, reactive enough to functionalize C—H bonds, but still capable of doing so in a selective manner. Also, a collection of new chiral dirhodium catalysts were needed with defined structural features to control which C—H bond is functionalized. This program began over 30 years ago and at the onset of the work, the intent was simply to explore new carbene chemistry. During the course of these studies, however, a number of the proposed reactions failed and surprising results were obtained. As the general area of chemistry was relatively unexplored, these "failures" opened up interesting new opportunities in synthesis, which ultimately led to the C—H functionalization method described herein. The key discoveries which ultimately resulted in the highly selective intermolecular C—H functionalization method will be highlighted in this perspective.



Scheme 1

The first example of C—H functionalization by means of metal-carbene induced C—H insertion was reported by Scott in 1974 for a copper-catalyzed reaction of ethyl diazoacetate with cyclohexane as solvent.[6] Soon, thereafter, Teyssié demonstrated that the dirhodium tetracarboxylates were even better

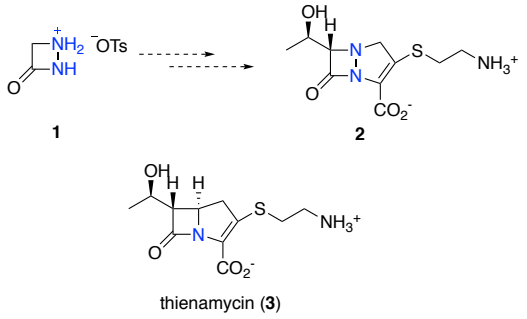
catalysts for C—H insertions into alkanes, but generally the reactions gave mixtures of products when the substrates contained multiple C—H bonds.[7] To overcome the site selectivity issue, the intramolecular version of the reaction was developed in the 1980's and 1990's, most notably by the groups of Taber, Doyle and Hashimoto, and this intramolecular version has become a broadly useful synthetic process (Scheme 2A).[2a, 8] However, the intermolecular version remained relatively undeveloped because the site selectivity issues could not be effectively controlled (Scheme 2B).[9] Indeed, in Doyle's comprehensive book on the chemistry of diazo compounds, published in 1997, it was stated that "*intermolecular C—H insertions are of mechanistic interest but are not synthetically useful*".[10] Ironically, our first publication on enantioselective intermolecular C—H functionalization with rhodium carbenes was also published in the same year,[11] but a considerable amount of earlier work brought us to the position of being able to solve the selectivity challenges.



Scheme 2

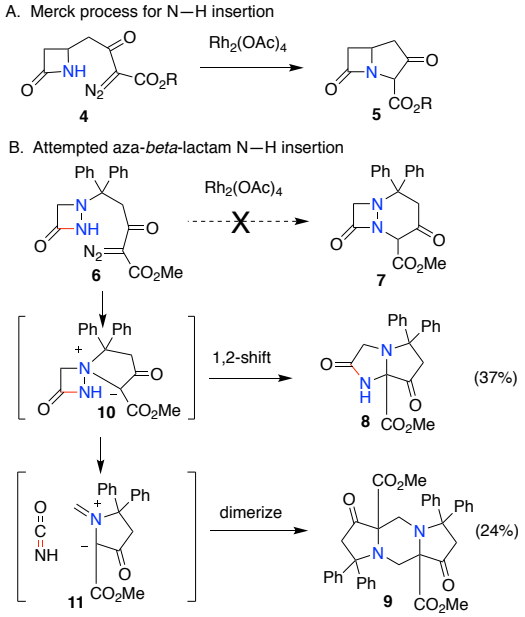
Early Exposure to Rhodium Carbene Chemistry

The genesis of the ideas for an independent research career often occurs during one's graduate or post-doctoral studies. In my case, it originated during my post-doctoral studies at Princeton University (1980-1983) with Professor E. C. Taylor, an expert in nitrogen rich heterocycles. During my time in his laboratory, he had two collaborative medicinal chemistry projects supported by Eli Lilly. The first was the study of pteridine derivatives, which ultimately resulted in the development of a major anticancer agent, Alimta (premetrexed).[12] The second involved aza-β-lactams (**1**) and their conversion into aza analogues **2** of β-lactam antibiotics such as thienamycin (**3**) (Scheme 3). I chose to work on the second project because I was attracted to strained rings, but it quickly became apparent that the aza-β-lactam ring was likely to be too fragile to lead to a potential drug candidate, especially as the fusion of a second ring system onto it would add considerable strain to an already delicate system.



Scheme 3

As the desired targets of the project were likely to be unreachable, a different outlook was needed for this project to be successful. I decided to apply the best annulation methods known at the time for the synthesis of fused β-lactams to the aza-β-lactam system because the contrast between successful reactions with β-lactams and the anticipated failed reactions with aza-β-lactams was likely to be mechanistically interesting and potentially insightful. Indeed, a number of unusual transformations were discovered,[13] but in the context of this perspective, the most relevant one came during efforts to mimic the dirhodium-catalyzed carbene N—H insertion approach (**4** to **5**) developed by Merck,[14] a transformation that was ultimately applied to the large scale synthesis of penem antibiotics (Scheme 4). The Merck industrial approach was audacious because it required large-scale utilization of diazo compounds and at that time, a relatively newly developed catalyst, dirhodium tetraacetate. Application of this method to the aza-β-lactam **6**, generated none of the desired N—H insertion product **7**.[13a] Instead, a mixture of the fused pyrrolidinone **8** and the tricyclic system **9** was obtained. The likely cause of the unexpected products is the preferential attack of the carbene by the more nucleophilic amine nitrogen to form ylide **10**, which then underwent a Stevens rearrangement to form **8** or elimination of isocyanic acid to form a second ylide **11**, which dimerized to form **9**.



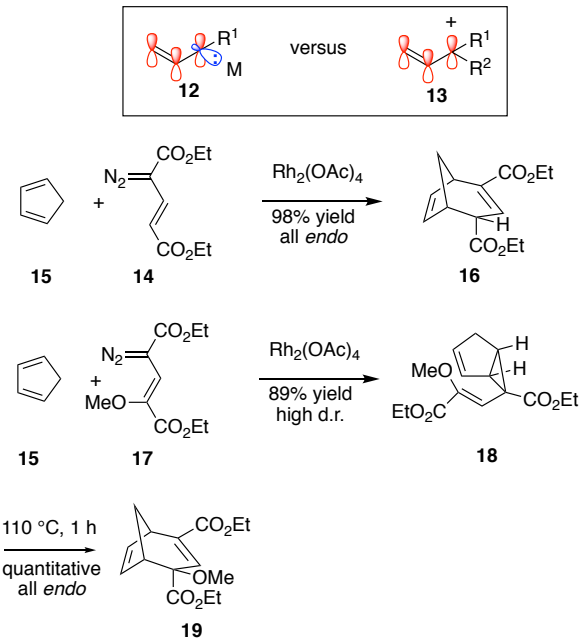
Scheme 4

Even though the reaction outcome was a complete failure in terms of the synthetic goals of the project, it was intriguing to me for several reasons:

- Rhodium acetate gives much cleaner reactions compared to the traditional copper catalysts, and so there appeared to be an opportunity for a new era of discovery in metal carbene chemistry.
- The amide bond in the aza-β-lactams remained intact. When one is considering normal nucleophilic behavior, the weakest link in β-lactams is the amide bond, yet even though the formation of **8** and **9** involve elaborate rearrangement pathways, the amide bond never broke.
- Carbenes derived from diazo esters have natural *umpolung* reactivity. The site next to the ester is electrophilic, which is likely to lead to unusual disconnection strategies for organic synthesis
- Carbenes are prone to undergo unusual reactions, and this could lead to unexplored avenues for methodology development
- Even though the carbene chemistry involves highly reactive organometallic intermediates, the chemistry is procedurally very simple and does not require any specialized equipment.

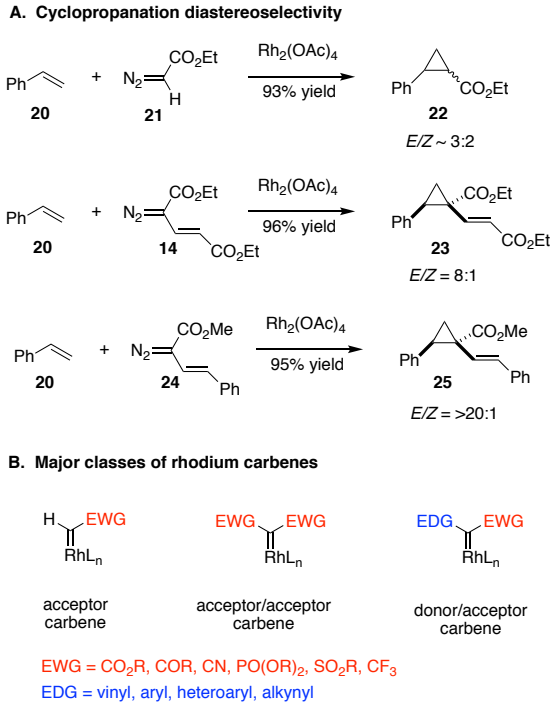
Discovery of Donor/Acceptor Carbenes

When I started my independent career at Wake Forest University in 1983, I decided to make rhodium-carbene chemistry the central focus of my research program. The first question that needed to be answered, however, was what specific carbene reaction would I examine? At that time, the vast majority of the metal-carbene chemistry was derived from diazo compounds substituted with one or two electron withdrawing groups, such as diazoacetates, diazomalonates or α-diazo-β-ketoacetates. I wanted to explore other carbene structural types and so, decided to examine whether vinylcarbene **12** could act as a 2π system similar to allyl cation **13**, and be capable of undergoing [4+3] cycloadditions (Scheme 5).[15] The first vinylcarbene precursor we made was diazo glutaconate **14** and we examined its rhodium acetate-catalyzed reaction with cyclopentadiene **15**. The result was spectacular! The desired [4+3] cycloadduct **16** was formed in essentially quantitative yield, exclusively as the *endo* diastereomer. We were worried, however, because the result seemed too good to be true! Cycloaddition reactions, such as the Diels-Alder reaction, tend to form preferentially the *endo* diastereomer and the stereospecific nature of our reaction was highly unusual. Therefore, we began to consider whether the reaction may have occurred by a different mechanism, an initial cyclopropanation, followed by a Cope rearrangement. It is well known that the Cope rearrangement of divinylcyclopropanes proceeds through a boat transition state, and thus, it would explain why the formation of **16** is stereospecific. This hypothesis was tested by conducting the reaction with the *cis*-substituted vinyldiazoacetate **17** because *cis* substituents are known to sterically interfere and slow down the rate of divinylcyclopropane rearrangements. This control experiment resulted in the clean formation of the *cis*-divinylcyclopropane **18**, which on heating in refluxing toluene underwent the Cope rearrangement to form the formal [4+3] cycloadduct **19** as a single diastereomer. Thus, we had obtained exactly what we had proposed from the vinylcarbene 2π system, but the reaction actually proceeds by a totally different mechanism.



Scheme 5

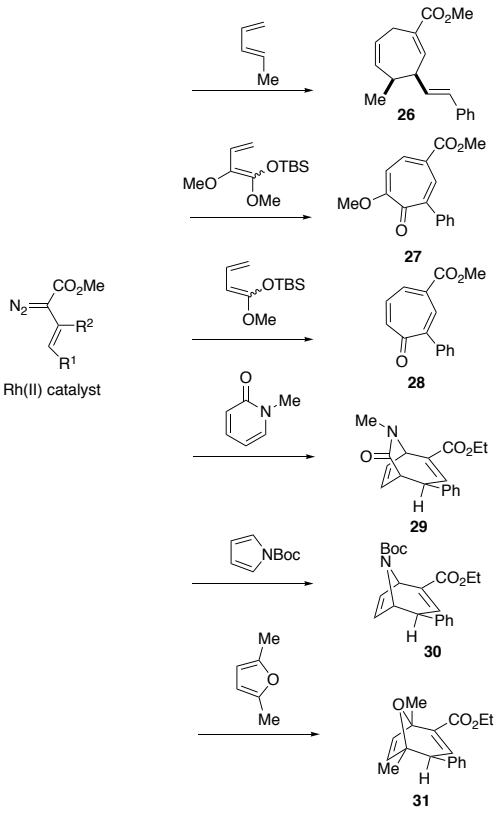
Even though the control experiment was very informative, it raised another area of concern. The cyclopropanation must have been highly diastereoselective, yet the literature precedence showed that this was not typically the case for rhodium-catalyzed cyclopropanations. For example, the rhodium-catalyzed cyclopropanation of styrene (**20**) with ethyl diazoacetate (**21**) gave the cyclopropane **22** as a 3:2 mixture of diastereomers (Scheme 6A).[16] Therefore, we examined the reaction of styrene (**20**) with **14** and found that cyclopropanation was much more diastereoselective.[17] The cyclopropane **23** was produced as a 8:1 diastereomeric mixture. When the reaction was conducted with styryldiazoacetate **24**, which has a stronger donor group, the cyclopropane **25** was formed in a highly diastereoselective manner with >20:1 d. r. Furthermore, the carbene dimerization problem that is often seen in reactions with ethyl diazoacetate were greatly reduced with the vinyldiazoacetate **14** and **24**. This led to the realization that the presence of the donor group has a major influence on the reactivity/stereoselectivity profile of the carbenes and this could open up interesting opportunities for the discovery of selective carbene transformations. Thus donor/acceptor carbenes became the central focus of my research program. We introduced a classification system for the three major types of metal carbene intermediates: acceptor, acceptor/acceptor and donor/acceptor (Scheme 6B), because the three types of carbenes have very different reactivity profiles.[18] We have emphasized this classification system in the various reviews we have published on rhodium carbene chemistry, and it has become a commonly used terminology for the field.[19] All three types of carbenes are very reactive, but the donor group attenuates the reactivity of the donor/acceptor carbenes, leading to more selective transformations, especially in the case of intermolecular reactions.



Scheme 6

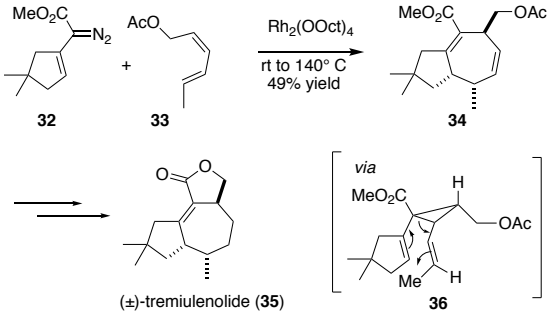
Development of the Tandem Cyclopropanation/Cope Rearrangement and Some Unexpected Observations.

