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Investigating Sustainable Precious Metal Catalysis: Routine Dirhodium Catalyzed Carbene Reactions with High Yield and Enantioselectivity at Low Loadings

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By

Matthew D. Chuba

B.S., Allegheny College, 2014

Advisor: Huw M. L. Davies, Ph.D.

An abstract of
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Abstract

Investigating Sustainable Precious Metal Catalysis: Routine Dirhodium Catalyzed Carbene Reactions with High Yield and Enantioselectivity at Low Loadings

By Matthew D. Chuba

Precious metal catalysts have been established to have highly desirable reactivity and selectivity profiles in carbene reactions. Three approaches have emerged to make this transformation more sustainable: reproducing the reaction with earth abundant catalysts, improving recyclability through immobilization of the precious metal catalysts and optimizing the reaction of the precious metal catalysts. This project focuses on the last approach, an avenue the findings of which is expected to have significant impact on the previous two. To date, our investigations have focused on developing routine conditions that provide high yields and enantioselectivity in carbene reactions such as cyclopropanation and C−H functionalization reactions. Using methyl 2-furoate as a model substrate, we were able to demonstrate that cyclopropanation can be performed reproducibly with TONs close to 2 million employing loadings as low as 0.00005 mol% of Rh_2(*S*-TCPTTL)$_4$. Using 0.001 mol% of Rh_2(*S*-TCPTTL)$_4$ as the optimum catalyst loading, cyclopropanation and C−H insertion reactions were performed on a variety of substrates demonstrating the robustness of the developed conditions.

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List of abbreviations

APCI atmospheric pressure chemical ionization

Ar aryl

Bn benzyl

Bu butyl

DBU 1,8-diazabicycloundec-7-ene

Cy cyclohexyl

DCC *N*,*N*-dicyclohexylcarbodiimide

1,2-DCE 1,2-dichloroethane

DCM dichloromethane

DMAP *N*,*N*-4-(dimethylamino)pyridine

DMB 2,2-dimethylbutane

DMF dimethylformamide

d.r. diastereomeric ratio

EDG electron-donating group

e.e. enantiomeric excess

Et ethyl

equiv. equivalents

ESI electrospray ionization

EWG electron-withdrawing group

FTIR Fourier transform infared spectroscopy

HMPA hexamethylphosphoramide

HPLC high performance liquid chromatography

HRMS high-resolution mass spectrometry

Imid. Imidazole

IR infrared spectroscopy

L ligand

LAH lithium aluminium hydride

LC/MS liquid chromatography mass spectrometry

LDA lithium diisopropylamide

Me methyl

mmol millimoles

NMR nuclear magnetic resonance

N.R. no reaction

NSI nanospray ionization

***o*-NBSA** *ortho*-nitrobenzenesulfonyl azide

***p*-ABSA** *para*-acetamidobenzenesulfonyl azide

Ph phenyl

Piv pivaloyl

Pr propyl

RM reaction mixture

RXN reaction

TBAF tetrabutylammonium fluoride

TBS *tert*-butyldimethylsilyl

TCE 2,2,2-trichloroethyl

TEA triethylamine

temp temperature

THF tetrahydrofuran

TLC thin layer chromatography

Introduction:

Developing robust catalytic reactions that perform with high turnover numbers (TONs) is an important challenge in noble metal catalysis.[1,2] Achieving high TONs provides the ability to reduce the amount catalyst employed, in turn reducing the amount of heavy-metal waste produced, significantly improving the sustainability of these transformations. Many of these catalytic processes use expensive metals such as rhodium, palladium, and ruthenium. There has been some progress in asymmetric high TON carbon-carbon bond forming reactions that suggest very low catalyst loading can be effective.[3-5] High TON reactions require fast and robust catalytic cycles.

Diazo compounds, effective precursors to carbenes, offer the opportunity to be used in high TON reactions because of their ability to be decomposed readily by a variety of metal catalysts to form metal-stabilized carbenes, highly reactive reagents the selectivity of which can be guided by the metal catalyst employed.[6] Metal carbenes can be classified by the electronic nature of the substituents that flank the carbene carbon, and typically fall under three categories: acceptor-only, acceptor/acceptor, and donor/acceptor metallocarbenes. (Fig. 1).[7] Donor groups can be a variety of functionalities including vinyl and aryl groups. The acceptor portion can be a variety of electron-withdrawing groups including esters or ketones.

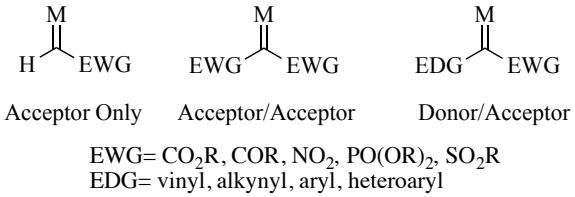
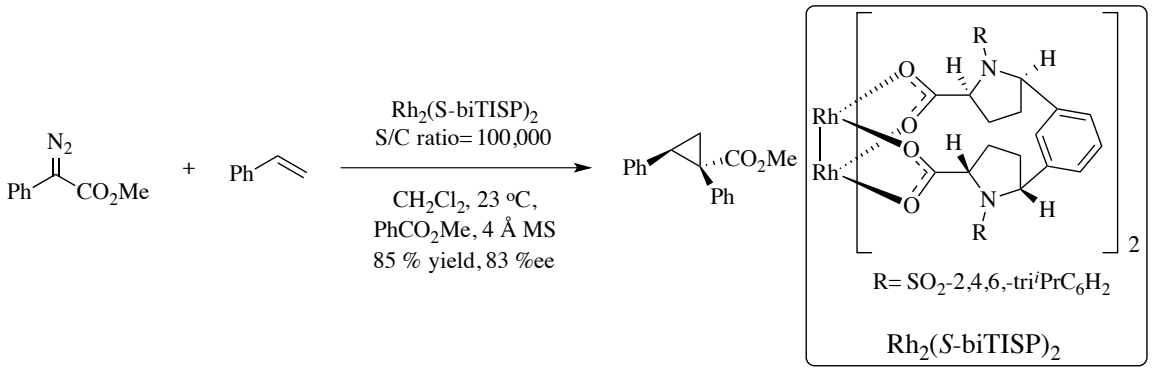


Figure 1. Classes of Metal Carbenes.

Acceptor-acceptor carbenoids have been established as the most reactive of the three classes.[8,9] The commercially available ethyl diazoacetate has received extensive investigation, typically requiring precious-metal catalyst loadings on the level of 1 mol%.[6,10] There has been one study in which 11,000 TONs were achieved using ethyl diazoacetate and a ruthenium porphyrin catalyst.[11] Typically, donor/acceptor carbenoids are more stable due to the complimentary 'push-pull' nature of the substituents. This stability imparts a level of selectivity greater than the other two common carbene classes, and in turn donor/acceptor carbenes have been demonstrated to be the least reactive out of the three classes.[7]

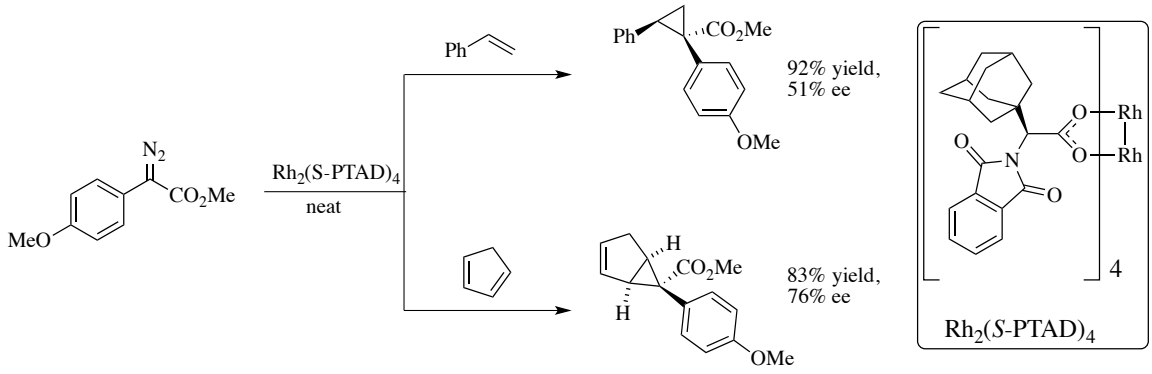
One the first reports of donor/acceptor diazo compounds being used for high-turnover cyclopropanations was reported in 2003 by Davies and co-workers.[12] In this report, Rh_2(*S*-biTISP)$_2$ was used to catalyze the cyclopropanation of styrene (Scheme 1) using methyl phenyldiazoacetate as the carbene precursor.



Scheme 1. Cyclopropanation of Styrene using Rh_2(*S*-biTISP)$_2$.

Using methyl benzoate and molecular sieves as additives, 92,000 TONs were achieved with an 85% yield and 83% ee. Without the additives the cyclopropanation occurs in an 82% yield and 65% ee. Additives were needed in this case, to develop robust conditions that give high yield and enantioselectivity. Methyl benzoate is believed to stabilize the rhodium carbenoid complex either by coordinating to the carbenoid or the other rhodium center but the exact role of methyl benzoate is still unknown.[12]

Achieving close to 100,000 turnovers was a ground-breaking accomplishment but it required the use of an exotic bridged catalyst and additives were needed to achieve the high TONs. It was proposed that the bridged catalyst was required due to its increased stability. In 2010, Davies and coworkers were able to demonstrate that TONs over 1 million using donor/acceptor diazo compounds could be reached.[13] Through *in situ* FTIR spectroscopy studies they showed that the catalyst was inactive after 400 TONs when ethyl diazoacetate was used; however, when donor/acceptor diazo compounds were used the catalyst remained active even though the reaction proceeded more slowly. In order for high TONs, neat conditions were required. Several substrates were tested including both styrene and cyclopentadiene. Using *p*-(methoxy)phenyldiazoacetate and 0.00005 mol% of Rh_2(*S*-PTAD)$_4$ the cyclopropanated product derived from styrene was formed in 92% yield and 51% ee (Scheme 2). Under very similar conditions except using 0.00006 mol% of catalyst the cyclopropanation of cyclopentadiene occurs in an 83% yield and 76% ee (Scheme 2). These reactions represent TONs of 1.3 million for cyclopentadiene and 1.8 million for styrene. The activity of the catalyst in these transformations, an order of magnitude greater than any previous studies, currently represents the frontier of reported activity for these systems.



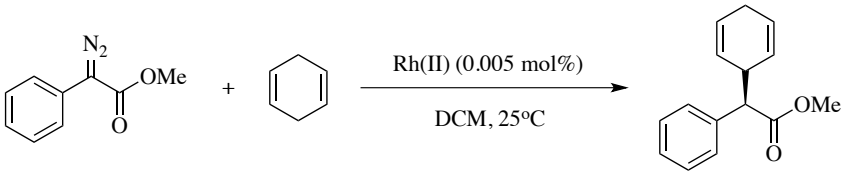
Scheme 2. Cyclopropanation of Styrene and Cyclopentadiene with Rh_2(*S*-PTAD)$_4$.

Since these reports, work has been done on these systems in the form of understanding the kinetics of these reactions when trying to achieve high turnover numbers. The cyclopropanation of styrene using various dirhodium tetracarboxylate catalysts and aryl diazoacetates was studied in collaboration with Prof. Donna Blackmond at The Scripps Research Institute. These studies used various techniques and equipment most of which was done using *in situ* FTIR spectroscopy studies. The results from these experiments gave insight into issues that may arise during the reaction. The kinetic studies showed that coordination of the styrene trap and cyclopropane product results in lower reaction rates.[14] Other common substrates used for dirhodium(II) carbene chemistry containing either Lewis basic sites or an olefin should have a similar effect on the reaction rate because of their ability to coordinate to the axial positions of the dirhodium catalyst and prevent product formation. The interactions between the catalyst and olefin are crucial for high turnovers even though it slows the reaction rates.[14] It was also determined, through multiple injection calorimetry studies, that the catalyst itself is

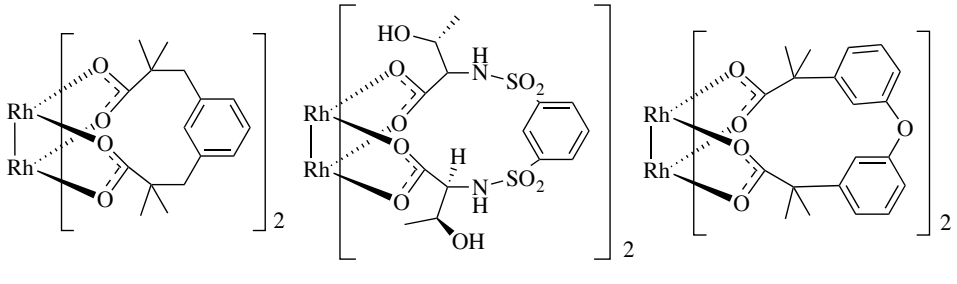
altered as the reaction progresses. This resulted in lower enantioselectivity due to the modified catalyst. One way to stabilize the enantioselectivity is to increase the temperature. The rate law was derived for cyclopropanation of styrene (Equation 1).[14]

$$r = k'[\text{diazo}]^{0.8}[\text{styrene}]^{-1}[\text{product}]^{-1}[Rh_T] \qquad (1.0)$$

Similar work has also been done studying C−H insertion into 1,4-cyclohexadiene using aryl diazoacetates and various dirhodium(II) catalysts (Table 1). The results that came out of this study are similar to those of the cyclopropanation study in which, concentration of catalyst and diazo compound are reaction-driving forces.[14]



Entry	Catalyst	% Conv.	% ee	TON	TOF_{avg} (hr^{-1})
1	Rh_2(*S*-DOSP)$_4$	90	27	18,000	6,000
2	Rh_2(*S*-PTAD)$_4$	92	52	18,400	767
3	Rh_2(*S*-biTISP)$_2$	44	42	8,800	367
4	Rh_2(esp)$_2$	>99	--	20,000	24,000
5	MK-1-235	>99	30	20,000	6,250
6	KWF-V-049	>99	--	20,000	20,000



Rh_2(esp)$_2$ MK-1-235 KWF-V-049

Table 1. C−H Insertion Into 1,4-Cyclohexadiene Using Various Dirhodium(II) Catalysts.