The tandem cyclopropanation/Cope rearrangement can be widely applied to the synthesis of seven membered rings, generating up to three stereogenic centers in a stereospecific manner.[20] We conducted an extensive study on the scope of the reactions and showed a variety of dienes are compatible with the chemistry as illustrated in the formation of **26-31** (Scheme 7). The reaction with oxygenated dienes can lead to the synthesis of tropones[21] or tropolones.[22] A range of aromatic heterocycles are compatible with the chemistry,[23] including furans,[24] pyrroles[25] and pyridinones.[26] Even benzene is prone to the tandem cyclopropanation/Cope rearrangement although electron-rich aromatic rings lead to alkylation products formed by means of zwitterionic intermediates instead of initial cyclopropanation.[27]



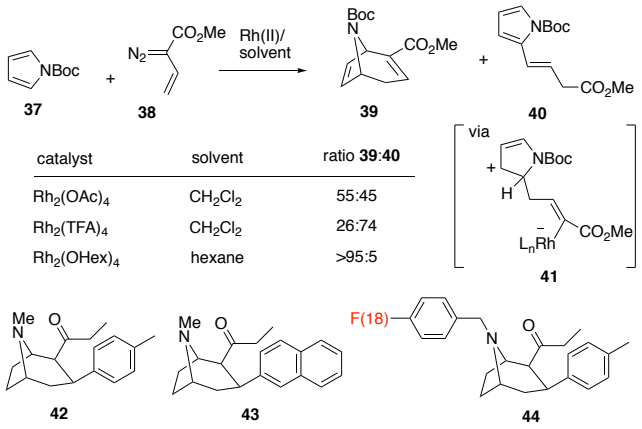
Scheme 7

During the studies of the reactions with dienes we learned that donor/acceptor carbenes unexpectedly displayed demanding steric effects. The regiochemistry of the formal [4+3] cycloaddition depends on which double bond of the diene is cyclopropanated.[20a] An unsubstituted double bond is easily cyclopropanated as well as an internally substituted double bond. A *cis* disubstituted double bond is less reactive than a mono-substituted double bond, whereas reaction at a *trans* double bond is considerably less favorable. An example, illustrating the significance of the steric effect, was seen in the reaction of the cyclopentenyldiazoacetate **32** the (*E*,*Z*)-hexadiene **33**, which generated the cycloheptadiene **34** as a key step in the synthesis of (±)-tremulenolide (**35**) (Scheme 8).[28] The reaction proceeds via the intermediacy of the divinylcyclopropane **36** in which the *cis* alkene has been cyclopropanated selectively, setting up both the high regiocontrol and diastereocontrol of the reaction. The high regioselectivity observed with these donor/acceptor carbenes is far more pronounced than what is typically seen in rhodium catalyzed cyclopropanations with the acceptor carbene derived from ethyl diazoacetate.



Scheme 8

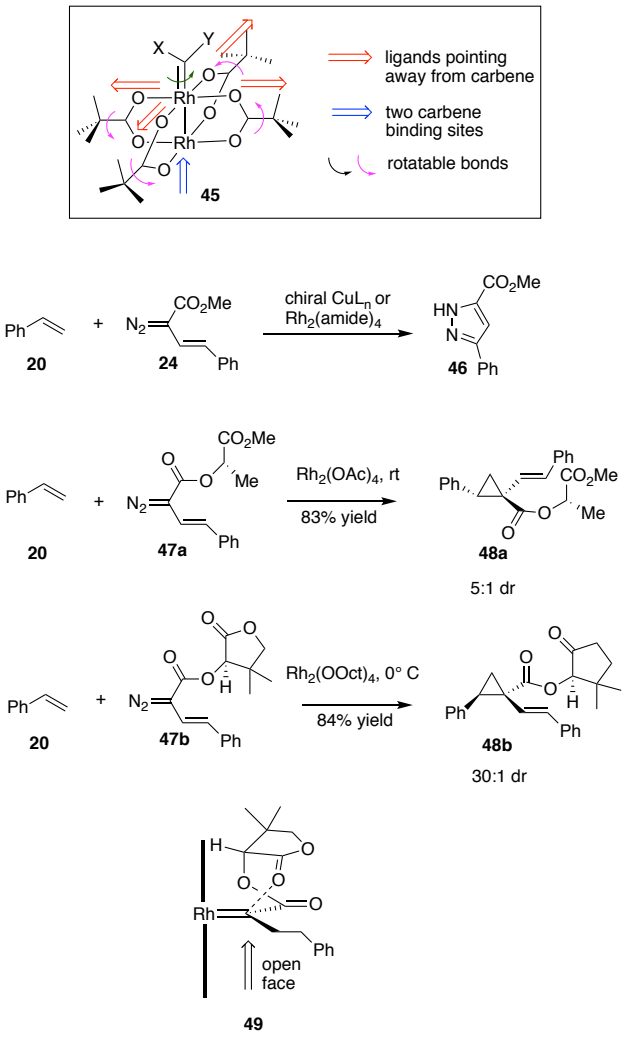
Another surprising discovery during the early development of the vinylcarbenes is the tendency of the unsubstituted vinylcarbenes to react at the vinylogous position rather than the carbene site.[29] This type of reactivity was later developed by us[30] and others[31] into a useful synthetic transformation but that topic is outside the scope of this perspective. An early example of this phenomenon is the reaction of *N*-Boc-pyrrole (**37**) with the vinyldiazoacetate **38**, which gave a mixture of the formal [4+3] cycloadduct **39** and the vinylogous alkylation product **40** (Scheme 9).[29b] Fortunately, the ratio of the products can be controlled by the right combination of catalyst and solvent. The formation of the vinylogous product is considered to involve the zwitterionic intermediate **41** and is enhanced when a relatively polar solvent such as dichloromethane and an electron-deficient catalyst such as $Rh_2(TFA)_4$ are used. The selectivity for reactions at the carbene site is enhanced when a non-polar solvent is used, such as pentanes or hexanes. The effective control of site selectivity of unsubstituted vinyl carbenes was important because the reaction with pyrrole became a useful entry to molecular probes and potential therapeutic agents for cocaine addiction.[32] For example the tolyl derivative **42** has been extensively studied as a potential therapeutic agent to block cocaine self-administration,[32b, 32c] the 1-naphthyl derivative **43** is highly potent and has been used as a chemical knockout of the dopamine transporter,[32d] and **44** has been used as a PET radioligand.[32e] Ironically, due to the enhancement of the carbene reactivity over vinylogous reactivity, pentane and hexanes became the routine solvent for the rhodium-catalyzed reactions of donor/acceptor carbenes. The donor/acceptor carbenes are sufficiently selective to react cleanly with the π-system substrates without interference from the hydrocarbon solvents.



Scheme 9

Dirhodium Tetraprolinates as Chiral Catalysts for Donor Acceptor Carbenes.

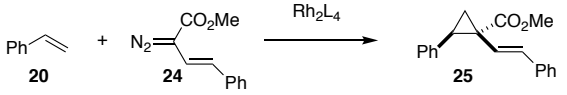
Even though dirhodium tetracarboxylates quickly became widely used as the catalysts of choice for the reactions of diazo compounds, in the early 1990's their lantern structure (**45**) was not considered to be particularly promising for the design of chiral catalysts.[33] The carbene would have two possible binding sites and the carboxylate ligands would be pointing away from the carbene (Scheme 10). A study of enantioselective cyclopropanation of styrene with ethyl diazoacetate with 40 different chiral dirhodium catalysts gave a maximum of 12% ee,[34] and the only reasonable enantioselective reactions with dirhodium tetracarboxylates that were known at that time were intramolecular reactions.[35] Chiral catalysis for intermolecular carbene chemistry were dominated by C_2 symmetric copper catalysts and dirhodium tetracarboxamidate catalysts.[19a] We became interested in achieving asymmetric transformations with the donor/acceptor carbenes but when these types of catalysts were applied to vinyldiazoacetate cyclopropanation, none of the cyclopropane was formed.[36] Instead the vinyldiazoacetate **24** underwent a thermal 6π electrocyclization to form pyrazole **46** because the catalysts were not sufficiently active to generate a rhodium carbene intermediate before the thermal cyclization occurred. Therefore, we needed to explore another approach to achieve asymmetric induction. Chiral auxiliaries had not been particularly successful in carbene chemistry before but we discovered methyl (*S*)-lactate (**47a**) and (*R*)-pantolactone (**47b**) were particularly effective with donor/acceptor carbenes as illustrated in the formation of the cyclopropanes **48a** and **48b**.[36] A model (**49**) was proposed to explain the asymmetric induction in which the carbonyl of the ester auxiliary interacts with the carbene to block one face of attack but the carbonyl interactions is limited and does not go all the way to an ylide intermediate. Even though the chiral auxiliary approach was successful with a variety of substrates,[37] the timing of this work was not ideal. It occurred during the era where the use of chiral catalysis was starting to dominate over the use of chiral auxiliaries, and so we still needed to solve the chiral catalysis problem.

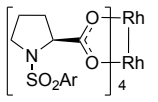


Scheme 10

The copper and rhodium carboxamidate catalysts are sluggish compared to the dirhodium tetracarboxylate catalysts.[36] Therefore, we needed to return to the dirhodium tetracarboxylates as the scaffold for chiral catalysis, even though the established precedence was not promising. We made the hypothesis that the background precedence on acceptor carbenes may not be relevant to the reactions of donor/acceptor carbenes because the reactivity profile between the two classes of carbenes is very different. This turned out to be a good decision because when we conducted the first cyclopropanation with the *N*-phenylsulfonyl prolinate dirhodium catalyst Rh_2(*S*-BSP)$_4$ (**50**) in dichloromethane as solvent (Scheme 11), the product was formed in 74% ee![38] We quickly discovered that the enantioselectivity was far superior in non-polar solvents such as pentane and consequently, we developed the *tert*-butylphenyl derivative Rh_2(*S*-

TBSP)$_4$ (**51**) and then the dodecylsulfonylprolinate Rh$_2$(*S*-DOSP)$_4$ (**52**), which are soluble in hydrocarbons even at low temperatures. The solvent change resulted in the formation of the cyclopropane **25** in 90% ee at rt and 98% ee when the reaction was started at -78 °C and allowed to gradually warm to rt. Highly enantioselective cyclopropanations are possible with a variety of alkenes and vinyldiazoacetates, aryldiazoacetates, hetereoaryldiazoacetates and alkynyldiazoacetates.[18, 39] The alkenes need to be 1-substituted, 1,1-disubstituted[39c] of cis-1,2-disubstituted as trans-1,2-disubstituted[39e] or more highly substituted alkenes are generally too sterically crowded for cyclopropanation. Particularly noteworthy is the reaction of 1,1-diphenylethylene which is highly enantioselective and as will be described later, became the foundation of a new class of catalysts that are very important for site-selective C—H functionalization. It has also been widely used in enantioselective versions of the tandem cyclopropanation/Cope rearrangement, leading to the formation of the cycloheptadiene derivatives with high asymmetric induction.[40]





Ar = C_6H_5 Rh$_2$(*S*-BSP)$_4$ (**50**)

Ar = *p*-^{t}BuC_6H_4 Rh$_2$(*S*-TBSP)$_4$ (**51**)

Ar = *p*-$C_{12}H_{25}C_6H_4$ Rh$_2$(*S*-DOSP)$_4$ (**52**)

Rh_2L_4	solvent	temp, °C	ee, %
Rh$_2$(*S*-PSP)$_4$	CH_2Cl_2	rt	74
Rh$_2$(*S*-TBSP)$_4$	pentane	rt	90
Rh$_2$(*S*-DOSP)$_4$	pentane	rt	87
Rh$_2$(*S*-DOSP)$_4$	pentane	-78° - rt	98

Scheme 11

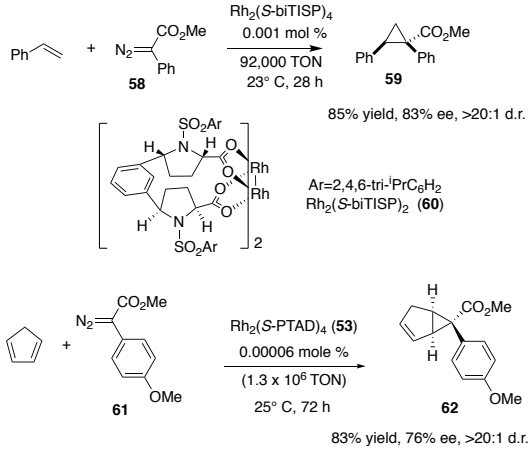
Rh$_2$(*S*-DOSP)$_4$ routinely gives high asymmetric induction as long as the donor/acceptor carbenes has a methyl ester as the acceptor group.[19a] Another catalyst, Rh$_2$(*S*-PTAD)$_4$ (**53**) was developed and it is capable of high asymmetric induction with donor/acceptor carbenes containing a variety of acceptor groups (Scheme 12).[41] Rh$_2$(*S*-PTAD)$_4$ is related to the series of phthalimido catalysts developed by Hashimoto,[42] but the adamantyl group in Rh$_2$(*S*-PTAD)$_4$ tends to give higher asymmetric induction than the Hashimoto catalysts, which have smaller alkyl groups. Excellent asymmetric induction was obtained in cyclopropanations with aryldiazophosphonates **54**,[41] aryldiazoacetonitriles **55**,[43] and trifluoromethylphenyldiazomethanes **56**,[44] and aryldiazoketones **57**.[45]

Rh$_2$(S-PTAD)$_4$ (**53**)

Compound	EWG	Yield, %	d.r	ee, %
54	$PO(OEt)_2$	86	>30:1	99
55	CN	up to 90	up to >30:1	up to 90
56	CF_3	up to 80	>30:1	up to 95
57	COR	up to 95	up to >30:1	up to 98