The inhibitors of the reaction are the starting olefin and product of the reaction via coordination to the axial positions of the dirhodium catalyst.[14] Another interesting fact from this study to note was that bridging catalysts were more kinetically active than non-bridging catalysts, which could potentially influence catalyst development in this area. The rate law for C−H insertion into 1,4-cyclohexadiene was determined in this study (Equation 1.1).[14]

$$r = k'[\text{diazo}]^{0.5}[\text{1,4-cyclohexadiene}]^{-1}[\text{product}]^{-1}[Rh_T] \qquad (1.1)$$

With a better understanding of the kinetics of these types of reactions, the catalyst as a whole needs to be discussed in terms of stability, symmetry and substrate trajectories. Dirhodium(II) tetracarboxylate catalysts are very stable compared to other metal-based catalysts (Figure 2). They tend to be stable towards heat, moisture, and ambient atmosphere. When designing catalysts symmetry plays an important role because it can reduce the amount of substrate trajectories.[15,16] Asymmetric induction can thus be controlled by the symmetry of the complex. Rh_2(*S*-DOSP)$_4$ is a proline derived catalyst that has D_2 symmetry in which the ligands are oriented in an up-down up-down manner. There are two equivalent active sites with sterically bulky groups that restrict the nucleophile trajectory to the axial carbene ligand.[16] Another set of catalysts that include Rh_2(*S*-PTAD)$_4$ and Rh_2(*S*-PTTL)$_4$ are phthalimido based (Fig. 2). The tetrachloro

versions in which the aryl hydrogens are substituted for chlorine atoms were also synthesized. Rh_2(*S*-PTTL)$_4$ has been shown to adopt a chiral crown structure in which the phthalimide groups point in the same direction. This would result in C_4 symmetry. These types of structures guide selectivity towards the open face.[16] The latest generation of ligand architectures are the triarylcyclopropane carboxylates. These are considered to be the bulkiest of the ligand environments discussed so far but not of all dirhodium catalysts. Rh_2(*S*-BPCP)$_4$ is an example of this class of catalysts and it has *pseudo*-C_4 symmetry (Fig. 2). These types of catalysts incorporate a very rigid and tunable ligand environment.[17] They tend to have the same sense of enantioinduction as Rh_2(*S*-DOSP)$_4$.

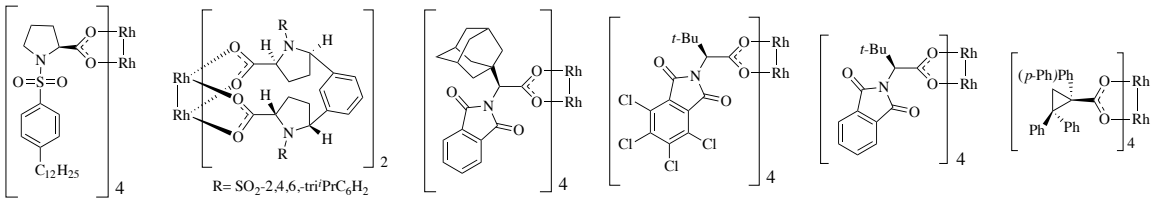
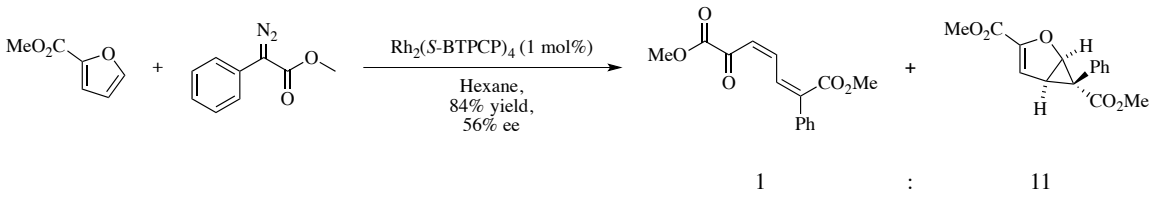


Figure 2. Structures of Various Dirhodium(II) Tetracarboxylates.

High turnover cyclopropanations remain an important perspective within the Davies group. The cyclopropanation of methyl 2-furoate has been re-visited because of the recent development of new dirhodium(II)-catalysts and carbene reagents.[18] Initial catalyst screenings showed that with standard Davies catalysts, Rh_2(*S*-DOSP)$_4$, Rh_2(*S*-PTAD)$_4$ and the bulkier Rh_2(*S*-BTPCP)$_4$, the product can be formed but the ring-opening product is also produced (Scheme 3). After a more comprehensive catalyst screening, Rh_2(*S*-TCPTTL)$_4$ gave the best results with only trace formation of the ring-opened

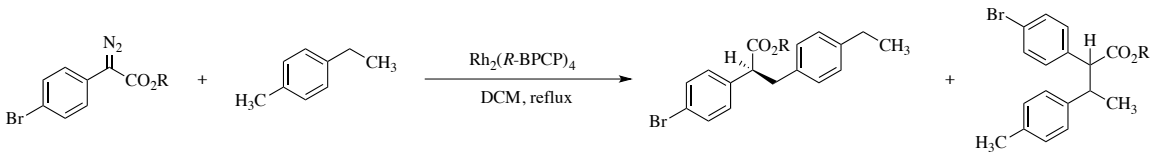
product. After further optimization of the reaction using 0.001 mol% of Rh_2(*S*-TCPTTL)$_4$ in hexane with methyl phenyldiazoacetate at 0 ^oC the cyclopropanated furan was synthesized in 86% yield and 96% ee.[18]



Scheme 3. The Formation of Cyclopropane and Ring-Opening Product.

Cyclopropanation reactions can be used to inform reactivity trends in carbene C−H functionalization chemistry. When a new tool is developed for one, it is essential to test it on the other type of reaction. Recently the Davies group has shown the benefits of using 2,2,2-trichloroethyl (TCE) aryldiazoacetates in both C−H functionalization and cyclopropanation reactions.[19,20] It has been shown that 2,2,2-trichloroethyl aryldiazoacetates are able to perform C−H insertion into methyl ether substrates. The TCE ester-based carbenes showed higher levels of enantioselectivity and regioselectivity for C−H insertion into 4-ethyltoluene when compared to the more established methyl ester-based carbenes (Scheme 4).[19] The bulkier ester is thought to prevent dimerization from occurring, allowing for the elimination of slow addition from the procedure.[18] In terms of methyl ether functionalization, the enantioselectivity was higher and the TCE ester also gave improved yields when heteroaryldiazo compounds were used.[19] Carbene dimerization and azine formation is a deleterious side reaction with these types of

transformations and the TCE ester has been shown, in comparison with the methyl ester, to be much less prone to homo-dimerization. When the reaction is performed with methyl phenyldiazoacetate, the diazo compound has to be added by syringe pump over a one-hour period. With the bulkier 2,2,2-trichloroethyl 2-diazo-2-phenylacetate, the diazo compound can be added into the reaction over 5 seconds without use of a syringe pump.

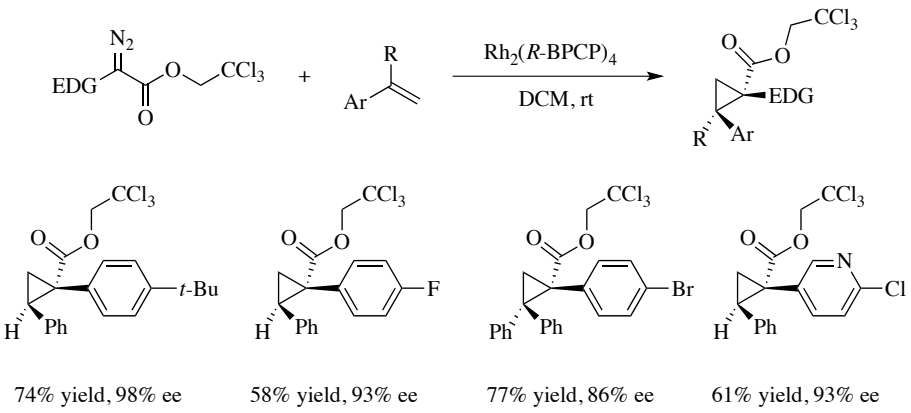


A **B**

R	A:B	Yield (%)	ee (%)
Me	5:1	74	92
CH_2CCl_3	13:1	75	98

Scheme 4. Effects of the TCE Ester on the C−H Insertion in 4-Ethyltoluene.

After the development of using TCE aryldiazoacetates in C-H functionalization, the cyclopropanation of styrene and its derivatives was studied using these bulkier ester functionalities.[20] Various diarylcyclopropane carboxylates were formed in yields ranging from 58-90% and enantioselectivities ranging from 86-98% (Scheme 5). This study demonstrates how ester size effects cyclopropanation of styrene and highlights trends from previous work with TCE esters in the C−H functionalization of methyl ethers.[19,20]



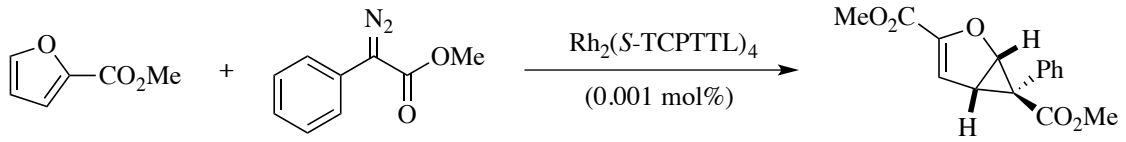
Scheme 5. Cyclopropanations of Styryl Derivatives Using TCE Esters.

TCE esters have been developed and shown to be robust reagents in dirhodium(II) catalyzed cyclopropanations and C−H functionalization. We wanted to explore the possibility that the TCE esters might provide a routine system capable of proceeding with high enantioselectivity and yield while maintaining low catalyst loadings. We hypothesized that the additional steric bulk and the more electron-withdrawing nature of the TCE ester would enhance yields and enantioselectivity when developing cyclopropanations employing low catalyst loadings.

Results and Discussion:

The first task in answering these questions was the synthesis of the diazoacetates required for this project. Using literature procedures, six different diazo compounds were synthesized on a scale of 10 grams.[19-21] With the diazo compounds in hand, a reaction was setup to repeat the previous cyclopropanation with methyl 2-furoate to see how the results compared. To a round bottom flask containing Rh_2(*S*-TCPTTL)$_4$ and methyl 2-furoate in hexane was then added a solution of methyl phenyldiazoacetate in

hexane over a 1-hour period via syringe pump. Previously, the cyclopropanation was accomplished in an 86% yield with an ee of 96% using 0.001 mol % of Rh_2(*S*-TCPTTL)$_4$ and this reaction was performed on a 74-mmole scale.[17] This reaction was repeated on roughly a third of the scale from the previous result and a 70% yield was obtained with an ee of 93% (Table 2, Entry 1). For both the above reactions the product precipitates out, as a white solid so there is an enrichment of the ee that occurs. The yield was lower than the previous result and the reaction was repeated on a 1-mmole scale several more times to gain an understanding as to why the yield was lower (Entries 2-3). In each case, the yield was roughly the same as the result obtained from the first repeat reaction. After gaining these results some reaction optimization was done to determine if better yields and enantioselectivities could be achieved for the reaction (Entries 4-6). Various conditions were tested and the results suggest that either dichloromethane or hexane can be used to run this reaction because both solvents give similar results. Dichloromethane was chosen as the solvent to maintain a homogeneous mixture, preventing any enantio-enrichment through product crystallization.



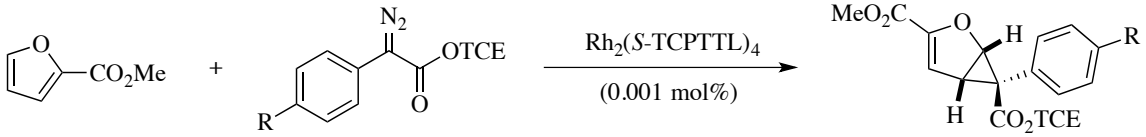
Entry	Other Conditions	Rxn Time (min)	Yield (%)	ee (%)
1	Hexane	70	70	93[a]
2	Hexane	70	67	91[a]
3	Hexane	65	61	87
4	DCM	70	69	88
5	DCM	70	62	87
6	0 °C, Hexane	70	57	89

[a]Product precipitated out *versus* purification by column chromatography

Table 2. Reaction Optimization Using Methyl Phenyldiazoacetate.

Having established optimized conditions for cyclopropanation reactions of methyl 2-furoate with methyl phenyldiazoacetate, comparison reactions were carried out using TCE phenyldiazoacetate. This was done to determine if the bulkier ester functionality would have an effect on the reaction. Running the reaction using the optimum conditions for methyl phenyldiazoacetate, the TCE cyclopropanated furan was isolated in a 90% yield and a 91% ee again using 0.001 mol% of Rh_2(*S*-TCPTTL)$_4$ (Table 3, Entry 1). A crystal structure was obtained of the cyclopropanated furan to confirm the stereochemical assignments (Fig. 3). The diazo was added over a few seconds compared to an hour with the reactions with methyl phenyldiazoacetate. Next we wanted to see if a nonpolar

solvent such as hexane effected the reaction of the TCE esters. The reaction yielded results essentially identical to the reaction with dichloromethane giving an 89% yield and an ee of 91% (Table 3, Entry 2). For the optimization reactions of both diazo compounds, the resulting crude mixture was purified by column chromatography even if the product precipitated out as a solid. The product would only crash out in hexane and the enantiomeric excess of these reactions was of the entire product isolated and not just the enriched product. Dichloromethane was chosen as the solvent for any future reactions to prevent any product from precipitating out in order to give a true indication of the enatioinducation. The TCE -*p*-bromophenyldiazoacetate was also tried to see if higher yields and enantioselectivity could be achieved. A higher enantioselectivity of 97% ee was achieved and the yield (80%) was comparable to the phenyl derivative (Table 3, Entry 4).



Entry	R	Other Conditions	Rxn Time	Yield (%)	ee (%)
1	H	DCM	30 min	90	91
2	H	Hexane	30 min	89	91
3	H	0 °C, DCM	15 min	87	93
4	Br	0 °C, DCM	1 hr	80	97

Table 3. Reaction Optimization Using TCE Phenyldiazoacetate.

Our focus turned to the investigation of the factors that impact this reaction when attempting high TON conditions because optimized conditions giving high asymmetric induction have been developed. We chose to use TCE phenyldiazoacetate as the carbene precursor because of the increased reaction yields and the practical ease of this reagent. To re-emphasize how robust the TCE esters are compared to the methyl esters, the reactions using TCE esters do not require slow addition and provided higher yields and enantioselectivity.[18]

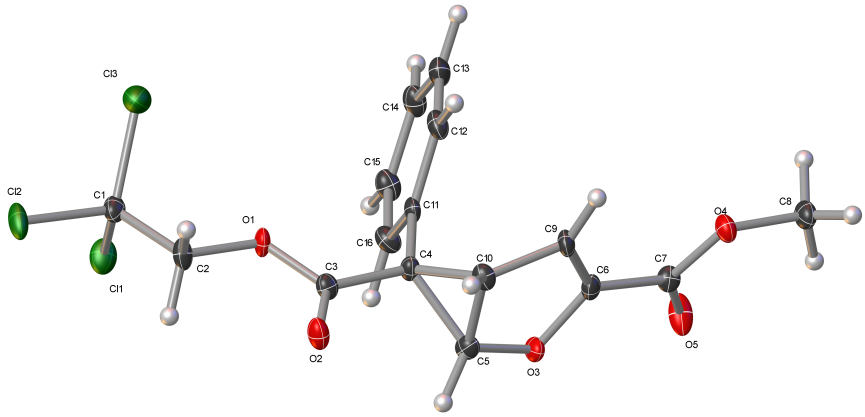
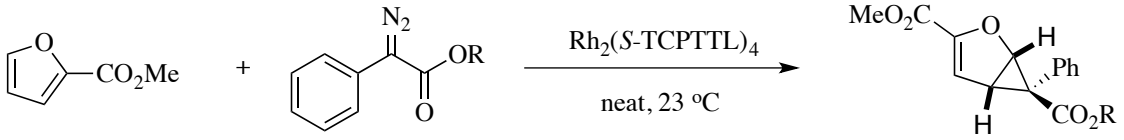


Figure 3. Crystal Structure of (−)-3-methyl 6-(2,2,2-trichloroethyl) (1*S*,5*S*,6*R*)-6-phenyl-2-oxabicyclo[3.1.0]hex-3-ene-3,6-dicarboxylate. Dr. John Bacsa at the Emory University X-Ray Crystallography Center was responsible for obtaining the crystal structure.

Initial reactions using dichloromethane as solvent with catalyst loadings of 0.0001 and 0.00001 mol% yielded no TCE cyclopropanated furan. After 6 days at 23 ^{o}C, only starting material was observed by crude ^{1}H NMR and TLC. With the previous results in mind, it was decided to run these reactions with low catalyst loadings neat because there may be impurities in the solvent that could be preventing the reaction from occurring.

The cyclopropanated furan was formed in an 85% yield with an ee of 77% when the reaction was performed neat (Table 4, Entry 1). This result demonstrated that when reactions are performed using catalyst loadings below 0.001 mol%, the conditions for the reaction are crucial. Loadings below 0.0001 mol% of Rh_2(*S*-TCPTTL)$_4$ gave either no reaction or <5% NMR yield of the cyclopropanated furan. Methyl phenyldiazoacetate was also tried using lower catalyst loadings to have data for comparison and it gave similar results to that of TCE phenyldiazoacetate (Table 4). One thing to note from these reactions is the huge difference in reaction times when decreasing the catalyst loading. If catalyst loading is at 0.001 mol%, the reaction takes 10 min but when the loading is decreased to 0.0001 mol% reaction time increases to 17 hours. If loadings below 0.0001 mol% are attempted the reaction does not proceed after 6 days or proceeds in low conversion. The key to achieving higher TONs will be focusing on figuring out what happens to the catalyst in the reaction when catalyst loading is decreased and why reaction time increases dramatically.



Entry	Catalyst Loading (mol%)	R	Rxn Time	Yield (%)	ee (%)
1	0.0001	TCE	17 hr	85	77
2	0.0001	Me	1 hr	73	73
3	0.00001	TCE	6 days	< 5[a]	---
4	0.00001	Me	6 days	---	---
5	0.000001	TCE	6 days	---	---
6	0.000001	Me	6 days	---	---

[a]Yield determined by ^{1}H NMR using mesitylene as a reference.

Table 4. Cyclopropanations with Catalyst Loadings Lower Than 0.001 mol%.

After initial experiments into finding a catalyst loading that would give consistent results in order to develop robust high turnover reactions, it was decided to study these reactions using *in situ* FTIR spectroscopy. Initial studies using catalyst loadings of 0.001 mol% in the cyclopropanation of methyl 2-furoate with TCE phenyldiazoacetate showed variable reaction times and induction periods (Figure 4). Induction times ranged from 40 minutes to a few hours causing inconsistent results that would potentially affect reactions carried out under lower loadings. In order to move forward in developing robust conditions for high turnover carbene reactions, the origins of the variable induction periods needed to be investigated.

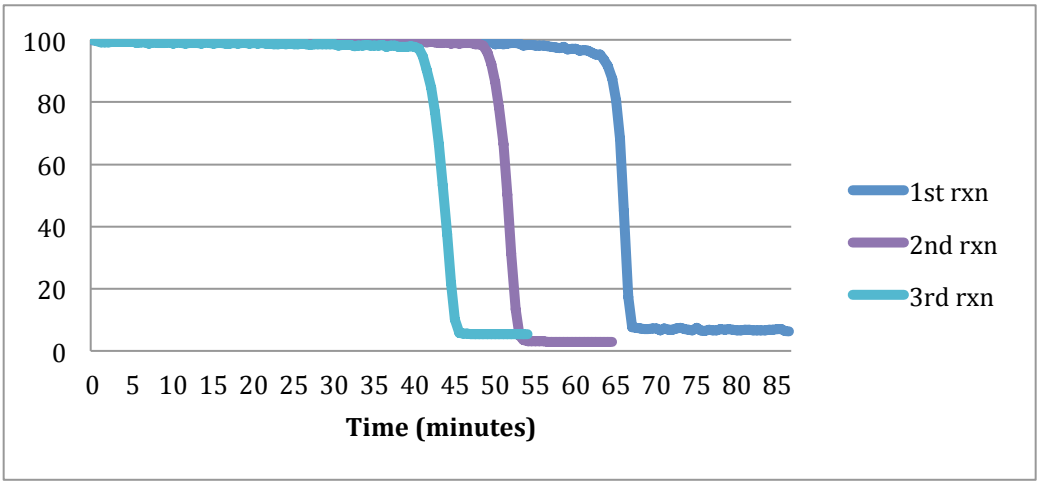
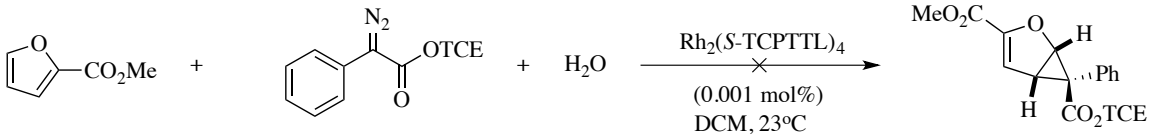


Figure 4. Decomposition of Diazo Over Time Showing Induction Time Variability Using Identical Conditions and 0.001 mol% of Rh_2(*S*-TCPTTL)$_4$.

Our first hypothesis regarding the materials put in the reactions was that trace amounts of water may have been the cause for this variable induction period. The diazo compounds we make are usually stored in a -20 ^{o}C freezer and water could have condensed inside the vessel the compound is stored in. To test this hypothesis, we wanted to see what happens to the induction period when the reaction is doped with 0.1 equivalents of water (Scheme 6). The reaction did not work after 12 hours according to ^{1}H NMR, TLC and *in situ* FTIR spectroscopy. This result confirmed that water can bind to the axial position of the catalyst and inhibit the reaction but it does not confirm that this is the case for the experiments run previously.



Scheme 6. Water Effect on the Cyclopropanation of Methyl 2-Furoate.

To confirm the hypothesis, the diazo compound was dissolved in benzene to azeotrope off the water in the diazo compound. This was done multiple times and the diazo was stored in a desiccator at room temperature to ensure that it was exposed to as little water as possible. When reactions were run using the anhydrous diazo there was still an induction period similar to that previously observed. In parallel to these studies, we investigated increasing the catalyst loading in small increments to see how this would impact the induction period (Figure 5). The induction period decreased when catalyst loading was increased showing there is a barrier that is overcome.

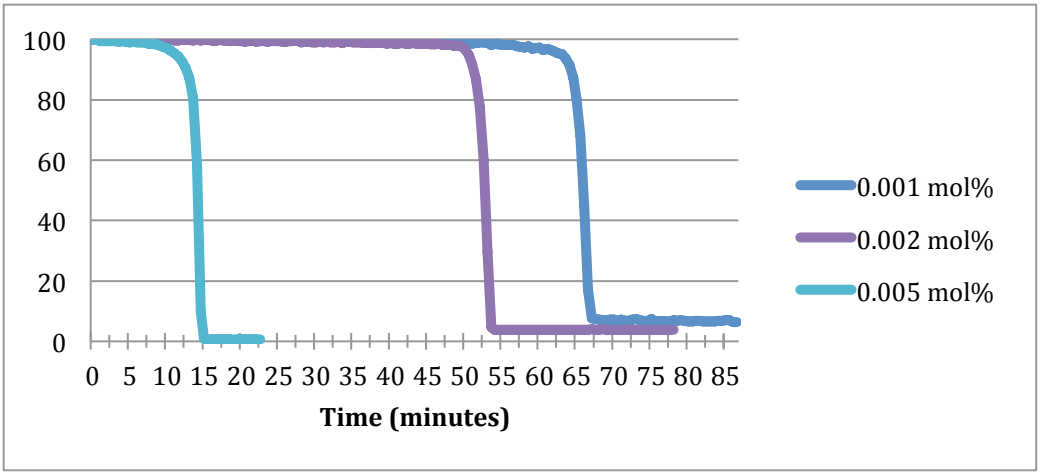
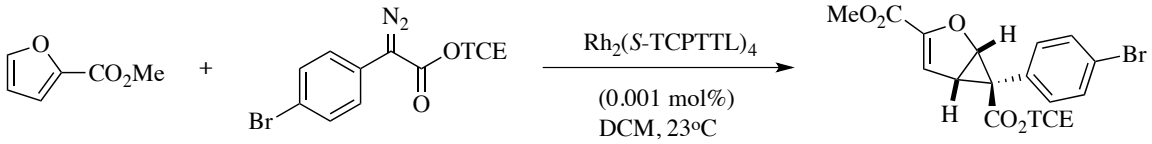


Figure 5. Decomposition of Diazo Over Time Showing Catalyst Loading Effects on Induction Time.