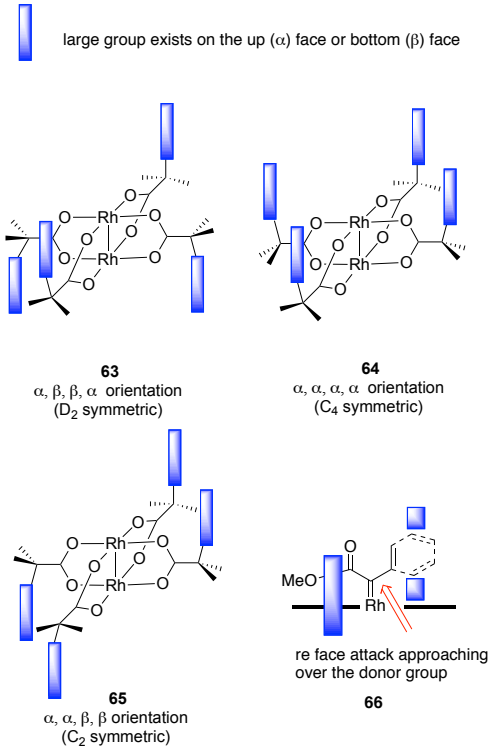
Scheme 12

Cyclopropanation with aryldiazoacetates can be conducted with very low catalyst loadings. Most of the exploratory reactions were conducted with 1 mol % catalyst loading but much lower catalyst loading could be used if desired. In the original studies with Rh$_2$(*S*-DOSP)$_4$, high asymmetric induction was still obtained with 0.1 mol % catalysts loading but dropped to below 60% ee with 0.01 mol % catalyst loading.[38b] Later it was shown that in the cyclopropanation of styrene with methyl phenyldiazoacetate (**58**) to form **59**, the bridged prolinate catalyst Rh$_2$(*S*-biTISP)$_2$ (**60**), maintained high asymmetric induction (92% yield and 85% ee) with a catalyst loading of 0.001 mol % (Scheme 13).[46] Subsequent studies revealed that much lower catalyst loadings could be used if the reactions were conducted without solvent. The lowest catalyst loadings were obtained with Rh$_2$(S-PTAD)$_4$ as catalyst, *p*-methoxyphenyldiazoacetate **61** as the carbene precursor, and cyclopentadiene as a very reactive trapping agent.[47] The stronger donor group is considered to stabilize the carbene, allowing productive reactions with the reactive trapping agent to occur rather than unimolecular destruction of the rhodium carbene complex. This system was effective at a catalyst loading on 0.00006 mole % and under these conditions, the cyclopropane **62** was formed in 83% yield and 76% ee (1,300,000 turnovers). Even though these are impressive TON's, the reaction still has some significant challenges that need to be overcome before carbene reactions with extremely low catalyst loadings become routine. The enantioselectivity tends to drop under high TON reaction conditions especially if a less reactive trapping agents is used. Also, the optimum conditions using no solvent would not be safe on large scale.



Scheme 13

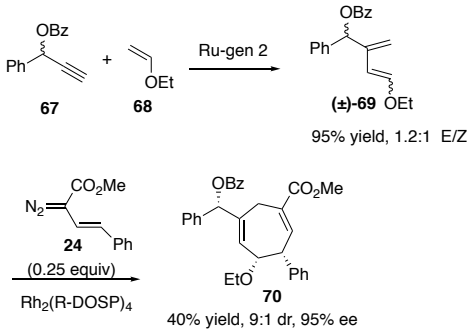
Once Rh_2(*S*-DOSP)$_4$ was established as an outstanding chiral catalysts for the reactions of donor/acceptor carbenes, we needed to rationalize how the asymmetric induction occurred. We proposed in 1996 that the arylsulfonylprolinate ligand was too big to exist in the periphery of the dirhodium tetracarboxylate lantern structure.[38b] It would then be forced to be either on the top face or the bottom face of the catalyst. If all four ligands have a similar constraint, then we recognized that the complex could adopt a higher symmetry structure than the ligands itself as illustrated in Scheme 14. The complex could be either D_2 symmetric (**63**), C_4 symmetric (**64**) or C_2 symmetric (**65**). We proposed that Rh_2(*S*-DOSP)$_4$ adopted a D_2 symmetric structure, primarily because of the extreme solvent effect where the highest asymmetric induction is obtained in non-polar solvent and the polar *N*-sulfonyl groups would tend to cancel each other out in the D_2-symmetric agents. A predictive model was then developed (**66**) to explain why the *Re* face of the carbene is always attacked when Rh_2(*S*-DOSP)$_4$ is used as catalyst. Even though this model is highly predictive, the D_2 symmetric structure of Rh_2(*S*-DOSP)$_4$ has not been validated experimentally or computationally and recent studies indicate that the *N*-arylsulfonyl groups are not that big and could align in the periphery of the complex.[48] However, the concept of generating higher symmetry complexes depending on how the lower symmetry ligands align has become a central design element for generating new chiral dirhodium tetracarboxylate catalysts,[49] as will become clear later in this perspective when our second and third generation chiral catalysts are introduced.



Scheme 14

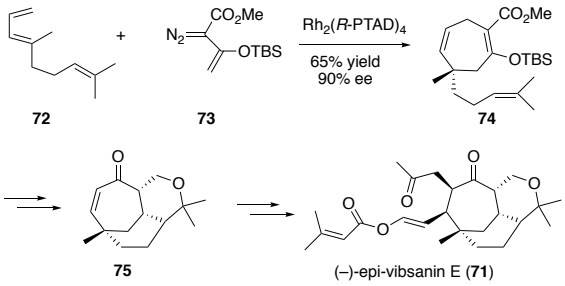
Early Collaborations with Synthetic Organic Chemists to Enhance the Scope of the Tandem Cyclopropanation Cope rearrangement.

Having invested extensively into the cyclopropanation chemistry of donor/acceptor carbenes, we wished to demonstrate the broader utility of the chemistry. Certainly, we have applied the chemistry in total synthesis independently,[28, 40b] but we began collaborating with other synthetic experts to maximize the potential of our chemistry. Our first collaboration was with Dr. Steven Diver, in which we combined his enyne metathesis chemistry to make dienes with subsequent tandem cyclopropanation/Cope rearrangement reactions of those dienes with our vinylcarbenes (Scheme 15).[50] This led to some interesting observations as illustrated in the conversion of the diene **69** to the cycloheptadiene **70**. The diene **69** was prepared from the enyne metathesis of alkyne **67** with vinyl ether **68** and is formed as a racemate and a 1.2:1 *E*/*Z* mixture. Even so, the Rh_2(*R*-DOSP)$_4$-catalyzed reaction results not only in kinetic resolution but also with selective reaction with the *E*-diene of **69**, forming **70** in 95% ee and 9:1 dr. The *Z*-diene of **69** was considered to be unable to remain planar and thus, the alkene undergoing the initial cyclopropanation in the *E*-diene would be more electron rich than the corresponding alkene in the Z-diene. This collaboration was a great learning experience, showing that beneficial collaborations can arise between organic chemists with relatively similar skill sets, especially when the project builds on combining the expertise of the two groups.



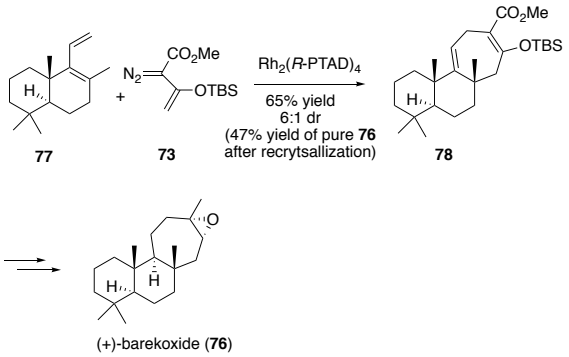
Scheme 15

When it comes to total synthesis, our interest is to demonstrate the utility of donor/acceptor carbene chemistry in a key step or steps in the synthetic endeavor rather than necessarily be the first to achieve the synthesis of a particular target. Consequently collaborating with experts in total synthesis to bring such applications to fruition is beneficial to our program. An illustration of this approach is the total synthesis of epi-vibsanin E (**71**), which we conducted in collaboration with Dr. Craig Williams (Scheme 16). The $Rh_2(R\text{-PTAD})_4$ catalyzed tandem cyclopropanation/Cope rearrangement between the diene **72** and the vinyldiazoacetate **73** generate the cycloheptadiene **74** with good asymmetric induction of the key quaternary stereocenter.[51][52] In a few steps, **74** was readily converted to the tricyclic system **75** on a multigram scale. Completion of the synthesis required a conjugate addition to a sterically challenging unsaturated ketone followed by trapping of the resulting enolate. As the Williams group had explored related chemistry on other members of the vibsanin class of natural products,[53] we combined forces to complete successfully the total synthesis of **71**.



Scheme 16

Another collaborative study is the synthesis of bakerolide (**76**) with Dr. Richmond Sarpong (Scheme 17).[54] The Sarpong group had been interested in using asymmetric reactions of donor/acceptor carbenes with chiral dienes to generate either diastereomer of the product, controlled by the chiral catalyst.[55] We knew we had exceptional systems for conducting such reactions, so we combined resources to carry out model studies on elaborate chiral dienes available from the Sarpong lab and then, we showcased the chemistry in the total synthesis of barekoxide (**76**).[54] The key step is the $Rh_2(R\text{-PTAD})_4$ catalyzed reaction of the chiral diene **77** with the vinyldiazoacetate **73** to form **78**. This is the miss-matched reaction but **78** could still be formed in a 6:1 dr and could be recrystallized to the pure diastereomer in 47% overall yield. In a few additional steps, **78** was readily converted to bakerolide **76**.



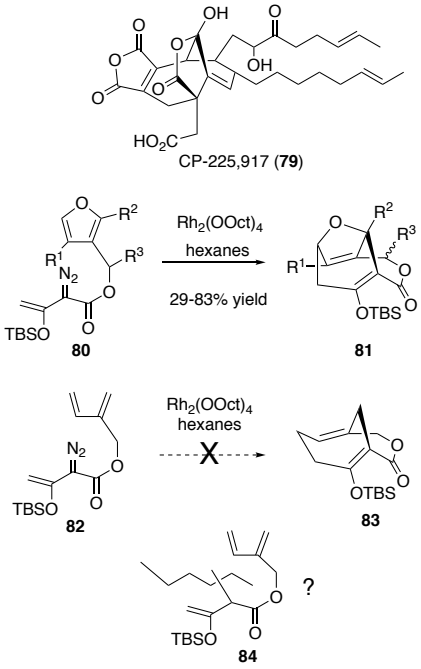
Scheme 17

The positive experiences in collaborating with biologists using tropanes as molecular probes and potential medications for cocaine addiction, followed by fruitful collaborations with other synthetic organic chemists convinced me of the value of the team approach to chemistry research. It led to my belief that in general, chemists can tackle bigger problems working together than when they are working alone, and ultimately became the inspiration for proposing the NSF Center for Selective C—H Functionalization.

Discovery of Intermolecular C—H Functionalization with Donor/Acceptor Carbenes

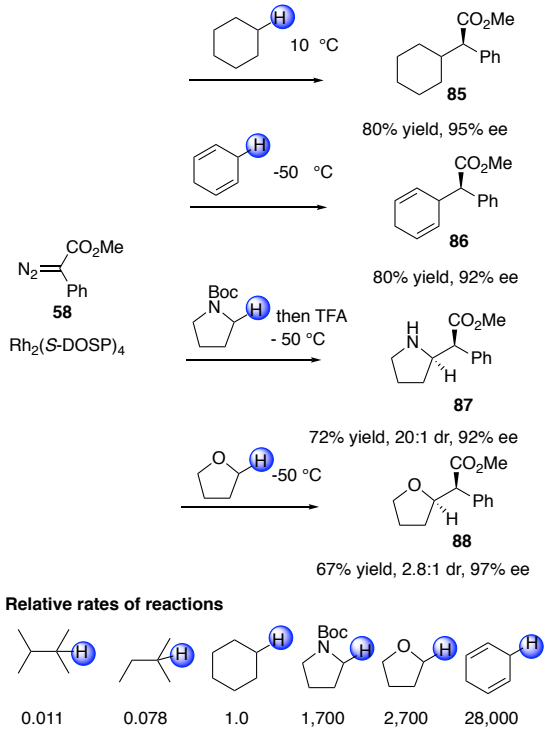
During the mid 1990's as the group transitioned to the State University on New York at Buffalo, it was routine for us to carry out the reactions of donor/acceptor carbenes in hydrocarbon solvents, such as pentane or hexanes because the chiral rhodium prolinate catalysts gave much higher levels of enantioselectivity in hydrocarbon solvents. Furthermore, the undesired reactions at the vinylogous position of the vinylcarbenes could be blocked when non-polar solvents were used. Ironically, I believed at that time that one of the reasons why cyclopropanations with donor/acceptor carbenes were so clean was because these carbenes do not readily undergo C—H insertion reactions. This prevailing view changed quickly during model studies directed towards the total synthesis of CP-225,917 (**79**), which in the mid 1990's was a very popular natural product target because it had promising biological activity and had an unusual structure, containing an anti-Bredt double bond (Scheme 18).[56] We became intrigued with this compound because we envisioned that a type 2 intramolecular reaction between a diene and a vinylcarbene could potentially lead to the bicyclic core of the natural product. Indeed we were successful in an

intramolecular reaction with furan **80** (although the product **81** was too labile to lead to a serious campaign to the natural product).[57] However, when we conducted the reaction with the diene **82** in hexanes as solvent, none of the desired product **83** was obtained.[57] The NMR of the crude material showed the diene and the vinyl group of the carbene remained intact but there were some broad undefined peaks between 1 and 2 ppm.[58] These broad peaks were an indication that the carbene may have reacted with the hydrocarbon solvent to form the mixture **84**, the first time we had seen any evidence of intermolecular C—H insertion with the donor/acceptor carbenes.



Scheme 18

We then conducted a survey to determine what types of substrates would be susceptible to C—H functionalization with donor/acceptor carbenes.[11, 59] It quickly became apparent that the donor/acceptor carbenes were far superior to the acceptor carbenes at intermolecular C—H insertion. Illustrative examples from the early studies are the Rh_2(*S*-DOSP)$_4$-catalyzed reactions of phenyldiazoacetate **58** to form **85-88** (Scheme 19). Cycloalkanes were readily functionalized and electronically activated C—H bonds, such as allylic sites and C—H bonds adjacent to oxygen or nitrogen were particularly favorable. A competition study was conducted between some simple substrates, which gave an indication of the relative reactivity of C—H bonds. Cyclohexadiene was 28,000 times more reactive than cyclohexane. Tetrahydrofuran and N-Boc-pyrrolidine were 2700 and 1,800 times more reactive than cyclohexane. In contrast, 2-methylbutane was 1/10th as reactive as cyclohexane. Taking into account the number of reactive C—H bonds, the tertiary C—H bond in 2-methylbutane is about as reactive as the secondary C—H bond in cyclohexane. If the tertiary bond is more sterically crowded, as seen in 2,3-dimethylbutane, the substrates is a further factor of 10 less reactive.



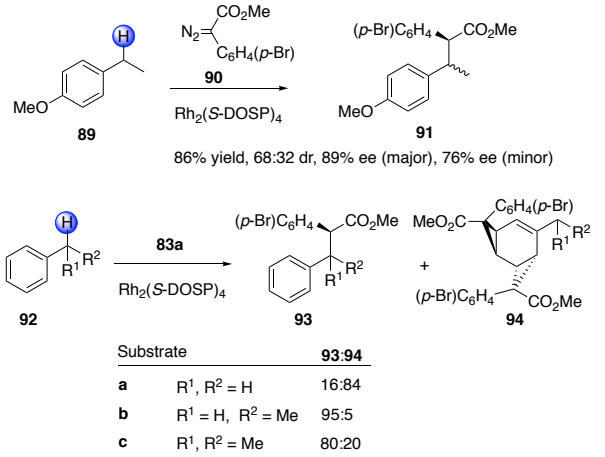
Scheme 19

Four advantageous features of the donor/acceptor carbenes became readily apparent form the early studies on their C—H functionalization reactions:

- Their C—H functionalization reactions are much more selective than the corresponding reactions of acceptor carbenes.
- C—H functionalization is feasible in the presence of functional groups.
- Donor/acceptor carbenes are far less prone to dimerization than acceptor carbenes, causing the trapping of the carbene by the substrate to be more efficient.
- Rh-DOSP-catalyzed reactions with the donor/acceptor carbenes derived from methyl aryldiazoacetates generally proceed in 85-95% ee as long as the reaction is conducted in nonpolar solvents.

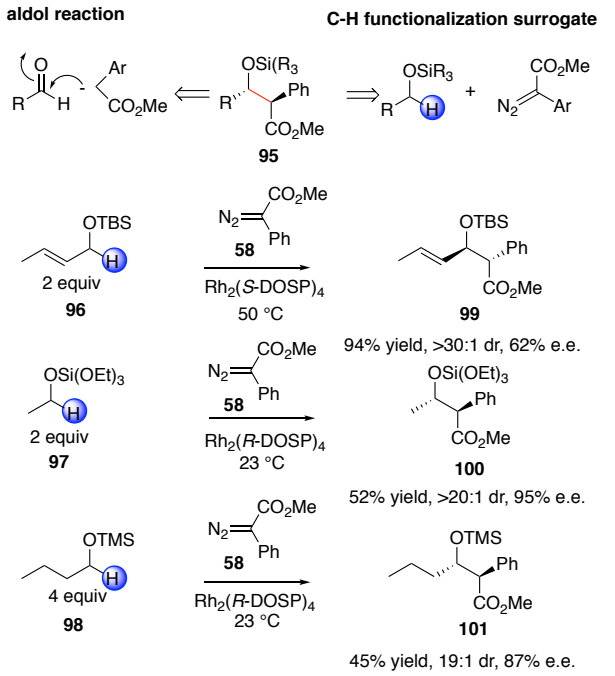
The C—H functionalization at benzylic sites further revealed the role of sterics on the reaction of donor/acceptor carbenes.[60] When a benzene ring is 1,4-disubstituted, the ring is sterically protected and the C—H functionalization is cleanly formed as illustrated in the reaction with *p*-ethylanisole (**89**) with the p-bromophenyl diazoacetate **90** to form **91**. In contrast, with mono-substituted benzenes **92**, C—H functionalization to form **93** is competing with double cyclopropanation of the aromatic ring to form **94**

(Scheme 20). The influence of the steric effect is seen on comparing the reactions of toluene (**92a**), ethylbenzene (**92b**) and isopropyl benzene (**92c**). All three substrates have a competing double cyclopropanation reaction (two regioisomers with toluene (**92a**)) with the C—H functionalization but the amount of C—H functionalization is greatest for ethyltoluene, suggesting that the methylene benzylic site is the preferred site for C—H functionalization. Indeed, in the Rh-DOSP catalyzed reactions, C—H functionalization of a methylene site is generally preferred because it is a good balance between an electronically preferred site versus a sterically accessible site. A similar steric protection of an aromatic ring has been seen in other substrates such as *N*,*N*-dimethylanilines[61] and indole derivatives.[62] A less substituted substrate is prone to cyclopropanation but as soon as the ring is at least 1,4-disubstituted the ring is sterically protected.



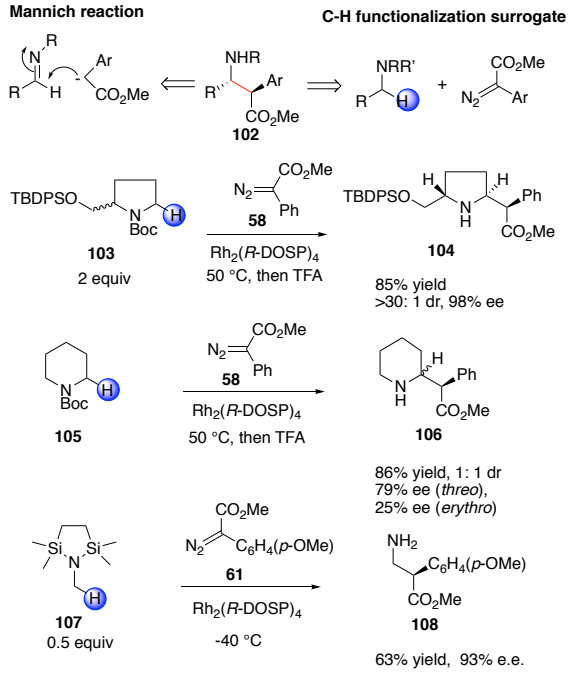
Scheme 20

C—H Functionalization offers an opportunity to generate new disconnection strategies for the synthesis of complex targets. In order to demonstrate how C—H functionalization could be considered to be a strategic reaction, we have reported several examples of the carbene-induced C—H functionalization acting as a surrogate to some of the classic reactions. C—H functionalization at sites α to oxygen would generate protected β-alkoxycarboxylates **95**, the typical products of an aldol reaction (Scheme 21).[63,64] Particularly useful substrates are silyl allyl ethers (**96**),[63] tetraalkoxy silanes (**97**)[64b] and alkyl silyl ethers (**98**),[64a] although the yields were relatively low for the alkyl silyl ethers. In each case the products **99-101** were formed with excellent diastereocontrol, which is typical for C—H functionalization at methylene sites in which there is considerable difference in size between the two substituents. The allyl silyl ether **96** is a very active substrate but the enantioselectivity is relatively moderate. The reaction with butyl silyl ether **98** is the least effective, proceeding in relatively low yield but with excellent stereocontrol. The roles of steric and electronic factors were also seen in these reactions. Tetraethoxysilane was much more reactive that tetramethoxysilane and tetratisopropoxysilane. Also, even though *E*-allyl silyl ethers were excellent substrates for C—H functionalization, unsubstituted and internally substituted allyl silyl ethers preferentially underwent cyclopropanation whereas *Z*-allyl silyl ethers generated a mixture of the cyclopropane and the C—H insertion.



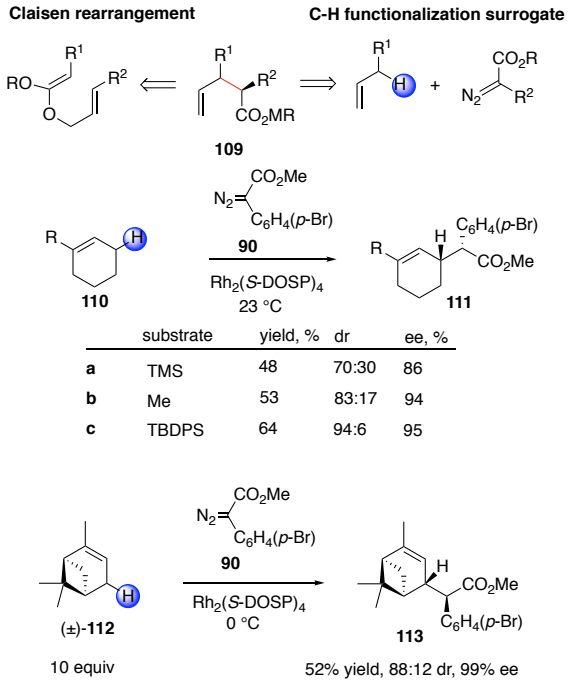
Scheme 21

C—H Functionalization α to nitrogen generates β-amino esters **102**, the products typical of a Mannich reaction (Scheme 22).[61, 65] The Rh_2(*S*-DOSP)$_4$-catalyzed reaction with N-Boc-pyrrolidine is highly stereoselective favoring the *erythro* diastereomer and can even be used in kinetic resolution reactions of 2-substituted pyrrolidines as illustrated in the conversion of **103** to **104**.[65a, 65c] The Rh_2(*S*-DOSP)$_4$-catalyzed reaction with *N*-Boc-piperidine (**105**) gives a mixture of *threo* and *erythro* diastereomers **106**. Studies have been conducted independently by Winkler[66] and us[65a, 65c] to improve the diastereoselectivity to favor the *threo* diastereomer because this would represent a quick enantioselective entry to threo-methylphenidate (Ritalin, **106**). Improved diastereoselectivity was obtained using the bridged catalyst Rh_2(S-biDOSP)$_2$[65a, 65c] and a chiral dirhodium tetracarboxamidate catalyst developed by Doyle, favoring the threo isomer. A bis-silyl protected methylamine **107** is also an effective substrates leading to the synthesis of beta-amino carboxylates **108** with high enantioselectivity.[65d] This transformation has been used for the asymmetric synthesis of the antidepressant venlafaxine.



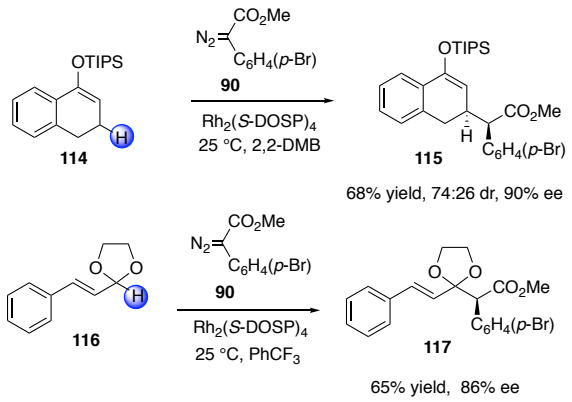
Scheme 22

C—H Functionalization at allylic C—H bonds gives rise to γ,δ-unsaturated esters **109**, products equivalent to a Claisen rearrangement (Scheme 23).[67] Exceptionally favorable substrates are cyclohexadiene and cycloheptatriene because the buildup of positive charge during the C–H functionalization is favored. The reaction with 1-silylcyclohexanes **110** to form **111** illustrates the influence of steric factors on the diastereoselectivity of the C—H functionalization. The reaction with cyclohexene gives a mixture of the allylic C—H functionalization and cyclopropanation whereas 1-substituted cyclohexenes give only the C—H functionalization products. As the size of the substituent increases from TMS to TBDPS the diastereoselectivity of **111** improves from 70:30 dr to 96:4 dr. The reaction can also be conducted on α-pinene, leading to kinetic resolution when racemic (±)-α-pinene (**112**) are used, as illustrated in the conversion of **112** to **113** in 99% ee.



Scheme 23

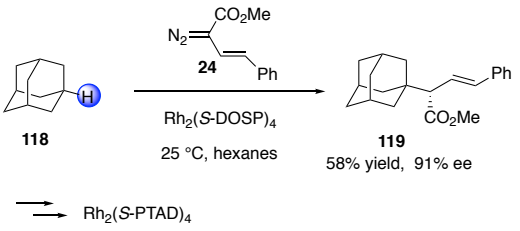
Two other example of transformations, which are surrogate to conventional chemistry is the reaction with silyl enol ethers **114** to form **115**, which correspond to a Michael addition equivalent[68] and the C—H functionalization of acetals **116** to form **117**, which corresponding to the Claisen condensation equivalent (Scheme 24).[69] An advantage of the C—H functionalization approach is that it can generate products that would not be feasible using the conventional transformation. For example the enone required to form formal Michael adduct **115** would be the tautomer of 1-naphthol, which is not a viable substrate. In the Claisen condensation equivalent the product **117** has the keto carbonyl protected as a ketal and so it is not prone to facile epimerization as would be the case for an unprotected β-keto ester.



Scheme 24

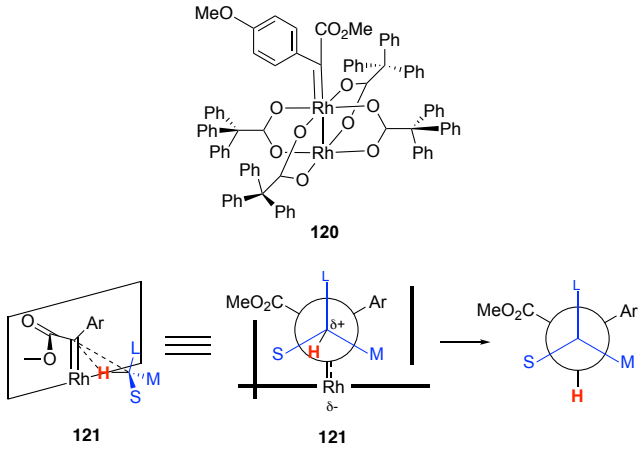
In general the C—H functionalization with Rh_2(*S*-DOSP)$_4$ preferentially occurs at secondary sites

although it is possible to have selective C—H functionalization at primary sites if the position is sufficiently activated and there are not competing secondary sites. C—H Functionalization at tertiary sites is limited with Rh_2(S-DOSP)$_4$ and does not proceed with high asymmetric induction. One notable exception is the reaction of styryldiazoacetate **24** with adamantane **118** which produced **119** in 95% ee (Scheme 25).[41] Indeed this particular reaction was the inspirations for the synthesis of the secondary generation catalyst Rh_2(*R*-PTAD)$_4$ because oxidative cleavage of the alkene in **119** followed by a Curtius rearrangement lead to the formation of the required adamantyl amino acid derivative. This is an early example of how we tend to approach the design of new chiral catalysts by maximizing the opportunities of our new enantioselective reactions.