A complimentary study using Rh_2(*S*-TCPTAD)$_4$ and TCE -*p*-bromophenyldiazoacetate was also being studied during the same time as these other experiments and it gave no induction period with a reaction time of approximately one minute. This experiment and the experiments mentioned above led us to believe that trace amounts of water was not the issue. We next turned our focus to the differences between the reactions and one of them being a different diazo compound, the next thing we decided to test was diazo purity. The diazo was purified using flash chromatography again and an interesting result occurred in which there was no induction period with a reaction time of approximately one minute (Figure 6). The impurity causing the induction time variability is coming from the diazo compound and the next step was figuring out what was that impurity. Several techniques were used to try and figure out the identity of the impurity including ^{1}H NMR, HPLC, and LC/MS but these were unsuccessful and the impurity could not be identified.



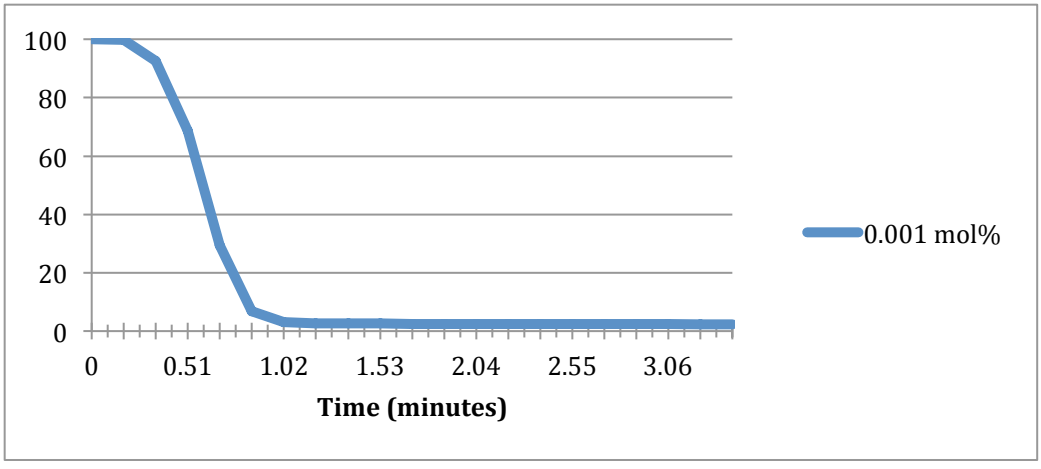
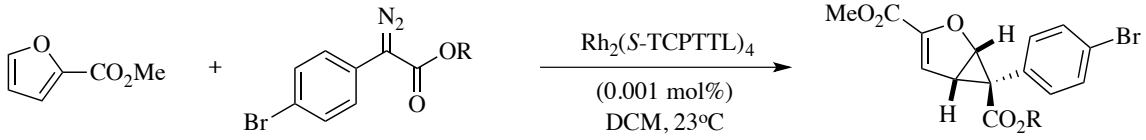


Figure 6. Decomposition of Diazo Over Time Showing Reaction Progress Without an Induction period.

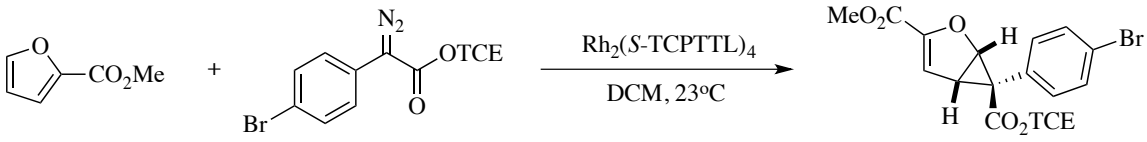
With a better understanding of the model reaction the ester functionality on the diazo compound was re-examined to see if TCE-*p*-bromophenyldiazoacetate is more robust than methyl-*p*-bromophenyldiazoacetate. Reactions were carried out using *in situ* FTIR spectroscopy so that kinetic data could eventually be gathered. Reactions using both diazo compounds were studied using two different addition times (Table 5). First, the diazo was added over one hour and the second addition time was over a few seconds. In both cases the methyl ester gave higher enantioselectivity but the yields suffered compared to the TCE ester. From these results, the TCE ester is more effective in this high turnover cyclopropanation. An interesting result from this study showed the methyl ester gave similar results when both lengths of addition were used even though the methyl ester is usually added over an hour period to prevent dimers from forming.



Entry	R	Addition Time	Yield (%)	ee (%)
1	TCE	Few Seconds	90	91
2	OMe	Few Seconds	74	93
3	TCE	One Hour	90	91
4	OMe	One Hour	75	95

Table 5. TCE Ester versus Methyl Ester in the Cyclopropanation of Methyl 2-Furoate.

With conditions developed for the model substrate, lower loadings were explored again. Since diazo purity seems to play a big role in these reactions, we expect the model cyclopropanation to give higher yields and enantioselectivity than the results observed in the past. When loadings were decreased to 0.0001 mol% of Rh_2(*S*-TCPTTL)$_4$ the reaction proceeded with 84% yield and 91% ee (Table 6, Entry 2). This result furnishes similar yields to the results seen before but with improved enantioselectivity. The loadings can be decreased even further to 0.00005 mol% to give 93% yield and 80% ee (Entry 3). This loading is equivalent to approximately 1.8 million turnover numbers and the enantioselectivity is higher than past studies.[13,14] Loadings lower than 0.00005 mol% were attempted but there was no reaction (Entry 4). Since the lower loadings are on such a small scale factors including impurities in the solvent, diazo, and glassware play an increasing role. Any of these impurities could be coordinating to the axial position of the dirhodium and the catalyst is present in such a low quantity that a sufficient concentration of active catalyst is not achieved.



Entry	Catalyst Loading (mol%)	Yield (%)	ee (%)
1	0.001	90	91
2	0.0001	84	91
3	0.00005	93	80
4	0.00001	NR	--

Table 6. Catalyst Loading Effects on the Cyclopropanation of Methyl 2-Furoate.

The next step in developing robust conditions for general high turnover carbene reactions was to determine a loading level that would give consistent results across a range of substrates and transformations. During some initial experiments with the model substrate using 0.0001 mol% of Rh_2(*S*-TCPTTL)$_4$ there were problems of reproducibility. Even after re-purification of the starting diazo compound reaction times varied significantly from 10 minutes to 1 hour. Also, the diazo did not react at times making this reaction tough to reproduce. If our goal is to develop robust conditions for general high turnover carbene reactions then 0.0001 mol% is not the catalyst loading to demonstrate the versatility of these conditions. Moving forward 0.001 mol% of catalyst was used because the results could be easily reproduced and still represent a significant increase in catalyst efficiency.

Now that a general set of conditions had been developed, a variety of substrates could be tested in terms of both cyclopropanation and C−H insertion reactions. Cyclopropanation reactions were the first set of reactions explored and a variety of different substrates were found to be effective including styrene, 1,1-diphenylethylene, *cis*-β-methylstyrene, and 2,3-benzofuran (Table 7). *Cis*-substituted alkenes tend to give high enantioselectivity compared to styrene and 1,1-diphenylethylene. Interestingly, when 2,3-dihydrofuran was used there was no enantioselectivity in the reaction giving racemic material (Table 7). A couple of factors could account for this, one being that there was litte chiral influence in the pocket of the catalyst because of the small size of the substrate. The substrate could potentially approach the carbene from any position

because of its small size. Another possible reason for no enantioselectivity would be a ring-opening event occurring that would then close giving racemic product. The cyclopropanation of cis alkenes with this system will need to be studied computationally to fully understand how these substrates fit into the catalyst pocket. Also, this would give insight into why 2,3-dihydrofuran gave racemic cyclopropane.

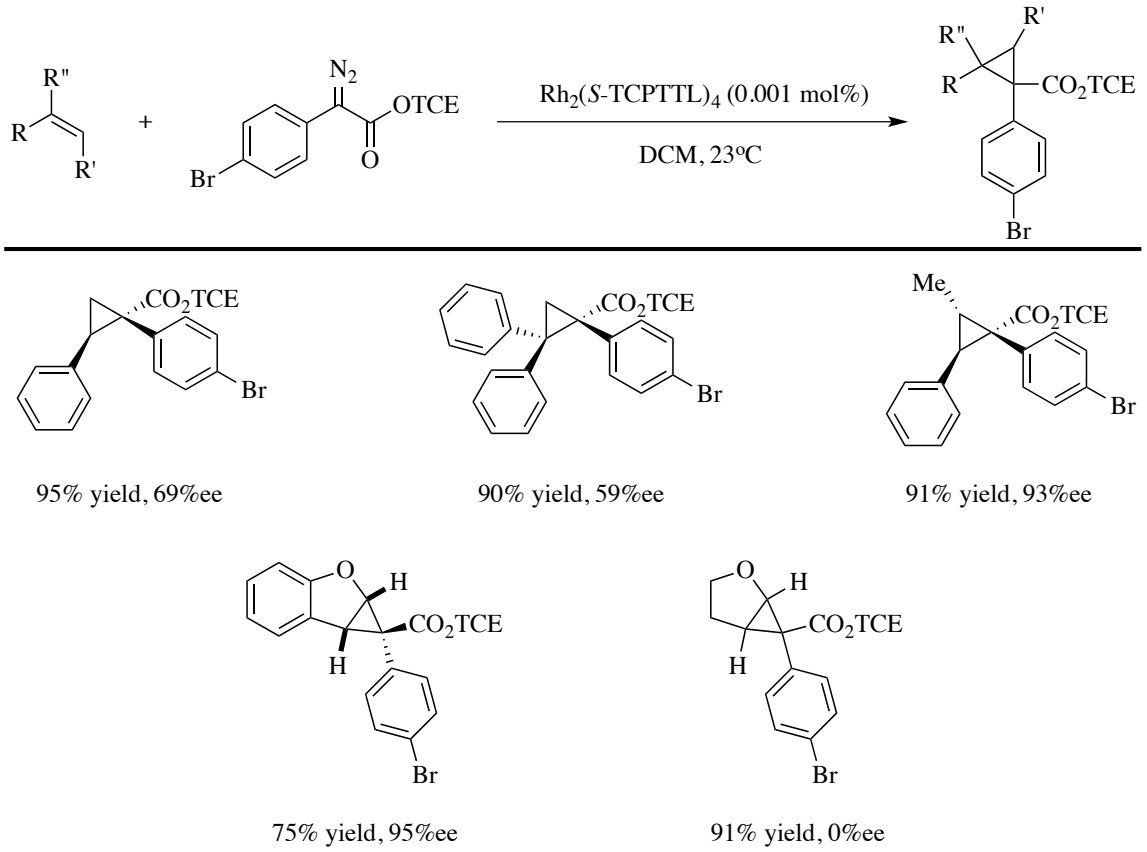


Table 7. Cyclopropanation Scope Using Rh_2(*S*-TCPTTL)$_4$ and TCE-*p*-bromophenyldiazoacetate.

Developing robust conditions for general high turnover carbene reactions is the goal and so far we have achieved part of this goal. The last and most difficult part is

going to be applying the developed conditions to C−H functionalization. A variety of substrates were tested including different types of C−H bonds. Substrates that work in this reaction include 1,4-cyclohexadiene, phthalan, and silylated crotyl alcohol (Table 8). All of these substrates have activated C−H bonds so substrates with less activated and non-activated C−H bonds were also tested (Table 8). Some of the substrates that did not work include THF, N-boc-pyrrolidine, and 4-ethyltoluene. The results from all of the experiments suggest the C−H bonds need to be more activated in order for the insertion to occur with 0.001 mol% of catalyst. In general, the high turnover conditions developed are applicable to cyclopropanation and activated C−H bonds.

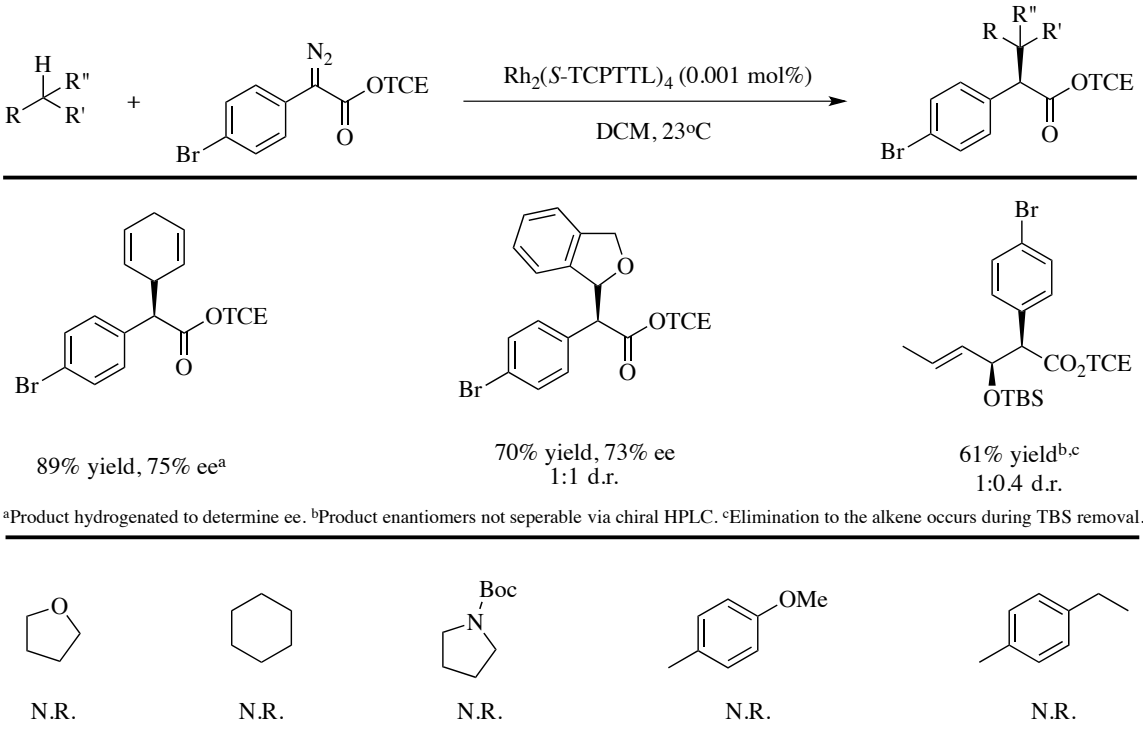


Table 8. C−H insertion Scope Using Rh_2(*S*-TCPTTL)$_4$ and TCE-*p*-bromophenyldiazoacetate.

After studying all of the above C−H insertion substrates, additives were explored once more. Methyl benzoate played a role in the first high turnover cyclopropanation paper.[12] To further understand the role of methyl benzoate in the reaction, C−H insertion into phthalan was studied by *in situ* FTIR spectroscopy. Reactions with and without methyl benzoate were tested to get an accurate picture of how methyl benzoate affects the reaction (Figure 7). The reaction without methyl benzoate proceeded in 70% yield and 73% ee. When methyl benzoate was added to the reaction, the reaction gave essentially identical results with a 70% yield and 75% ee. The difference between the two reactions was the reaction times. The reaction time without methyl benzoate was approximately 20 hours and the reaction with methyl benzoate was approximately 12 hours.

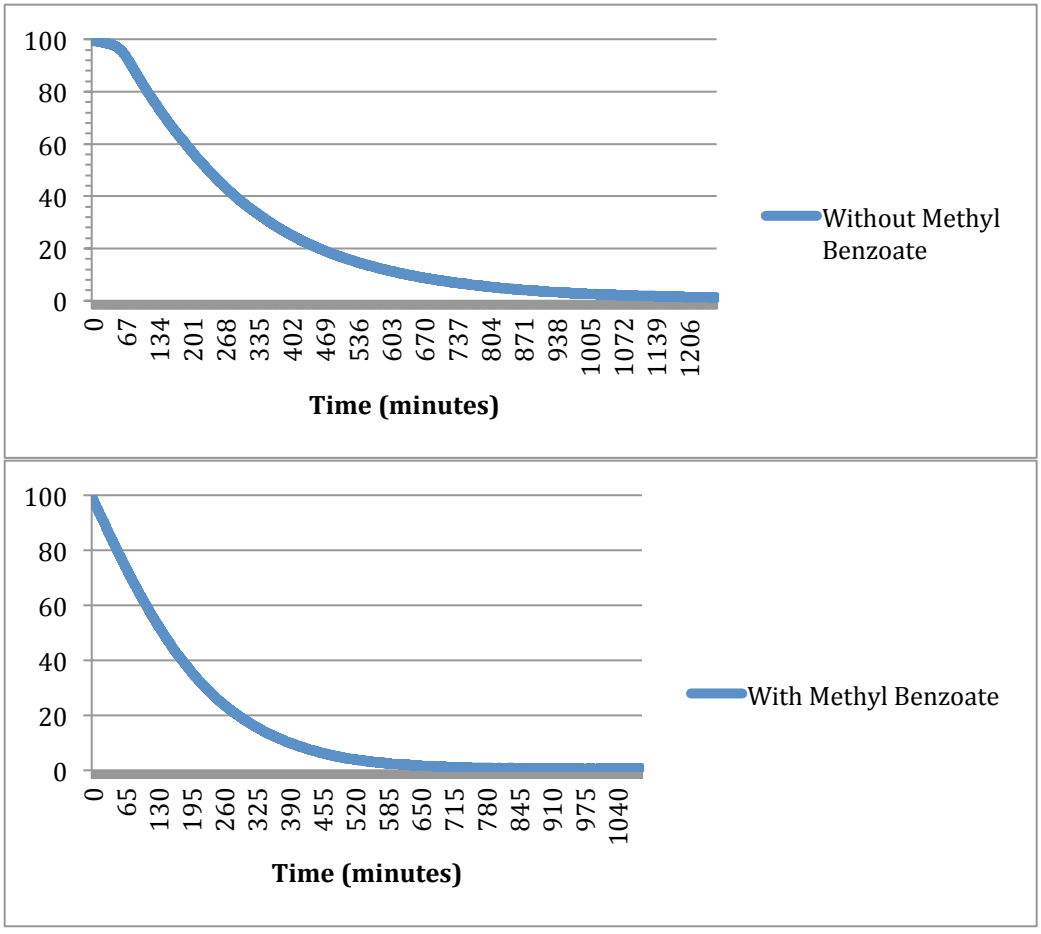


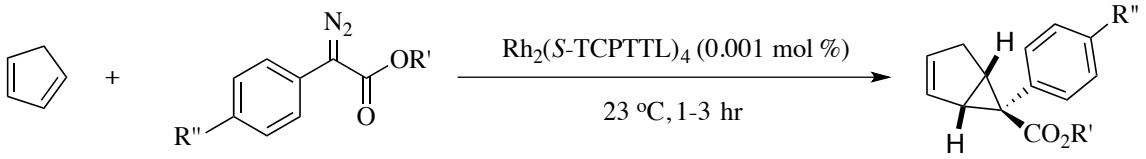
Figure 7. Decomposition of Diazo Over Time Showing Methyl Benzoate Effects of Rhodium(II) Catalyzed Diazo Decomposition of Phthalan.

To explore the methyl benzoate effect further it was decided to run a reaction with a substrate that did not work. Methyl benzoate should help create a more stabilized carbene allowing more time for the reaction with the substrate to occur. A reaction was conducted with THF to determine if our hypothesis was correct. The reaction occurred in a 12% yield. This result does not confirm our hypothesis but it warrants further investigation. The effect of methyl benzoate on carbene chemistry will need to be studied kinetically and computationally. This will give us information about how the mechanism of the reaction is affected by the addition of methyl benzoate. Also, more work needs to be done in order to figure out why some of the substrates tested do not work. So far only a select number of substrates work and in order for this to be a robust set of conditions a broader generality is required. In order to do so, the reaction kinetics would need to be studied to figure out what is going on off-cycle or why the reaction is maybe only turning over once.

In parallel to our studies on the cyclopropanation of methyl 2-furoate, we wanted to attempt the cyclopropanation of cyclopentadiene using Rh_2(*S*-TCPTTL)$_4$. Cyclopentadiene has previously been shown to undergo cyclopropanation with loadings around 0.00006 mol%. Using Rh_2(*S*-TCPTTL)$_4$ in combination with 2,2,2-trichloroethyl aryldiazoacetates, we hypothesized the TON and enantioselectivity would increase. Cyclopropanation with cyclopentadiene using TCE phenyldiazoacetate yielded the cyclopropane in 84% yield (Table 9). The two enantiomers were not separable via chiral

HPLC so the ester was reduced via lithium aluminum hydride. The alcohol was isolated in a 63% yield with a 71% ee.

Methyl phenyldiazoacetate was used in a comparison reaction and the cyclopropane was formed in a 71% yield with a 39% ee (Entry 5). Both dichloromethane and hexane were used as solvent when running this reaction and gave similar results. Based upon these results we decided to try a range of diazo compounds to explore the impact on enantioselectivity. The electron-rich *p*-methoxy derivative was chosen based on previous experience within the Davies group.[13] Both the methyl and trichloroethyl esters were used to gain data for comparison. With the methyl ester the cyclopropane was formed in 63% yield and 9% ee (Entry 8). When the TCE ester was used the TCE substituted cyclopropane would form in 85% yield and 47% ee (Entry 3).

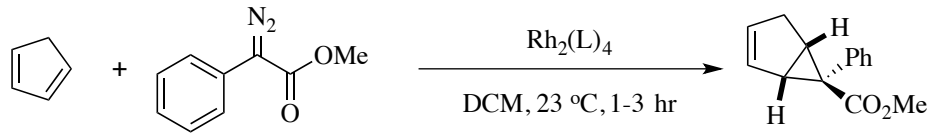


Entry	Solvent	R'	R"	Yield (%)	ee (%)
1	Hexane	TCE	H	84	71[a]
2	Hexane	TCE	OMe	65	37
3	DCM	TCE	OMe	85	47
4	Hexane	OMe	H	65	35
5	DCM	OMe	H	71	39
6	neat	OMe	H	40	33
7	Hexane	OMe	OMe	56	9
8	DCM	OMe	OMe	63	9

[a]Reduced to the alcohol.

Table 9. Cyclopropanations of Cyclopentadiene Using Rh_2(*S*-TCPTTL)$_4$.

Other dirhodium tetracarboxylate catalysts were screened because Rh_2(*S*-TCPTTL)$_4$ gave similar results to the results previously reported using Rh_2(*S*-PTAD)$_4$. Various catalysts were screened at 1 mol% loading and methyl phenyldiazoacetate, which gave similar or worse results than what was reported previously by the Davies Group (Table 10).[13]

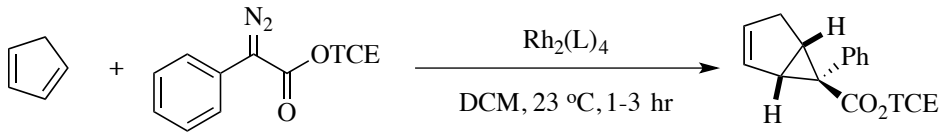


Entry	Catalyst Loading (mol%)	Catalyst	Yield (%)	ee (%)
1	0.001	Rh_2(*S*-TCPTTL)$_4$	71	39
2	1.0	Rh_2(*S*-BTPCP)$_4$	61	56
3	1.0	Rh_2(*S*-*BPCP*)$_4$	53	69
4	1.0	Rh_2(*S*-TCPTAD)$_4$	64	7
5	1.0	Rh_2(*S*-DOSP)$_4$	66	77

Table 10. Catalyst Screen for the Cyclopropanation of Cyclopentadiene.

Rh_2(*S*-DOSP)$_4$ gave the best asymmetric induction with methyl phenyldiazoacetate. Based on a 30% increase in enantioselectivity going to the bulkier

TCE ester when using Rh_2(*S*-TCPTTL)$_4$, several reactions were performed using the bulkier diazo compound with Rh_2(*S*-DOSP)$_4$, Rh_2(*R*-PTAD)$_4$, Rh_2(*S*-TCPTAD)$_4$, Rh_2(*R*-BTPCP)$_4$, and Rh_2(*R*-BPCP)$_4$. Unfortunately, the enantioselectivity decreased when using the TCE ester (Table 11, Entries 1-3). When going to the bulkier triarylcyclopropane carboxylate catalysts the enantioselectivity increased. Rh_2(*R*-BPCP)$_4$ gave the best results with a 77% yield and 89% ee (Entry 5). A newly developed catalyst within the group, Rh_2(*S*-(*p*-^{t}BuC$_6$H$_4$)TPCP)$_4$, gave 84% yield and 83% yield (Entry 6). The optimium catalyst for cyclopropanation of cyclopentadiene was determined to be Rh_2(*R*-BPCP)$_4$.