Scheme 25

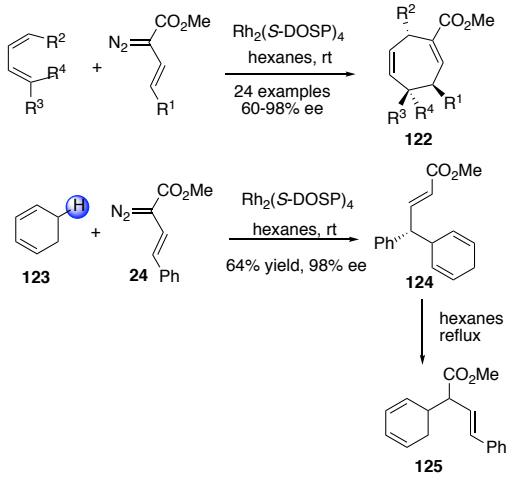
Detailed mechanistic studies on the rhodium-catalyzed reactions of diazo compounds are difficult because the reactions are so fast and for quite some time there was even a question about the structure of the rhodium carbene intermediates and they were called rhodium carbenoids because of the ambiguity. In 2013, we were able in a collaborative study with Dr. John Berry to isolate the rhodium carbene intermediate **120** and obtained considerable spectral data that helped to confirm it did indeed have a rhodium carbene structure (Scheme 26).[70] Since then, Fürstner has obtained crystal structures of several rhodium carbene complexes, demonstrating convincingly that a metal bound carbene is involved in these reactions.[71] We have conducted computational studies in collaboration with Dr. Jochen Autschbach on the rhodium carbene intermediates and shown that the C—H functionalization proceeds by a hydride transfer event leading to build-up of positive charge on the carbon of the C—H bonds.[72] This resulted in the development of model **121** for the relative and absolute stereochemistry of the C—H functionalization. These calculations also showed that the donor/acceptor carbenes are much more stable than the acceptor carbenes and the activation energy for the C—H functionalization, covers a range of values from 5 kcal/mole for the reaction with cyclohexadiene to 15 kcal/mole for the reaction with cyclopentane. In contrast, the activation energy for C—H functionalization with the acceptor carbene from ethyl diazoacetate is much less covering a range 2-5 kcal/mole. Thus, it is much harder to have selective C—H functionalization with acceptor carbenes because the C—H functionalization activation energies are so small, analogous to the difference in selectivities for free radical bromination versus free radical chlorination.



Scheme 26

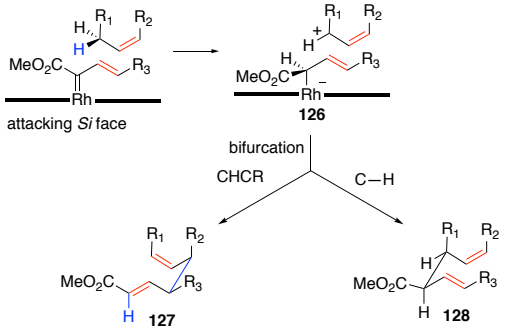
Combined C—H Functionalization/Cope Rearrangement: Discovery and Applications

When we developed Rh_2(S-DOSP)$_4$ as a chiral catalyst, we had already established the tandem cyclopropanation/Cope rearrangement as a general method for the synthesis of cycloheptadiene. Consequently, we had an obvious study that needed to be completed, the enantioselective version of the tandem cyclopropanation/Cope rearrangement to form **122** (Scheme 27). Three students were given a set of diene substrates each to explore and in a matter of weeks the study was complete.[40c] However, one substrate did not behave as planned. The reaction with 1,3-cyclohexadiene (**123**) resulted in the formation of an unexpected major product, the 1,4-cyclohexadiene **124**, in which the new C-C bond had been formed at the vinylogous position of the vinylcarbene.[73] Initially, we considered that the reaction was a C—H functionalization followed by a Cope rearrangement, but control experiments quickly ruled out this possibility because on heating, **124** rearranged to the formal C—H functionalization product **125**, which shows that **125** is the thermodynamic product.



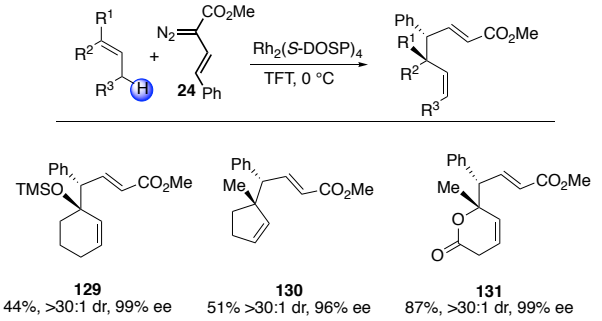
Scheme 27

When first discovered, the reaction was described as a combined C—H activation/Cope rearrangement (later changed to "combined C—H functionalization/Cope rearrangement") because it had the essence of both types of reactions.[74] Later computational studies revealed that the competition between the direct C—H functionalization and the combined C—H functionalization/Cope rearrangement involved a bifurcating process (Scheme 28).[75] It was initiated by a hydride transfer event to form the rhodium bound allyl anion and the allyl cation (**126**), followed by rapid C-C bond formation to form **127** and **128**. Thus, even though the reaction has an apparent step-wise process, the intermediates do not have time to equilibrate and the reaction proceeds with very high stereocontrol.



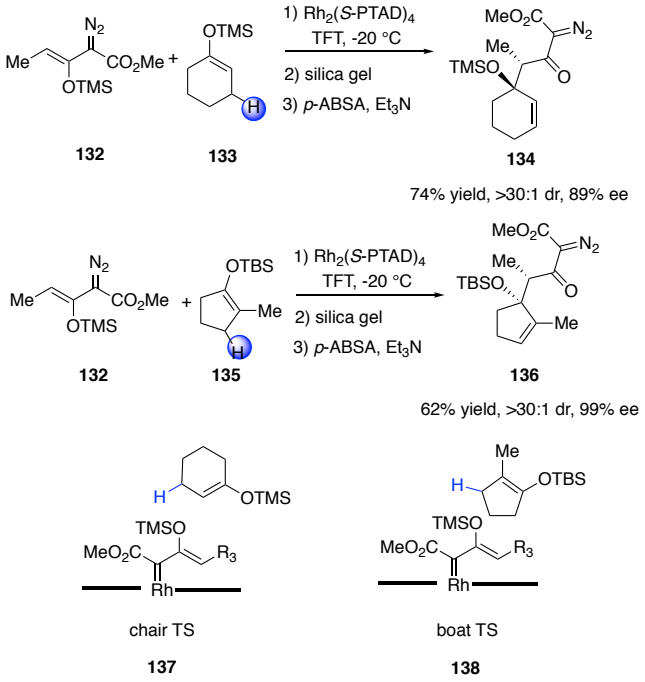
Scheme 28

The combined C—H functionalization/Cope rearrangement starting from *E*-styryldiazoacetate **24** was applied to a variety of substrates. Some representative examples are shown in Scheme 29.[74] In all cases the products **129-131** were generated with extremely high enantioselectivity and diastereoselectivity, consistent with a reaction proceeding though a chair transition state.



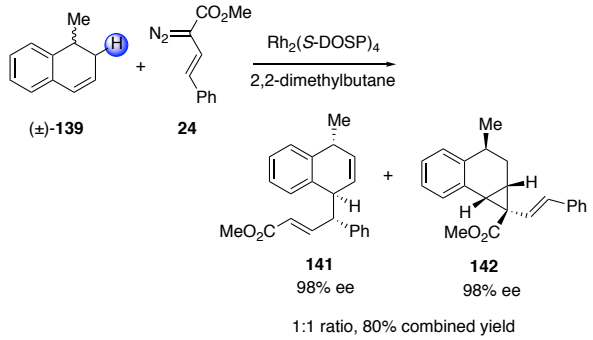
Scheme 29

Most examples of the combined C—H functionalization/Cope rearrangement especially with *E*-vinyldiazoacetates proceed through a chair TS.[74] However, this ensures that bulky functionality points away from the rhodium catalyst surface. However, in certain systems, it is possible to achieve a complete switch of the diastereoselectivity by causing the reaction to proceed through a boat transition state. An illustration of this effect is seen in Scheme 30.[76] The Rh_2(S-PTAD)$_4$-catalyzed reaction of the vinyldiazoacetate **132** with the siloxycyclohexene **133** generates after silyl hydrolysis and a diazo transfer reaction the product **134** as a single diastereomer in 89% ee. In contract when the same reaction is conducted on the silylcyclopentene **135**, the product **136** is produced in the opposite diastereomeric series. The carbene produced from **132**, will adopt the s-*cis* configuration and will react with **133**, so that the cyclohexene ring is pointing away from the catalysts surface, leading to a chair TS **137**. In the case of **132**, the methyl group preferentially points away from the catalyst, whereas the cyclopentane ring can be accommodated and the reaction proceeds through the boat TS **138**.



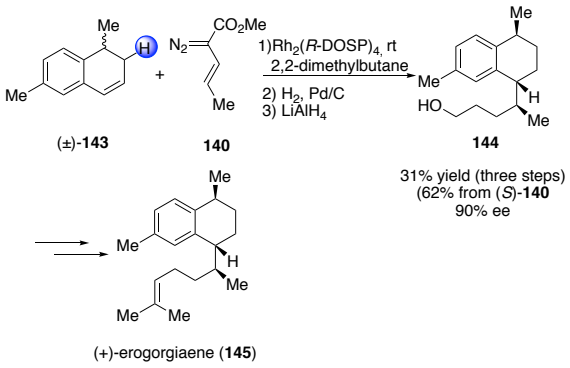
Scheme 30

A synthetically useful class of substrates are (±)-4-methyl-1,2-dihydronapthalenes (Scheme 31).[77] As illustrated for the parent system (±)-**139**, the Rh_2(S-DOSP)$_4$-catalyzed reaction of the vinyldiazoacetate **24** results in kinetic resolution and the formation of two products **141** and **142**. The *R* enantiomer of **139**, preferentially undergoes the combined C—H functionalization/Cope rearrangement to form **141** as a single diastereomer in 98% ee. In contrast (*S*)-**139** preferentially undergoes cyclopropanation to form **142** in 98% ee.



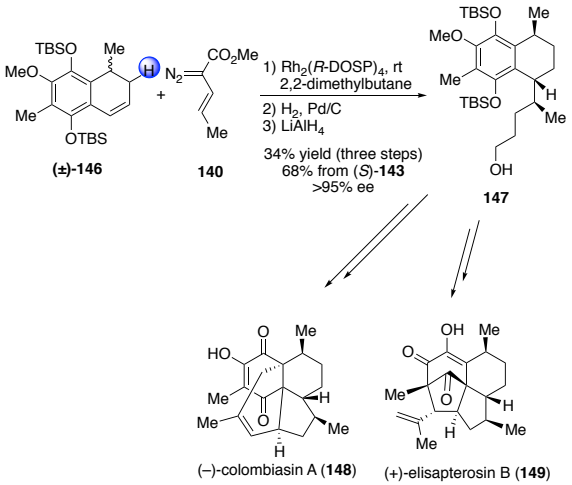
Scheme 31

Once the enantiomer differentiation methodology was established, several natural products became accessible using this chemistry. The first natural product we examined was erogorgiaene (**145**), and this total synthesis became a folklore of the group (Scheme 32).[77] The whole total synthesis, from the 5-step synthesis of the dihydronaphthalene, the key enantiomer differentiation step and then the end game strategy was accomplished in a total of 10 days – truly a "*time economical synthesis*"! In the Rh_2(*R*-DOSP)$_4$-catalyzed reaction of the dihydronaphthalene (±)-**143** with the vinyldiazoacetate **140**, the *S* enantiomer of **143** preferentially underwent the combined C—H functionalization/Cope rearrangement and after hydrogenation and lithium aluminum hydride reduction, the alcohol **144** was isolated in 31% yield from (±)-**143** and 90% ee. Oxidation of the alcohol in **144** to the aldehyde followed by a Wittig reaction resulted in the formation of **145**.



Scheme 32

A more elaborate example is the total synthesis of (-)-colombiasin A (**148**) and (+)-elisapterosin B (**149**) (Scheme 33)[78] In this case the highly functionalized dihydronaphthalene (±)-**146** is required. The additional functionality in (±)-**146** does not interfere with the site for C—H functionalization and the desired carbene-induced reaction proceeds in a similar way to form the key intermediate **147** in >95% ee. The completion of the total syntheses follows strategies previously developed by Nicolaou,[79] with a late stage intramolecular [4+3] cycloaddition used to form (-)-colombiasin A (**148**) and a late stage intramolecular [5+2] cycloaddition used to form (+)-elisapterosin B (**149**). The distinctive feature of our C—H functionalization strategy is the ready one-step synthesis of three stereogenic centers, which had been very challenging using more conventional methodology.

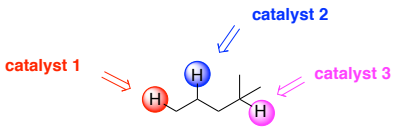


Scheme 33

Development of Second and Third Generation Chiral Catalysts for Site Selective C—H Functionalization

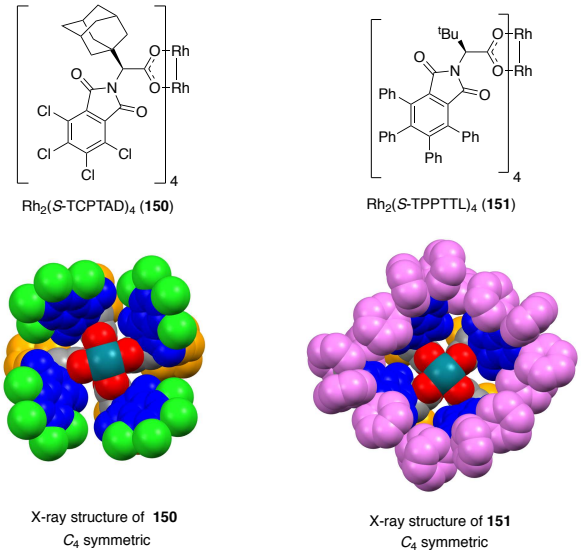
The Rh_2(DOSP)$_4$-catalyzed C—H functionalization with donor/acceptor carbenes has resulted in wide range of synthetic application,[19a] but it does suffer from the fact the methodology needs to be matched to suitable substrates. The C—H functionalization often works well on substrates with an activated secondary C—H bond (allylic, benzylic, alpha to O or N), but if a substrate failed to give a clean reaction, then there were very few options available to improve the selectivity. An additional limitation is that high asymmetric induction requires the use of a non-polar solvent. Hexanes or pentanes can be used when the trapping agent is very reactive but with less active trapping agents 2,2-dimethylbutane, a very expensive solvent needs to be used. Rh_2(DOSP)$_4$ has been designed to be hydrocarbon soluble but many of the substrates will not be. A blend of hydrocarbon and trifluorotoluene can be used to mitigate solubility issues but invariably the enantioselective is slight lowered in a mixed solvent.

After moving to Emory University in 2008, we began the Phase I NSF Center for Chemical Innovation on Selective C—H Functionalization, which grew into a phase II Center in 2012, consisting of 26 professors from 15 universities.[80] The central goal of the Center has been to develop methods that would allow C—H functionalization to be under catalyst control. Consequently, we became interested in developing new catalysts of different sizes and shapes, in order to be able to control which C—H bond in a substrate will react by simply choosing the appropriately designed catalyst (Scheme 34).[81] We worked on the hypothesis that the steric environment around the dirhodium catalysts could be very influential. A less bulky catalyst may favor reaction at a tertiary C—H bond, which is electronically the preferred site of attack. However, if a catalyst is very bulky, it could overcome the electronic preference for tertiary C—H bonds and cause the reaction to occur preferentially at secondary or even primary C—H bonds.



Scheme 34

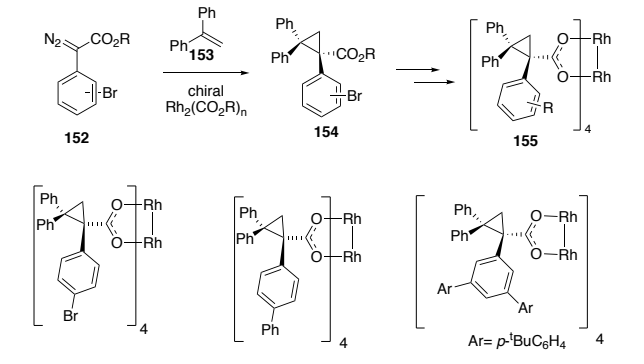
The second generation catalyst Rh_2(*S*-PTAD)$_4$ has been useful for a range of enantioselective cyclopropanation reactions but has not been especially useful in controlling C—H functionalization reactions. Charette and Fox have shown that the related tert-butyl catalyst is conformationally mobile but the corresponding tetrachlorphthalimido catalyst is much more rigid.[49b, 49c] We have found the same characteristic is also the case with Rh_2(*S*-TCPTAD)$_4$ (**150**) and it adopts a C_4 symmetric structure (Scheme 35).[82] Another important new catalyst is Rh_2(*S*-TPPTTL)$_4$ (**151**).[83] It also adopts a C_4 symmetric arrangement but it has an additional stereochemical feature. The phenyl groups are all tilted and in the X-ray structure of the catalyst, 12 are tiled one way and 4 are tilted the other way, but computational studies in collaboration with the Musaev group, reveal that the structure with all 16 phenyl groups tilting one way is the most preferred arrangement. This means the fixed stereogenic centers in the ligands have induced a propeller like chirality in the complex due to the arrangement of the phenyl rings.

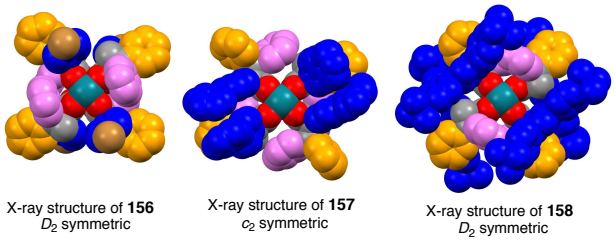


Scheme 35

The third generation catalysts have triarylcyclopropane carboxylate ligands and are much more sterically demanding than the other two classes of catalysts (Scheme 36).[84] The ligands are readily generated from the asymmetric cyclopropanation by aryldiazoacetates **152** of 1,1-diphenylethylene (**153**) to form **154** followed by enantioenrichment through recrystallization, ester hydrolysis and then ligand exchange to form the chiral dirhodium complex. Further catalyst diversification is possible through multifold Suzuki coupling on the preformed catalyst to form **155**. At this stage, five distinctive members of the TPCP catalysts have been developed. The first two members of this class were Rh_2(*R*-p-BrTPCP)$_4$ (**156**) and Rh_2(*R*-p-PhTPCP)$_4$ (**157**). The former catalyst adopts a D_2 symmetric structure, whereas the latter adopts a C_2 symmetric structure due to π-stacking between the biphenyl groups.[84a] Further refinement of this general structures led to the development of another D_2 symmetric catalyst Rh_2(*R*-3,5-di(p-tBuC$_6$H$_4$)TPCP)$_4$

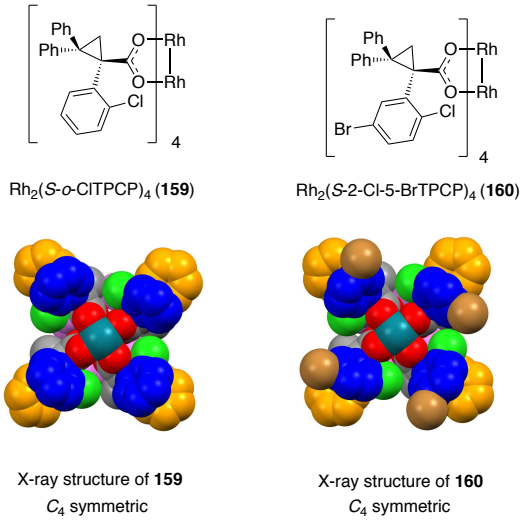
(**158**), which is selective for C—H functionalization at the most sterically accessible methylene sites.[84b]





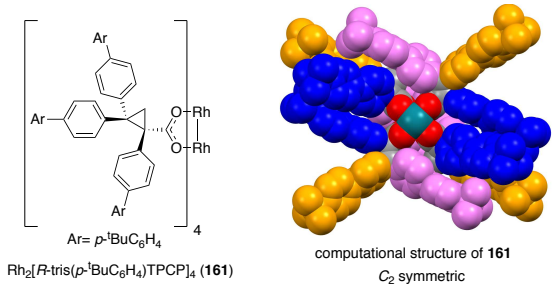
Scheme 36

Another class of TPCP catalysts that exhibits special features are those with an *o*-Cl substituent on the C1-aryl ring (Scheme 37). The original member of this class was[85] Rh_2(*S*-o-ClTPCP)$_4$ (**159**) but Rh_2(*S*-2-Cl-5-BrTPCP)$_4$ (**160**) is considerably better at achieving high asymmetric induction. These catalysts adopt a C_4 symmetric arrangement in which the fixed stereogenic center of the ligand induces a center of axial chirality in the complex, because of hindered rotation between the cyclopropane and the o-Cl-aryl ring. The *o*-ClTPCP catalysts are very effective at C—H functionalization at the most accessible methylene site.



Scheme 37

An even more sterically demanding catalysts can be generated by a 12 fold Suzuki coupling of a preformed catalysts. Rh_2[*R*-tris(p-^{t}BuC$_6$H$_4$)TPCP]$_4$ (**161**) has 12 biphenyl groups (Scheme 38). Computational studies in collaboration with the Houk group showed that due to the pi-stacking between these groups, the C_4 symmetry is broken and the catalyst adopts a C_2 symmetric shape instead.[86] It is so sterically demanding that it will cause C—H functionalization to occur preferentially at a primary C—H bond.

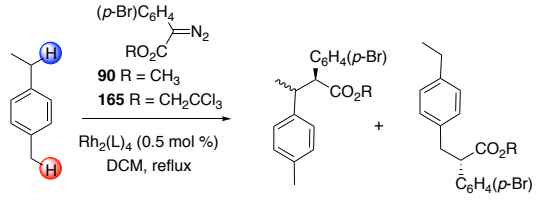


Scheme 38

A further advantage of all the second and third generation catalysts is that they are much more rigid compared to Rh_2(DOSP)$_4$. They no longer require the use of hydrocarbon solvents for high asymmetriuc induction. Dichloromethane is generally the optimum solvent, which expands the overall practicality of the chemistry.

Catalyst-Controlled Site-Selective C—H Functionalization

Once the TPCP catalysts became available, they were evaluated in C—H functionalization reactions. It became readily apparent they behaved as sterically crowded catalysts. Applying these catalysts to site selective C—H functionalization at benzylic sites resulted in a dramatic effect, as illustrated in Scheme 39.[87] The Rh_2(*R*-DOSP)$_4$-catalyzed reaction of methyl aryldiazoacetate **90** with p-ethyltoluene (**162**) resulted in clean C—H functionalization at the secondary C—H bond to form **163a**. However, when the reaction was catalyzed by Rh_2(*p*-PhTPCP)$_4$ the major product **164a** was derived from primary C—H functionalization. Even further enhancement of the site selectivity could be achieved by using the trichloroethyl aryldiazoacetate **165** in which case, **164b** was formed with a 13:1 r.r. and 99% ee.

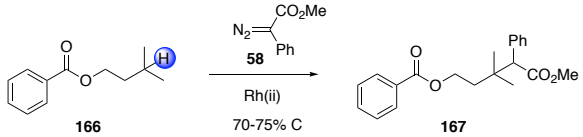


product	R	catalyst	163:164	yield (%)	ee, % 164
a	CH_3	Rh_2(*R*-DOSP)$_4$	>20:1	75	-
a	CH_3	Rh_2(*R*-p-PhTPCP)$_4$	1:5	74	92
b	CH_2CCl_3	Rh_2(*R*-p-PhTPCP)$_4$	1:13	75	99

Scheme 39

Having established that catalyst-control could have a dramatic influence on site selectivity, we initiated a campaign to develop protocols for site selective C—H functionalization occurring at unactivated C—H bonds. Even though we discovered the intermolecular C—H functionalization when hexanes were used as solvent, we had avoided an extensive study on reactions with alkanes as substrates because we did not have the tools for clean site selective reactions. With the development of the new bulky catalysts and the advantages of using carbene precursors containing trichloroethyl esters instead of methyl esters, we finally were in a position to take on the challenge of catalyst-controlled site selective functionalization of unactivated tertiary, secondary or primary C—H bonds. C—H functionalization at tertiary C—H bonds would be electronically preferred but by steadily increasing the sterically crowding around the catalyst, we would expect to block the electronically preferred sites and instead functionalize the most sterically accessible sites.

Even though C—H functionalization at a tertiary site is electronically preferred, it is still challenging because tertiary sites are a bit crowded for the rhodium-bound donor/acceptor carbenes. This effect was observed in an early study, in which effective C—H functionalization of unactivated tertiary sites could only be achieved with a limited range of substrates, as illustrated in the reaction of **166** with methyl aryldiazoacetate **58** to form **167** (Scheme 40).[88] Under normal conditions with solvent, the yields were very low so these reactions needed to be carried under virtually neat conditions and relatively high temperatures. The reactions catalyzed by either Rh_2(*S*-DOSP)$_4$ or Rh_2(*S*-PTAD)$_4$ generated **167** with good site selectivity but in relatively low yields and poor enantioselectivity.

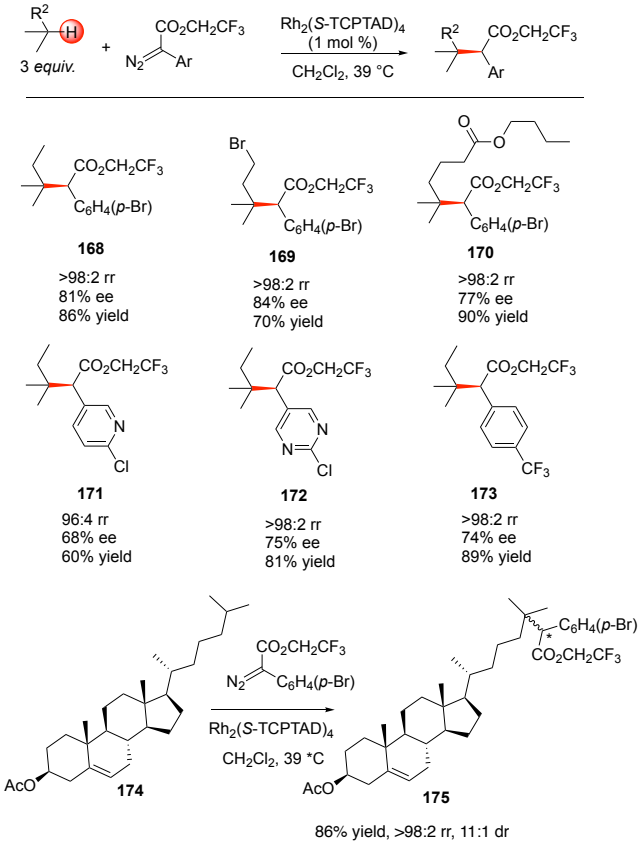


Rh_2(*S*-DOSP)$_4$ 41% yield, 30% ee

Rh_2(*S*-PTAD)$_4$ 32% yield, 23% ee

Scheme 40

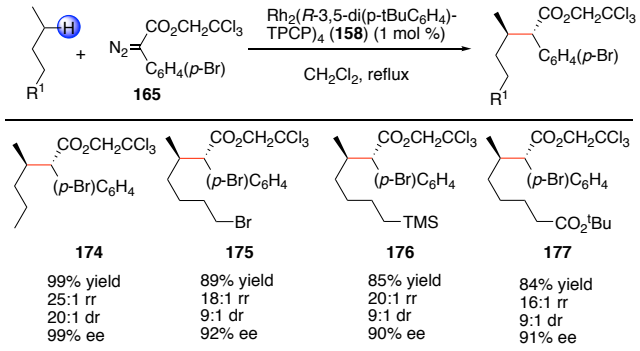
Recently, a much better system for tertiary C—H functionalization was identified, trifluoroethyl aryldiazoacetates with the conformationally much more rigid catalyst. Rh_2(*S*-TCPTAD)$_4$.[82] Some examples of the types of products that could be generated using this combination are shown in Scheme 41. In addition to the reaction with simple alkanes, some functional groups were compatible with the chemistry, as illustrated in the formation of **168-173**. Most notably the reaction could be carried out on elaborate substrates containing many tertiary C—H bonds, such as cholesteryl acetate **174**, and the C—H functionalization occurred cleanly at the most accessible tertiary C—H bond to form **175**.