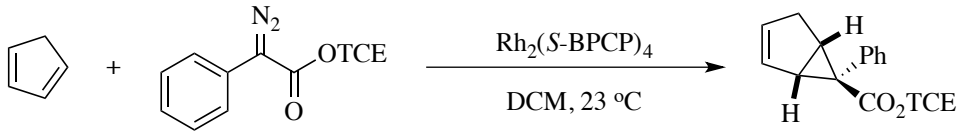


Entry	Catalyst Loading (mol%)	Catalyst	Yield (%)	ee (%)
1	1.0	Rh_2(*S*-DOSP)$_4$	85	57[a]
2	1.0	Rh_2(*R*-PTAD)$_4$	78	37[a]
3	1.0	Rh_2(*S*-TCPTAD)$_4$	74	42[a]
4	1.0	Rh_2(*R*-BTPCP)$_4$	74	74[a,b]
5	1.0	Rh_2(*R*-BPCP)$_4$	77	89[a,b]
6	1.0	Rh_2(*S*-(*p*-^{t}BuC$_6$H$_4$)TPCP)$_4$	84	83[a]

[a]Reduced to the alcohol. [b]Opposite enantiomer forms than one drawn.

Table 11. Catalyst Effects on the Cyclopropanation of Cyclopentadiene with the TCE Ester.

With the optimum catalyst determined, loadings lower than 1 mol% were explored. When 0.1 mol% of Rh_2(*S*-BPCP)$_4$ was used, the reaction proceeded in 73% yield and 93% ee (Table 12, Entry 1). These results are similar to the results seen with 1 mol% of Rh_2(*S*-BPCP)$_4$. The loading was decreased by another order of magnitude to 0.01 mol% and the reaction worked but with a 57% yield and 91% ee (Entry 2). Another aspect to note is the reaction time difference between the different loadings. Reactions employing 1 mol% had reaction times around 1-3 hours but when loadings are decreased the reaction times increased. The reaction time when 0.1mol % of catalyst was used was approximately 16 hours and 5 days when 0.01 mol% of catalyst was used.



Entry	Catalyst Loading (mol%)	Time	Yield (%)	ee (%)
1	0.1	16 hours	73	93[a]
2	0.01	5 days	51	91[a]

[a]Reduced to the alcohol.

Table 12. Catalyst Loading Effects on the Cyclopropanation of Cyclopentadiene.

One key observation that has not been discussed is the increase in enantioselectivity when using a combination of the bulkier TCE ester functionality and

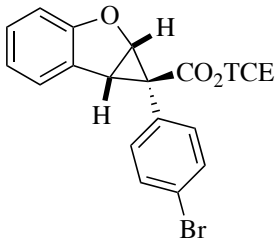
Rh_2(*S*-TCPTTL)$_4$. There is roughly a 30% increase in enantioselectivity. A number of theories can be considered for this increase in enantioselectivity. The methyl ester is much smaller which may allow for more freedom in the formation of the product causing the opposite enantiomer to be formed. However, sterics cannot be the only factor affecting the enantioselectivity of the cyclopropanations because if it were sterics alone the ee values for the other catalysts would have presumably been much higher. Electronic factors should also be considered to be contributing to the increase in enantioselectivity. The TCE esters are more electron withdrawing in nature, which may impact the stability of the carbenoid potentially leading to an increase in the enantioinduction. This significant increase in enantioselectivity warrants further investigation and we will be reaching out to collaborators within the Center for Selective C−H Functionalization to develop an understanding of this trend.

Conclusion and Future Work:

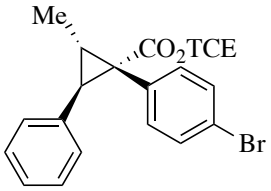
Investigations at the frontier of general high TON dirhodium catalyzed carbene reactions are well under way and show promise. With rhodium being an expensive metal, the long-term goal would be to achieve a robust system employing low enough catalyst loadings that cost would not become an issue when running either enantioselective cyclopropanation or C-H insertion reactions. Finding first-row transition metals that could perform these reactions with the same level of enantioselectivity as rhodium(II) tetracarboxylates would be the ultimate goal in this field but currently those metal complexes do not exist so efforts need to be made to lower the loadings of expensive second and third row transition metal catalysts. The lessons gained from exploring the

efficiency in these precious metal systems will inform the development of more earth-abundant catalyst systems.

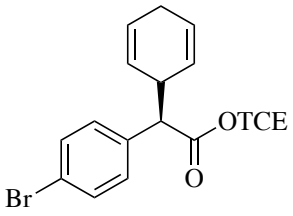
We were able to demonstrate that enantioselective cyclopropanations of methyl 2-furoate are possible using 0.00005 mol% of Rh_2(*S*-TCPTTL)$_4$ giving high yields and moderate selectivity. Due to some reproducibility issues when operating at loadings lower than 0.001 mol%, it was decided to develop a substrate scope using 0.001 mol% of Rh_2(*S*-TCPTTL)$_4$. A variety of alkenes formed cyclopropanes in high yields with high to moderate enantioselectivity. A trend developed demonstrating that *cis* alkenes, in this system, tend to give high enantioselectivity. C−H Functionalization is also possible with activated substrates such as 1,4-cyclohexadiene and phthalan. These substrates give moderate yields and enantioselectivities and further studies will need to be conducted with collaborators in the Center for Selective C−H Functionalization to understand the off-cycle pathway in order for substrates that do not have activated C−H bonds to be effectively used in this system. We have achieved part of our goal in finding general conditions that can perform carbene reactions at low loadings but the scope still needs to be expanded so these conditions can be applied to tougher substrates.



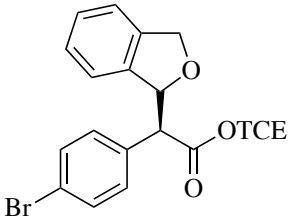
75% yield, 95%ee



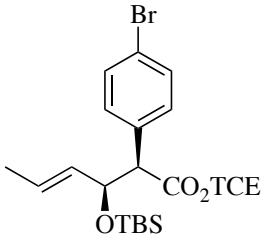
91% yield, 93%ee



89% yield, 75% ee



70% yield, 73% ee
1:1 d.r.



61% yield
1:0.4 d.r.

Table 13. Substrate Scope Using 0.001 mol% of Rh_2(*S*-TCPTTL)$_4$ in Both Cyclopropnations and C−H Insertion Reactions.

When switching to cyclopentadiene as a substrate the enantioselectivity is moderate with various conditions showing that thus far the conditions published by Davies remain the best conditions for this cyclopropanation.[14] A drop in yield occurs when the catalyst loading is reduced but enantioselectivity remains roughly the same. More studies will also need to be conducted to understand why the catalytic cycle shuts down when loadings are decreased. Again, this would be an opportunity to collaborate with a variety of professors in the Center for Selective C−H Functionalization.

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Experimental:

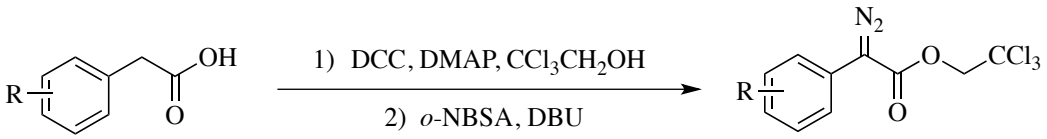
General remarks

All solvents were purified and dried by a Glass Contour Solvent System unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded at either 400 MHz (^{13}C at 100 MHz) on a Varian-400 spectrometer, 600Mz on an I-Nova spectrometer, or 500Mz on an I-Nova spectrometer. NMR spectra were run in solutions of deuterated chloroform ($CDCl_3$) with residual chloroform taken as an internal standard (7.26 ppm for ^{1}H, and 77.16 ppm for ^{13}C), and were reported in parts per million (ppm). Abbreviations for signal multiplicity are as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublet, app t = apparent triplet, etc. Coupling constants (*J* values) were calculated directly from the spectra. In situ FTIR spectroscopy data recorded with a Mettler Toledo ReactIR^{TM} 45M spectrometer. IR spectra were collected on a Nicolet iS10 FT-IR spectrometer. Mass spectra were taken on a Thermo Finnigan LTQ-FTMS spectrometer with APCI, ESI or NSI. Thin layer chromatographic analysis was performed with aluminum-backed silica gel plates, visualizing with UV light and/or staining with Vanillin or aqueous $KMnO_4$ stain.

General procedure for the synthesis and analysis data of diazo compounds

Diazo compounds with methyl esters were prepared following the procedure reported in the literature.[1] Yields for diazo compounds containing the 2,2,2-trichloroethyl ester were higher when prepared using o-nitrobenzenesulfonyl azide (*o*-NBSA) as the diazo transfer reagent[2] (CAUTION! POTENTIALLY EXPLOSIVE! USE PROPER

PRECAUTIONS FOR HANDLING THIS AZIDE). This reagent was prepared according to a literature protocol.[3]



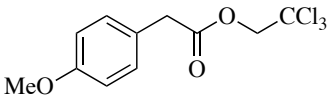
First step: preparation of the trichloroethyl ester

A solution of desired phenylacetic acid (10 mmol, 1.0 equiv), 2,2,2-trichloroethanol (1.7 g, 1.2 mL, 12 mmol, 1.2 equiv) and DMAP (122 mg, 1 mmol, 0.1 equiv) in CH_2Cl_2 (21 mL) was cooled to 0 °C in an ice/water bath. A solution of DCC (2.3 g, 11 mmol, 1.1 equiv) in CH_2Cl_2 (10 mL) was poured into the cold reaction mixture. The solution was stirred overnight, at which point it had reached ambient temperature. The precipitate was filtered and washed with Et_2O. The filtrate was concentrated and filtered on a short plug of silica gel. The product obtained was used without further purification in the diazo transfer reaction.

Second step: diazo transfer reaction

The ester from the previous step (7.6 mmol, 1.0 equiv) and *o*-NBSA (11.5 mmol, 1.5 equiv) were dissolved in acetonitrile (26 mL) and cooled to 0 °C. Then DBU (2.6 g, 2.5 mL, 16.8 mmol, 2.0 equiv) was added dropwise. The solution was stirred until full conversion of the ester and quenched with saturated aqueous NH_4Cl (25 mL) and water (20 mL) and extracted with Et_2O (50 mL). The organic layer was washed with water (25 mL) and brine (25 mL) and dried over $MgSO_4$.

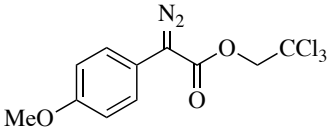
2,2,2-trichloroethyl 2-(4-methoxyphenyl)acetate



Starting from the corresponding phenylacetic acid (23.3 g, 140 mmol) and following the general procedure, the desired compound was obtained as a colorless oil (40 g, 96% yield) and used in the following step without further purification.

Rf = 0.48 (SiO_2, pentane:Et_2O, 9:1). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.74 (s, 2H), 3.80 (s, 3H) and 3.71 (s, 2H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.4, 159.0, 130.5, 125.0, 114.1, 95.0, 74.2, 55.3 and 40.1 ppm. **IR (neat):** 2116, 1752, 1512, 1247 and 1125 cm^{-1}. **HR-MS (EI)** *m/z* calculated for $C_{11}H_{12}Cl_3O_3^+$ 296.9847, observed 296.9848.

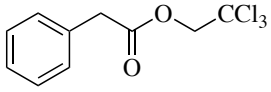
2,2,2-trichloroethyl 2-diazo-2-(4-methoxyphenyl)acetate



Starting from the corresponding ester (9 g, 50 mmol) and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 95:5) as an orange solid (2.2 g, 21% yield).

Rf = 0.53 (SiO_2, pentane:Et_2O, 9:1). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.38 (d, 2H, *J* = 8.7 Hz), 6.94 (d, 2H, *J* = 8.7 Hz), 4.88 (s, 2H) and 3.08 (s, 3H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.0, 158.5, 126.3, 116.1, 114.9, 95.2, 74.0, and 55.5 ppm (The resonance resulting from the diazo carbon was not observed). **IR (neat)**: 2085, 1704, 1511, 1239 and 1136 cm^{-1}. **HR-MS (APCI)** *m/z*: $[M+H-N_2]^+$ calculated for $C_{11}H_{10}O_3Cl_3$ 294.9690, observed 294.9688.

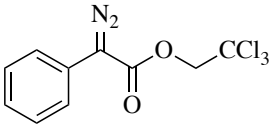
2,2,2-trichloroethyl 2-phenylacetate



Starting from the corresponding phenylacetic acid (1.4 g, 10

mmol) and following the general procedure, the desired compound was obtained as a colorless oil (2.0 g, quantitative yield) and used in the following step without further purification. **Rf** = 0.70 (SiO_2, pentane:Et_2O, 9:1). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39-7.29 (m, 5H), 4.77 (s, 2H) and 3.79 (s, 2H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.0, 133.0, 129.5, 128.7, 127.5, 94.9, 74.2 and 41.0 ppm. **IR (neat):** 2117, 1752 and 1125 cm^{-1}. **HR-MS (EI)** *m/z* calculated for $C_{10}H_{10}Cl_3O_2^+$ 266.9741, observed 266.9742.