Scheme 41

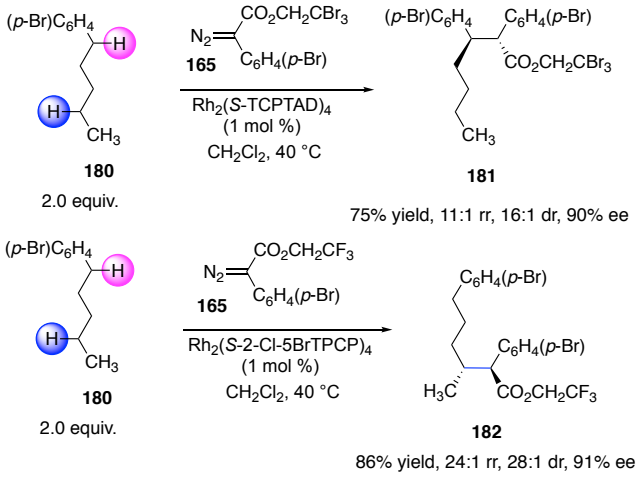
A selective C—H functionalization at an unactivated secondary C—H bond would require a sterically bulky catalyst to overcome the electronic preference for reactions occurring at tertiary sites. The D_2 symmetric catalyst, Rh_2(*R*-3,5-di(p-tBuC_6H_4)TPCP)$_4$ (**158**), was found to be an exceptional catalyst for site selective reactions at the most accessible methylene site (Scheme 42).[84b] In the model studies, the catalyst was shown to be effective at functionalization of the C2 of pentane, with no competing reactions occurring at the C3 methylene to form **173**. Other representative examples are the reaction with 1-bromohexane, 1-TMS-pentane and 1-acetoxyhexane to form **174-176**. These reactions

proceed with good site selectivity, diastereoselectivity and enantioselectivity, demonstrating the remarkable control exhibited by this catalyst.



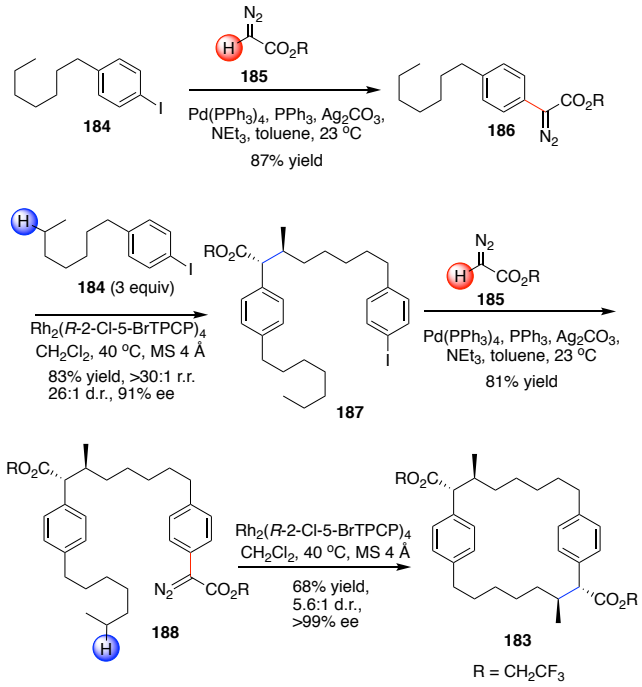
Scheme 42

Later, the *o*-ClTPCP catalysts were found to display even better site selectivity for the most accessible secondary C—H bond.[85a] Further studies revealed that Rh_2(2-Cl-5-BrTPCP)$_4$ was the better catalyst because it gave higher levels of asymmetric induction than Rh_2(*o*-ClTPCP)$_4$).[85b] Its subtle control was demonstrated in the reaction of n-alkylbenzenes (Scheme 43). The Rh_2(*S*-TCPTAD)$_4$-catalyzed reaction gave a strong preference for benzylic C—H functionalization with excellent diastereocontrol and enantiocontrol as illustrated in the conversion of **180** to **181**. In contrast the Rh_2(*S*-2-Cl-5-BrTPCP)$_4$-catalyzed reaction gave a clean reaction at the most accessible methylene site to form **182**, again with excellent stereocontrol. The general approach was applicable to a range of aryl and heteroaryl-substituted alkanes.



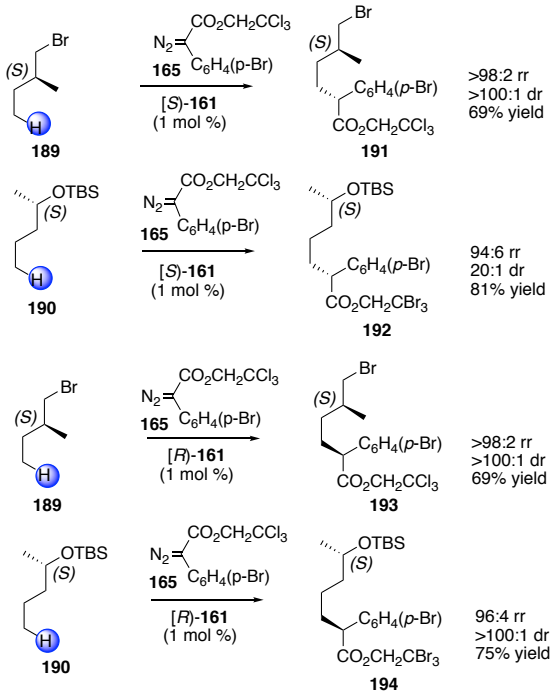
Scheme 43

The synthetic utility of the Rh_2(2-Cl-5-BrTPCP)$_4$-catalyzed reaction has been demonstrated in collaboration with the Stoltz group with a direct synthesis of the paracyclophane core **183** of the cylindrocyclophane class of natural products (Scheme 44).[85b] The palladium catalyzed C—H functionalization between the aryl iodide **184** and the diazoacetate **185** generated the carbene precursor **186**. The Rh_2(*R*-2-Cl-5-BrTPCP)$_4$-catalyzed reaction of **186** with the aryl iodide **184** occurred cleanly at the most accessible methylene site of **184** to form **187** in 83% yield, 91% ee and excellent site and diastereocontrol. A further palladium catalyzed C—H functionalization on **187** generate a second carbene precursor **188**, which on Rh_2(*R*-2-Cl-5-BrTPCP)$_4$-catalyzed reaction underwent a clean intramolecular reaction to form **183**. As the minor enantiomer in **187** would form preferentially a diastereomer product to **183**, the final product is formed with very high levels of enantioselectivity (>99% ee). The overall scheme illustrates the potential of catalyst-controlled C—H functionalization to generate complex structures with multiple stereogenic centers in a very direct way.



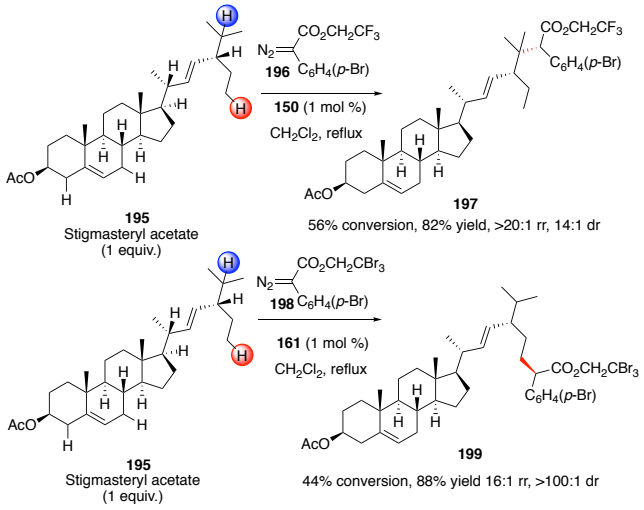
Scheme 44

The C—H functionalization of primary C—H bonds would have to overcome the inherent tendency to react at tertiary or secondary C—H bonds. Rh_2[*R*-tris(p-^{t}BuC$_6$H$_4$)TPCP]$_4$ (**161**) was found to be a sufficiently crowded catalyst to force the C—H functionalization to occur preferentially at primary C—H bonds as illustrated in Scheme 45.[86] The enantiomerically pure substrates **189** and **190** have two methyl groups but the reaction occurs only at the most accessible methyl group. The catalyst (*S*)-**161**) can achieve very high asymmetric induction leading to the diastereomers **191** and **192**. Clear demonstration that the reaction is under catalyst control is seen when (*R*)-**161**) because in this case the other diastereomers **193** and **194** are formed.



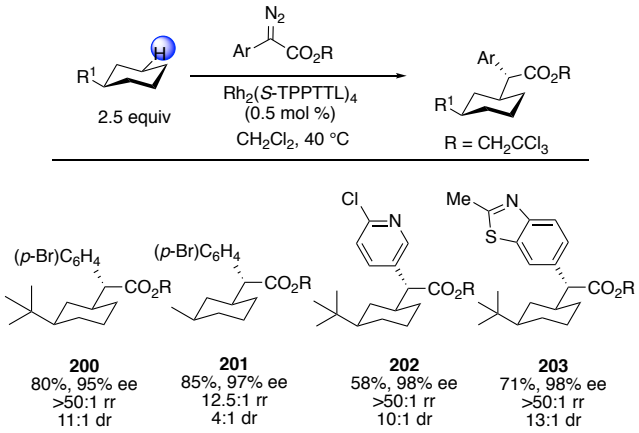
Scheme 45

An impressive example illustrating the effectiveness of the catalyst control is seen in the reaction with the steroid **195** (Scheme 46).[86] Even though this compound has several allylic sites, these sites are not functionalized because they are too sterically crowded. When Rh_2(*R*-TCPTAD)$_4$ (**150**) and the trifluoroethyl aryldiazoacetate **196** were used, the reaction occurs at the most accessible tertiary site to form **197**, whereas when Rh_2[*S*-tris(p-^{t}BuC$_6$H$_4$)TPCP]$_4$ (**161**) and trifluoroethyl aryldiazoacetate **198** were used, the most accessible primary C—H bond is the preferred site to form **199**. These reactions also proceed with high asymmetric induction. The site selectivity is primarily controlled by the nature of the catalyst although the nature of the trihaloethyl ester also has some influence.



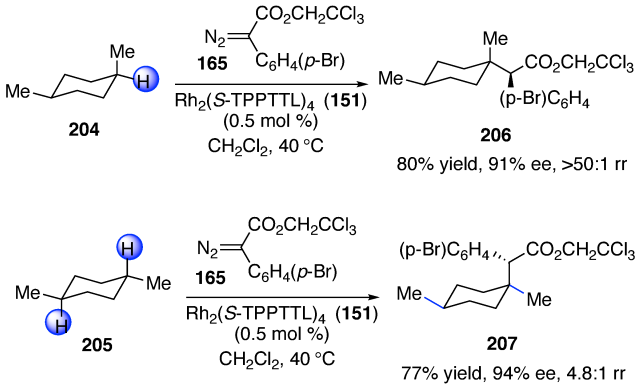
Scheme 46

Having established catalysts that are capable of selecting between primary, secondary and tertiary C—H bonds, we have begun examining the possibility of distinguishing between similar unactivated secondary C—H bonds. A particularly impressive example is the Rh_2(*S*-TPTTTL)$_4$ (**151**)-catalyzed reaction of aryldiazoacetates with alkylcyclohexanes, which results in desymmetrization of the cyclohexane with a clean reaction at the equatorial C3 C—H bond (Scheme 47).[83] Illustrative examples are the reactions to form **200-203**. The reactions are routinely highly enantioselective and diastereoselective at the C—H functionalization site and the dr in this case represents the kinetic resolution (reactions at C3 equatorial versus C5 equatorial). As expected the kinetic resolution in the reaction of tertbutylcyclohexane to form **200** is greater than in the case of methylcyclohexane to form **201**. Even though p-bromophenyldiazoacetate is the standard reference reagent used to evaluate the C—H functionalization selectivity, a range of aryl and hetereoaryldiazoacetates are compatible as illustrated in the formation of **202** and **203**. The site selectivity control exhibited by Rh_2(*S*-TPTTTL)$_4$ (**151**) is different from the other chiral catalysts. It is not simply due to the steric environment around the carbene because it behaves as if it is not that sterically crowded. An additional controlling factor is how the substrate fits within the pocket during the C—H functionalization.



Scheme 47

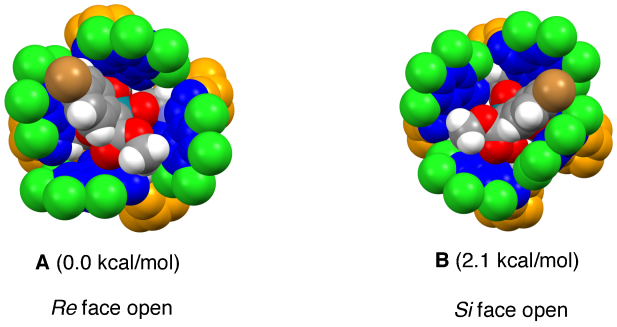
The Rh_2(*S*-TPTTTL)$_4$ (**151**)-catalyzed reaction with 1,4-dimethylcyclohexanes **204** and **205** gives an indication of the rate difference between C—H functionalization occurring at equatorial versus axial positions (Scheme 48).[83] Both **204** and **205** are capable of undergoing. C—H functionalization at tertiary C—H bonds, as illustrated in the formation of **206** and **207**. However, competition experiments reveal that the reaction with the cis isomer **204** is 70 times fasters than the trans isomer **205**, which indicates that attack at the equatorial position is 140 times more favorable than attack at the equatorial position.



Scheme 48

The site selectivity exhibited by the various chiral dirhodium catalysts prepared to date is considered to be primarily due to steric factors. In collaborations with Dr. John Bacsa we have been obtained extensive crystallographic information on a large number of the catalysts and combined with extensive computational studies in collaboration with Dr. Djamalddin Musaev and more recently with Dr. Ken Houk, we have gained insight about the dynamics of the catalysts and the catalyst-carbene complexes. A complete understanding of how these catalysts perform is challenging because the complexes are so large, but an illustration of the proposed models for how two of the catalysts are discussed below.

Rh_2(*S*-TCPTAD)$_4$ (**150**) adopts a C_4 symmetric bowl-like structure (Scheme 35).[82] The wall of the "bowl" spreads outward such that once the carbene is bound, a tertiary C-H bond, which is electronically preferred, can still approach closely to the carbene, but only if is uncrowded, such as an isopropyl group (Scheme 49). C_4 symmetric bowl-shaped catalysts would not normally be considered ideal for asymmetric induction, but in this case the donor group of the carbene is involved in π-stacking to a phthalimido group, Two π-stacking complexes **A** and **B** can be formed and the preferred orientation **B** leads to the observed asymmetric induction (*Re* face attack). The TPCP catalysts can adopt different symmetries but in each case the carbene will be contained within a sterically crowded environment. The catalyst wall in these cases is more directly upwards and the steric environment is much more severe. Rh_2(*R*-3,5-di(p-$tBuC_6H_4$)TPCP)$_4$ (**158**) and Rh_2(*S*-2-Cl-5-BrTPCP)$_4$ (**160**) (Schemes 36 and 37) have a strong preference for the most sterically accessible secondary site and Rh_2[*R*-tris(p-$^tBuC_6H_4$)TPCP]$_4$ (**161**) (Scheme 38) causes reaction to occur at the most accessible primary site.



A (0.0 kcal/mol)

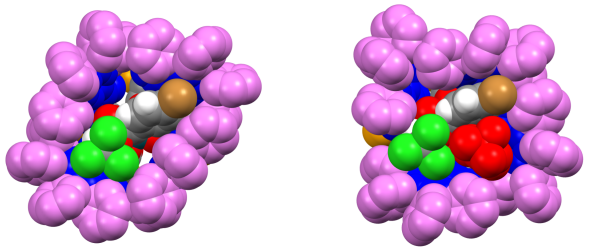
Re face open

B (2.1 kcal/mol)

Si face open

Scheme 49

The controlling elements in Rh_2(*S*-TPTTTL)$_4$ (**151**) is much subtler because it is not that sterically demanding at the carbene site.[83] The site selectivity come from how the substrate fits into the pocket and what features of the substrate interferes with the wall of the catalyst. Rh_2(*S*-TPTTTL)$_4$ (**151**) is also C_4 symmetric but has the additional feature of the indicated propeller chirality due to the tilting of the 16 phenyl ring (Scheme 35). The catalyst is relatively rigid but is still capable of some flexibility to allow the carbene to bind and then allow the substrate to approach the bound carbene complex (Scheme 50). Structure **C** shows the lowest energy form of the rhodium carbene complex and structure **D**, shows the lowest energy transition state for the *tert*-butylcyclohexane reacting with the carbene. The attack of the carbene is occurring at the equatorial C-3 position of the cyclohexane and the red *tert*-butyl group is pointing out of the pocket. The corresponding model of the complex with attack occuring at C-4 of the cyclohexane cannot be made because the *tert*-butyl group would have a serious steric class with the wall of the catalyst.



C (rhodium carbene complex)

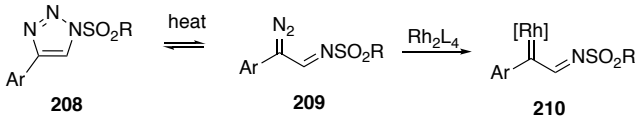
D (rhodium carbene/substrate TS)

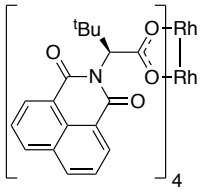
Scheme 50

Alternative Precursors to Donor/Acceptor Carbenes

Diazo compounds have been shown to be ideal precursors to the metal carbene intermediates, especially when conducting challenging C—H functionalization reactions because the nitrogen byproduct does not interfere with the reactions. However, there is considerable interest in developing alternative strategies to the carbene intermediates because this could broaden the scope of the type of

donor/acceptor carbenes that could be accessed. One particularly effective approach has been the ring-opening reaction of *N*-sulfonyltriazoles, initially developed by Fokin[89] and then popularized by several research groups (Scheme 51).[90] The *N*-sulfonyltriazoles **208** on heating in the presence of a dirhodium catalysts undergoes ring opening to a diazo compound **209**, which then loses nitrogen to generate the rhodium-bound imino carbene **210**. The best catalyst for asymmetric induction with this system is Rh_2(*S*-NTTL)$_4$ (**211**), a catalyst originally developed by Muller.[91]

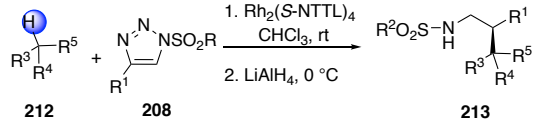


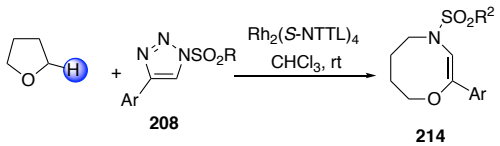


Rh_2(*S*-NTTL)$_4$ (**211**)

Scheme 51

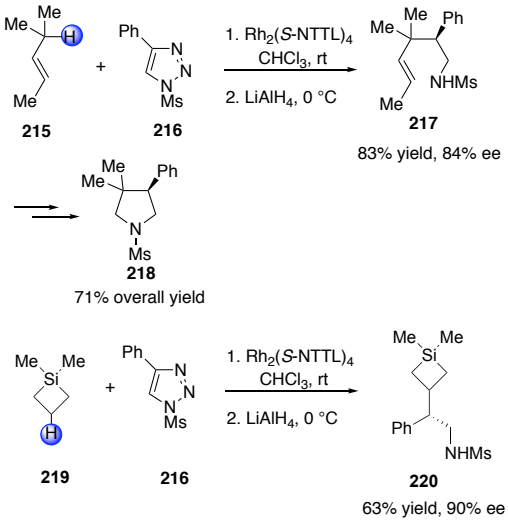
This approach has been widely used in a range of carbene reactions but its application in C—H functionalization reactions is still underdeveloped. Folkin showed that the Rh_2(*S*-NTTL)$_4$-cataltzed reaction was effective in enantioselective C—H functionalization of alkanes **212**, followed by reduction, to form the sulfonylated amines **213** (Scheme 52).[89] However, the initial studies revealed that extension to other substrates was limited as illustrated, in the reaction with tetrahydrofuran to form the ring expanded product **214**.[92] This is considered to occur first by oxonium ylide formation followed by 2,3-sigmatropic rearrangement. In contrast, in the case of aryldiazoacetates, there is evidence to suggest that the reaction of the carbene with heteroatoms can be reversible,[93] which explains why a range of functional groups are compatible with aryldiazoacetates even when functionalization is occurring at unactivated C—H bonds.





Scheme 52

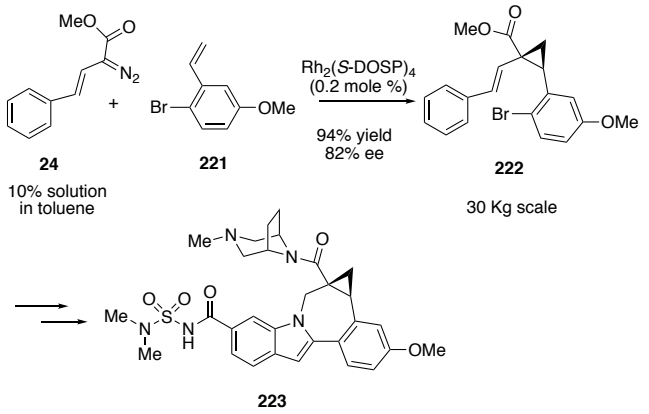
Recently, we have demonstrated that the *N*-sulfonyl triazoles can be applied to C—H functionalization reactions with more elaborate substrates than just alkanes, as illustrated in Scheme 53.[94] The Rh_2(*S*-NTTL)$_4$-catalyzed reaction of the trans alkene **215** with the triazole **216** results in clean allylic C—H functionalization at the tertiary site to form **217** in 84% yield after reduction. Ozonolysis of **217** followed by reductive amination generated the pyrrolidine **218**. The four steps could be conducted in a one-pot process to generate **218** in 71% overall yield from the triazole **215**. Another effective substrate is silacyclobutanes as illustrated by the Rh_2(*S*-NTTL)$_4$-catalyzed conversion of **219** to **220**.[95] So far, Rh_2(*S*-NTTL)$_4$ has been shown to be the superior chiral catalyst for the *N*-sulfonyltriazole system, and so, the option for effective catalyst-controlled site selectivity has not yet been realized in this system.



Scheme 53

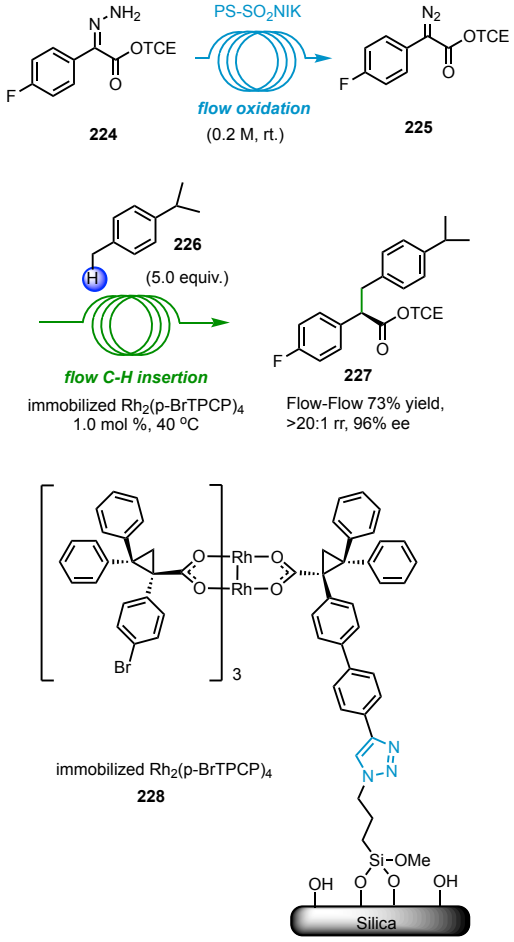
Enhancement of the Practicality of Rhodium-Catalyzed Reactions of Donor/Acceptor Carbenes

The rhodium-catalyzed reactions of donor/acceptor carbenes have resulted in a number of synthetically useful transformations. Even so, it is important to consider the practicality of these reactions generally because the dirhodium catalysts are expensive and diazo compounds have high energy and are potentially explosive. The Rh-DOSP-catalyzed enantioselective cyclopropanation of styrene **221** to form **222**, a key intermediate in the synthesis of the antiviral drug, Beclabuvir (**223**), has been conducted safely on a multi-Kilogram scale by keeping the styryldiazoacetate **24** as a 10% solution in toluene (Scheme 54).[96] We have already demonstrated that the rhodium catalysts can be used with very low catalyst loading, which mitigates the high cost of these catalysts.



Scheme 54

Another way to enhance the practicality of the chemistry has been to conduct the reactions with immobilized catalysts either in batch or in flow. In collaboration with the Jones group both Rh-DOSP and Rh-TPCP related catalysts have been immobilized and demonstrated that they are capable of a range of C—H functionalization reactions in flow, including reactions at unactivated C—H bonds.[97] An even more advantageous protocol would be the generation of the diazo compounds in flow because this would avoid the buildup of large quantities of it, as illustrated in Scheme 55.[97c] A potassium iodosulfonamide resin (PS-SO_2NIK) was found to be an effective oxidant for the conversion of a hydrazone **224** to the diazo compound **225** in flow, and after passing through a column containing a drying agent and sodium thiosulphite as a reductant, the diazo compound **225** can be directly reacted either in batch or in flow in subsequent C—H functionalization reactions, as illustrated in the benzylic primary C—H functionalization of **226** to form **227**. In the current system an immobilized version of Rh_2(*p*-BrTPCP)$_4$ (**228**) was used as the catalyst, The site- and stereoselectivity of the flow reactions compares very favorable with the results obtained with the corresponding homogeneous catalyst in batch.



Scheme 55

Summary and Future Outlook

In conclusion, this perspective illustrates the stages involved in the development of catalyst-controlled site-selective C—H functionalization reactions of donor/acceptor carbenes. Research progress rarely follows a straight line as exemplified by this research program. It began focusing on the discovery of new reactions of rhodium carbene intermediates, which lead to the recognition that donor/acceptor carbenes have modulated reactivity compared to the standard carbene intermediates lacking the donor group. This opened up the possibility for the development of highly selective synthetic methods and effective chiral dirhodium catalysts. A curious series of events led to the use of hydrocarbons as the routine solvents for these carbene reactions. For several years, it was not realized that these more stabilized carbenes would still be able to react with hydrocarbon solvents. However, once a failed reaction revealed that reactions with hydrocarbons were indeed possible, the program of selective intermolecular C—H functionalization with donor/acceptor carbenes began in earnest and continues unabated to this day.

Even though considerable progress has been made in catalyst controlled C—H functionalization, many challenges still remain. The remarkable selectivity

requires donor/acceptor carbene reagents so a major challenge is to broaden the scope of the chemistry. What other types of carbenes or other group transfer agents can be used? Can the donor group be expanded to amino or alkoxy leading to the formation of general useful chiral α-amino- and α-alkoxy acids? The catalysts so far simply rely on steric factors to control site selectivity. Is it possible to introduce other controlling elements into the catalyst structures, such as polar functionality or directing groups? The key take-home message so far is that exquisite site selectivity can be obtained using transition metal catalysts, and hopefully this will be an inspiration for others to identify other systems capable of exceptional catalyst-controlled C—H functionalization.

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Notes

The author is a named inventor on a patent entitled, Dirhodium Catalyst Compositions and Synthetic Processes Related Thereto (US 8,974,428, issued March 10, 2015).

Biography

Huw M. L. Davies was born in Aberystwyth, Wales, UK. He received his B. Sc. degree from University College Cardiff, Wales (1977) and his Ph. D degree from the University of East Anglia (1980). After a post-doctoral position at Princeton University (1980-1983), he joined the faculty at Wake Forest University (1883-1995). After being promoted to full professor he moved to the University at Buffalo, the State University of New York (1995-2008) where he held the positions of UB Distinguished Professor and Larkin Professor of Organic Chemistry. In 2008 he moved to Emory University as the Asa Griggs Candler Professor of Chemistry. He is currently the Director of the NSF Center for Chemical Innovation for Selective C—H Functionalization.

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