2,2,2-trichloroethyl 2-diazo-2-phenylacetate



Starting from the corresponding ester (2.0 g, 7.6 mmol) and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 95:5) as an orange solid (1.7 g, 76% yield).

Rf = 0.75 (SiO_2, pentane:Et_2O, 9:1). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.52 (d, *J* = 7.8 Hz, 2H), 7.43 (t, *J* = 7.8 Hz, 2H) and 7.24 (t, *J* = 7.4 Hz, 1H) and 4.93 (s, 2H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$):** 163.5, 129.2, 126.5, 124.8, 124.2, 95.2, 74.0, and 63.5 ppm (The resonance resulting from the diazo carbon was not observed). **IR (neat)**: 2094, 1707, 1498 and 1140 cm^{-1}. **HR-MS (EI)** *m/z*: calculated for $C_{10}H_7O_2Cl_3N_2Na^+$ 314.9471, observed 315.1891.

General procedure for the racemic cyclopropanation and C−H Insertion reactions of substrates with $Rh_2(OPiv)_4$: In a flame dried 10-mL round bottom flask equipped with a magnetic stir bar, substrate (2 equiv) and $Rh_2(OPiv)_4$ (0.01 equiv) were added and the flask went through vacuum/argon cycles 3 times. It was then dissolved in dry, degassed DCM (1 mL). A solution of the diazo ester (1.0 mmol, 1 equiv) in dry, degassed DCM (2-3 mL) was added using a syringe pump if using a methyl ester for the duration

of 1 h (the TCE ester was added over a few seconds instead of using a syringe pump). Afterwards the reaction mixture was concentrated under reduced pressure and purified using column chromatography by running a gradient (silica gel, hexanes/EtOAc = 50:1, 25:1, 15:1, 7:1).

General procedure A for the cyclopropanation with methyl esters:

In a flame dried 5-mL round bottom flask equipped with a magnetic stir bar, substrate (2 equiv) and Rh_2(S-TCPTTL)$_4$ (0.001 mol%) were added and the flask went through vacuum/argon cycles 3 times. It was then dissolved in dry DCM (0.1 mL). A solution of the diazo ester (1 equiv) in dry DCM (0.2 mL) was added using a syringe pump for the duration of 1 h. The syringe was washed with DCM (2x0.25 mL) and the reaction was stirred for an additional 10 minutes. It was then concentrated under reduced pressure and purified using column chromatography by running a gradient (silica gel, hexanes/EtOAc = 50:1, 25:1, 15:1, 7:1).

General procedure B for the cyclopropanation and C−H Insertion Reactions with TCE esters:

In a flame dried 5-mL round bottom flask equipped with a magnetic stir bar, substrate (2 equiv) and Rh_2(S-TCPTTL)$_4$ (0.001 mol%) were added and the flask went through vacuum/argon cycles 3 times. It was then dissolved in dry DCM (0.1 mL). A solution of the diazo ester (1 equiv) in dry DCM (0.2 mL) was added over a few seconds. The syringe was washed with DCM (2x0.25 mL) and the reaction was stirred for an additional 30 minutes. It was then concentrated under reduced pressure and purified using column chromatography by running a gradient (silica gel, hexanes/EtOAc = 50:1, 25:1, 15:1, 7:1).

General procedure C for the neat cyclopropanation of methyl 2-furoate:

In a flame dried 5-mL round bottom flask equipped with a magnetic stir bar, diazo ester (1 mmol, 1 equiv) and methyl 2-furoate (2 mmol, 2 equiv) were added and the flask went through vacuum/argon cycles 3 times. Rh_2(S-TCPTTL)$_4$ (0.0001 mol%) was then added and the reaction was stirred for an additional 30 minutes. It was then concentrated under reduced pressure and purified using column chromatography by running a gradient (silica gel, hexanes/EtOAc = 50:1, 25:1, 15:1, 7:1).

General procedure D for the cyclopropanation of cyclopentadiene using Rh_2(*S*-TCPTTL)$_4$ and TCE esters:

In a flame dried 5-mL round bottom flask equipped with a magnetic stir bar, Rh_2(S-TCPTTL)$_4$ (0.001 mol%) was added and the flask went through vacuum/argon cycles 3 times. It was then dissolved in dry DCM (0.1 mL) and cyclopentadiene (2 equiv) was added. A solution of the diazo ester (1 equiv) in dry DCM (0.2 mL) was added over a few seconds. The syringe was washed with DCM (2x0.25 mL) and the reaction was stirred for an additional 1-3 hours. It was then concentrated under reduced pressure and purified using column chromatography by running a gradient (silica gel, hexanes/EtOAc = 25:1, 15:1, 7:1).

General procedure E for the cyclopropanation of cyclopentadiene using Rh_2(*S*-TCPTTL)$_4$ and methyl esters:

In a flame dried 5-mL round bottom flask equipped with a magnetic stir bar, Rh_2(S-TCPTTL)$_4$ (0.001 mol%) was added and the flask went through vacuum/argon cycles 3 times. It was then dissolved in dry DCM (0.1 mL) and cyclopentadiene (2 equiv) was added. A solution of the diazo ester (1 equiv) in dry DCM (0.2 mL) was added using a

syringe pump over 1 hour. The syringe was washed with DCM (2x0.25 mL) and the reaction was stirred for an additional 1-3 hours. It was then concentrated under reduced pressure and purified using column chromatography by running a gradient (silica gel, hexanes/EtOAc = 25:1, 15:1, 7:1).

General procedure F for *in situ* FTIR Experiments (ReactIR™):

Experiments were carried out with a Mettler Toledo ReactIRTM 45m instrument equipped with a 9.5mm x 12" AgX 1.5m SiComp probe. Stock solutions of Rh_2(*S*-TCPTTL)$_4$ in dichloromethane was prepared. To a flame-dried 25 mL pear shaped flask diazo was added and the ReactIR™ probe was inserted into a flame-dried 15 mL two-neck round bottom flask. Both flasks then went through vacuum/argon cycles 3 times and DCM (3 mL) was added to the diazo. The diazo solution was added to the two-neck flask and the syringe was washed with DCM (1 mL). The substrate was then added to the diazo solution and a continuous scan experiment was started (time intervals varied depending on experiment from 5 sec-2 min). The catalyst was added and the reaction was stirred until completion. The reaction was then concentrated down and purified by flash column chromatography by running a gradient (silica gel, hexanes/EtOAc = 50:1, 25:1, 15:1, 7:1).

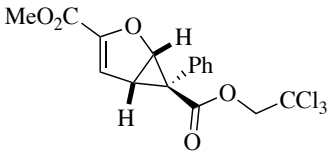
(−)-dimethyl (1*S*,5*S*,6*R*)-6-phenyl-2-oxabicyclo[3.1.0]hex-3-ene-3,6-dicarboxylate

Following general procedure A, the desired cyclopropanated product was obtained after purification by column chromatography (silica gel, hexanes/EtOAc = 50:1, 25:1, 15:1, 7:1) as a white solid (190 mg, 69% yield, 88% ee).

R_f= 0.26 (SiO_2= 5:1 Hex:EtOAc) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.29-7.18 (m, 5H), 6.11 (d, *J* = 3.0 Hz, 1H), 5.23 (d, *J* = 5.4 Hz, 1H), 3.63 (s, 3H), 3.59(s, 3H), and 3.37 (dd,

J = 5.3, 3.1 Hz, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.2, 158.9, 148.9, 132.4, 129.6, 128.1, 127.8, 114.2, 71.2, 53.0, 52.2, 39.6, and 28.6 ppm. **IR (neat)**: 1732, 1721, 1609 and 1437 cm^{-1}. **HR-MS (NSI)** *m/z*: calculated for $C_{15}H_{14}O_5H^+$ 275.0919, observed 275.0913. **(Chiralpak ADH 1% i-PrOH/hexanes, 1.0 mL/min):** tR = 24.4 (minor), 30.8 (major) min. **$[\alpha]_D^{20}$** (c=1.00): -24.7.

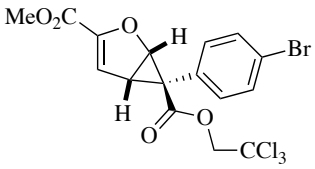
(−)-3-methyl 6-(2,2,2-trichloroethyl) (1*S*,5*S*,6*R*)-6-phenyl-2-oxabicyclo[3.1.0]hex-3-ene-3,6-dicarboxylate



Following general procedure B, the desired cyclopropanated product was obtained after purification by column chromatography (silica gel, hexanes/EtOAc = 50:1, 25:1, 15:1, 7:1) as a clear oil that solidified (353 mg, 90% yield, 91% ee).

R_f= 0.32 (SiO_2= 5:1 Hex:EtOAc) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.27-7.23 (m, 5H), 6.15 (dd, *J* = 3.0, 0.4 Hz, 1H), 5.36 (dd, *J* = 5.3, 0.4 Hz, 1H), 4.74 (dd, *J* = 11.9, 0.5 Hz, 1H), 4.65 (dd, *J* = 11.9, 0.5 Hz, 1H), 3.62 (s, 3H), and 3.51 (ddd, *J* = 5.4, 3.0, 0.5 Hz, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.1, 158.8, 149.3, 132.4, 128.7, 128.2, 128.1, 113.9, 94.8, 74.4, 71.3, 52.3, 40.2, and 28.8 ppm. **IR (neat)**: 3031, 2956, 1735, 1712 and 1614 cm^{-1}. **HR-MS (NSI)** *m/z*: calculated for $C_{16}H_{13}Cl_3O_5H^+$ 390.9907, observed 390.9903. **(Chiralpak ADH 5% i-PrOH/hexanes, 1.0 mL/min):** tR = 9.0 (minor), 11.2 (major) min. **$[\alpha]_D^{20}$** (c=1.33): -18.4.

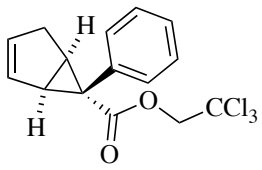
(−)-3-methyl 6-(2,2,2-trichloroethyl) (1*S*,5*S*,6*R*)-6-(4-bromophenyl)-2 oxabicyclo[3.1.0] hex-3-ene-3,6-dicarboxylate



Following general procedure B, the desired cyclopropanated product was obtained after purification by column chromatography (silica gel, hexanes/EtOAc = 50:1, 25:1, 15:1, 7:1, 3:1) as a yellow oil (375 mg, 80% yield, 97% ee).

R_f= 0.19 (SiO_2= 5:1 Hex:EtOAc), **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.42 (m, 2H), 7.13 (m, 2H), 6.15 (d, *J* = 2.9 Hz, 1H), 5.35 (d, *J* = 5.4 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 3.67 (s, 3H), and 3.52 (dd, *J* = 5.4, 3.0 Hz, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.6, 158.7, 149.6, 134.0, 131.6, 127.9, 122.4, 113.5, 94.7, 74.4, 71.28, 52.5, 40.3, and 28.1 ppm. **IR (neat)**: 2962, 1736, 1714 and 1612 cm^{-1}. **HR-MS (NSI)** *m/z*: calculated for $C_{16}H_{13}BrCl_3O_5H^+$ 468.9012, observed 468.9015. **(Chiralpak ADH 5% i-PrOH/hexanes, 1.0 mL/min):** tR = 13.3 (minor), 19.1 (major) min. **$[\alpha]_D^{20}$** (c=1.46): -42.9.

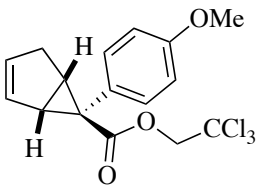
(+)-2,2,2-trichloroethyl (1*S*,5*R*,6*S*)-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate



In a flame dried 10-mL round bottom flask equipped with a magnetic stir bar, Rh_2(R-BPCP)$_4$ (1.0 mol%) was added and the flask went through vacuum/argon cycles 3 times. It was then dissolved in dry DCM (1.0 mL) and cyclopentadiene (1 mmol, 2 equiv) was added. A solution of the diazo ester (0.5 mmol, 1 equiv) in dry DCM (2.0 mL) was added over a few seconds. The reaction was stirred for an additional 20 minutes. It was then concentrated under reduced pressure and purified using column chromatography by running a gradient (silica gel, hexanes/EtOAc = 25:1, 15:1, 7:1) to give a pale yellow oil (127 mg, 77% yield).

R_f= 0.41 (SiO_2= 9:1 Hex:EtOAc), **^{1}H NMR (399 MHz, $CDCl_3$)** δ 7.30-7.20 (m, 3H), 7.14(m, 2H), 5.79 (dq, *J* = 5.6, 2.1, 2.1 Hz, 1H), 5.27-5.25 (m, 1H), 4.69 (d, *J* = 11.9 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 3.07 (ddd, *J* = 6.6, 3.5, 1.5 Hz, 1H), 2.76 (td, *J* = 6.7, 1.1 Hz, 1H), 2.69 (ddtd, *J* = 18.8, 7.0, 2.1, 0.7 Hz, 1H), and 2.15 (dq, *J* = 18.8, 2.4 Hz, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.3, 133.3, 133.0, 132.1, 129.5, 127.7, 127.1, 95.2, 74.3, 41.3, 37.9, 34.3, and 32.9 ppm. **IR (neat)**: 3060, 2904, 1727 and 1264 cm^{-1}. **HR-MS (NSI)** *m/z*: calculated for $C_{15}H_{13}Cl_3O_2NH_4^+$ 348.0325, observed 348.0320. **$[\alpha]_D^{20}$** (c=1.07): +20.7.

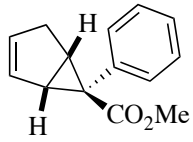
(−)-2,2,2-trichloroethyl (1*R*,5*S*,6*R*)-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate



Following general procedure D, the desired cyclopropanated product was obtained after purification by column chromatography (silica gel, hexanes/EtOAc = 25:1, 15:1, 7:1) as a yellow oil (154 mg, 85% yield, 47% ee).

R_f= 0.35 (SiO_2= 9:1 Hex:EtOAc), **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.09-7.00 (m, 2H), 6.85-6.76 (m, 2H), 5.78 (dq, *J* = 5.5, 2.1 Hz, 1H), 5.28 (dtd, *J* = 5.6, 2.2, 1.3 Hz, 1H), 4.70 (d, *J* = 11.9 Hz, 1H), 4.61 (d, *J* = 11.9 Hz, 1H), 3.78 (s, 3H), 3.06-3.03 (m, 1H), 2.76-2.63 (m, 2H), and 2.13 (dt, *J* = 18.3, 2.4 Hz, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.6, 158.5, 134.0, 133.4, 129.4, 124.1, 113.3, 95.2, 74.3, 55.2, 41.3, 37.1, 34.3, and 32.9 ppm. **IR (neat)**: 2060, 2905, 1727 and 1611 cm^{-1}. **HR-MS (NSI)** *m/z*: calculated for $C_{16}H_{15}Cl_3O_3H^+$ 361.0165, observed 361.0160. **(Chiralcel OJ 3% i-PrOH/hexanes, 1.5 mL/min):** tR = 10.6 (minor), 13.0 (major) min. **$[\alpha]_D^{20}$** (c=1.16): -10.4.

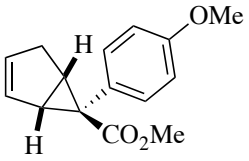
(−)-methyl (1*R*,5*S*,6*R*)-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate



Following general procedure E, the desired cyclopropanated product was obtained after purification by column chromatography (silica gel, hexanes/EtOAc = 25:1, 15:1, 7:1) as a white solid (151 mg, 71% yield, 39% ee).

R_f= 0.47 (SiO_2= 9:1 Hex:EtOAc), **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.35-7.18 (m, 3H), 7.14 -7.03 (m, 2H), 5.78-5.67 (m, 1H), 5.24-5.13 (m, 1H), 3.25 (s, 3H), 2.95-2.89 (m, 1H), 2.71-2.60 (m, 2H), and 2.13-2.02 (m, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.6, 133.2, 133.0, 132.9, 129.8, 127.7, 126.8, 52.5, 40.9, 37.9, 34.2, and 32.5 ppm. **IR (neat)**: 3041, 2953, 1698 and 1431 cm^{-1}. **HR-MS (NSI)** *m/z*: calculated for $C_{14}H_{16}O_2H^+$ 215.1072, observed 215.1068. **(Chiralcel OJ 3% i-PrOH/hexanes, 1.0 mL/min):** tR = 14.7 (minor), 19.0 (major) min. **$[\alpha]_D^{20}$** (c=1.08): -29.0.

(−)-methyl (1*R*,5*S*,6*R*)-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate

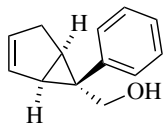


Following general procedure E using hexane as the solvent instead of DCM, the desired cyclopropanated product was obtained after purification by column chromatography (silica gel, hexanes/EtOAc = 25:1, 15:1, 7:1, 5:1) as a white solid (153 mg, 63% yield, 9% ee). The data obtained match literature values.[14]

R_f= 0.18 (SiO_2= 9:1 Hex:EtOAc), **^{1}H NMR (399 MHz, $CDCl_3$)** δ 7.01 (m, 2H), 6.80 (m, 2H), 5.77-5.71 (m, 1H), 5.23 (m,1H), 2.89 (m, 1H), 3.78 (s, 3H), 3.59 (s, 3H), 2.68-2.56 (m, 2H), and 2.04 (dd, *J* = 17.7, 2.4 Hz, 1H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$)** δ 174.9, 158.3, 133.9, 133.0, 129.7, 125.1, 113.2, 55.2, 52.5, 41.0, 37.1, 34.2, and 32.5

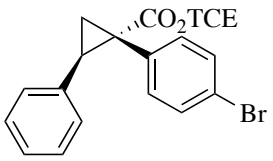
ppm. **IR (neat)**: 3071, 2992, 1705 and 1609 cm^{-1}. **(Chiralcel OJ 3% i-PrOH/hexanes, 1.5 mL/min):** tR = 15.6 (minor), 21.2 (major) min.

(+)-((1*S*,5*R*,6*S*)-6-phenylbicyclo[3.1.0]hex-2-en-6-yl)methanol



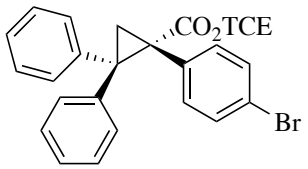
To a flame dried round bottom flask was added $LiAlH_4$ (16.4 mg, 0.43 mmol, 1.5 equiv) and THF (1 mL). The solution was cooled to 0 ^oC and a solution of the corresponding TCE ester (95.4 mg, 0.29 mmol, 1 equiv) in THF (1 mL) was added dropwise. The reaction was stirred for an additional 3.5 hours and water was added slowly. 1M NaOH was then added and the reaction was stirred for 30 minutes. The solid was removed by filtration and washed with DCM (50 mL). The organic phase was collected and dried over Na_2SO_4. It was concentrated down under reduced pressure and purified by column chromatography (silica gel, hexanes/EtOAc = 15:1, 7:1, 5:1) to give a white solid (33 mg, 61% yield, 89% ee). $\mathbf{R_f}$= 0.32 (SiO_2= 5:1 Hex:EtOAc). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.33-7.27 (m, 2H), 7.24-7.19 (m, 1H), 7.20-7.16 (m, 2H), 5.73 (dq, *J* = 5.6, 2.2 Hz, 1H), 5.12 (dtd, *J* = 5.6, 2.2, 1.1 Hz, 1H), 3.65 (dd, *J* = 11.2, 5.8 Hz, 1H), 3.43 (dd, *J* = 11.2, 6.6 Hz, 1H), 2.59-2.49 (m, 1H), 2.32 (m, 1H), 2.04 (m, 1H), 1.97-1.88 (m, 1H), and 1.36 (t, *J* = 6.4 Hz, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 136.6, 132.2, 131.0, 130.8, 128.1, 126.6, 71.5, 39.1, 35.2, 33.2, and 26.6 ppm. **IR (neat)**: 3263, 3052, 2896 and 1494 cm^{-1}. **HR-MS (NSI)** *m/z*: calculated for $C_{13}H_{14}ONa^+$ 209.0942, observed 209.0937. **(Chiralcel ODH 0.5% i-PrOH/hexanes, 0.5 mL/min):** tR = 95.1 (minor), 99.8 (major) min. **$[\alpha]_D^{20}$** (c=1.07): +39.0.

2,2,2-trichloroethyl(1S,2R)-1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate



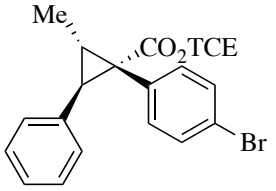
Following general procedure F using styrene as a substrate, the desired cyclopropane was isolated as a white solid (2.0g, 95% yield, 69% ee). $\mathbf{R_f}$= 0.45 (SiO_2= 15:1 Hex:EtOAc). **^{1}H NMR (500 MHz; $CDCl_3$)** δ 7.28-7.25 (m, 2H), 7.13-7.11 (m, 3H), 6.96-6.94 (m, 2H), 6.83-6.81 (m, 2H), 4.83 (d, 1H, J = 11.9 Hz), 4.64 (d, 1H, J = 11.9 Hz), 3.22 (dd, 1H, J = 9.3, 7.5 Hz), 2.28 (dd, 1H, J = 9.3, 5.2 Hz), and 1.97 (dd, 1H, J = 7.5, 5.2 Hz)ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ 171.5, 135.2, 133.6, 132.9, 130.9, 128.0, 128.0, 126.8, 121.5, 94.9, 74.4, 36.6, 33.9, and 20.2 ppm. **(SS-WHELK column, 1 mL/min, 1 % iPrOH in hexanes):** tR: Major: 10.20 min, Minor: 8.26 min. Data matches literature values.[21]

2,2,2-trichloroethyl (R)-1-(4-bromophenyl)-2,2-diphenylcyclopropane-1-carboxylate



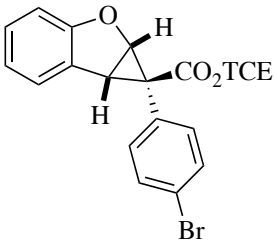
Following general procedure F using 1,1-diphenylethylene as a substrate, the desired cyclopropane was isolated as a white solid (2.4g, 90% yield, 59% ee). **^{1}H NMR (500 MHz; $CDCl_3$)** δ 7.57-7.55 (m, 2H), 7.37-7.26 (m, 7H), 7.06-7.03 (m, 5H), 4.51 (d, 1H, J = 11.9 Hz), 4.15 (d, 1H, J = 11.9 Hz), 2.78 (d, 1H, J = 5.7 Hz), and 2.52 (d, 1H, J = 5.7 Hz) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ 169.1, 141.3, 138.9, 134.0, 133.6, 130.8, 130.0, 128.7, 128.6, 128.0,127.4, 126.7, 121.5, 94.3, 75.3, 45.7, 42.2, and 23.0 ppm. **(SS-WHELK, 1 mL/min, 1 % iPrOH in hexanes, 230 nm):** tR= 7.29 (major), 20.05 (minor) min. Data matches literature values.[21]

2,2,2-trichloroethyl (1*S*,2*S*,3*R*)-1-(4-bromophenyl)-2-methyl-3-phenylcyclopropane-1-carboxylate



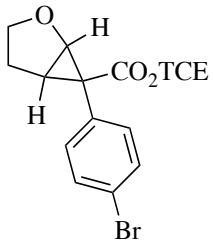
Following general procedure B using cis-β-methylstyrene as a substrate, the desired cyclopropane was isolated as a clear oil (677mg, 91% yield, 93% ee). $\mathbf{R_f}$= 0.57 (SiO_2= 9:1 Hex:EtOAc). **^{1}H NMR (600 MHz; $CDCl_3$)** δ 7.41-7.39 (m, 2H), 7.26-7.17 (m, 3H), 6.96-6.95 (m, 2H), 6.86-6.84 (m, 2H), 4.68 (s, 2H), 3.20 (d, *J* = 10.2 Hz, 1H), 2.50 (ddd, *J* = 10.3, 6.9, 0.8 Hz, 1H), and 1.32 (dd, *J* = 6.8, 0.8 Hz, 3H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$)** δ 172.7, 135.3, 134.9, 131.1, 130.6, 130.3, 127.8, 126.5, 121.8, 94.9, 74.5, 37.4, 37.0, 28.0, and 10.9 ppm. **IR (neat)**: 2954, 1730, 1489 and 1389 cm^{-1}. **HR-MS (NSI)** *m/z*: calculated for $C_{19}H_{16}BrCl_3O_2H^+$ 459.9399, observed 460.1339. **(Chiralcel ODR 1.0% i-PrOH/hexanes, 1.0 mL/min):** tR = 4.89 (minor), 5.93 (major) min. **$[\alpha]_D^{20}$** (c=0.94): -4.2.

2,2,2-trichloroethyl (1*R*,1a*S*,6b*S*)-1-(4-bromophenyl)-1a,6b-dihydro-1*H*-cyclopropa[*b*]benzofuran-1-carboxylate



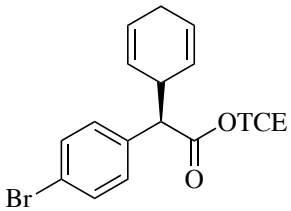
Following general procedure B using 2,3-benzofuran as a substrate, the desired cyclopropane was isolated as a white solid (558mg, 75% yield, 95% ee).. $\mathbf{R_f}$= 0.42 (SiO_2= 9:1 Hex:EtOAc). **^{1}H NMR (500 MHz; $CDCl_3$)** δ 7.38-7.36 (m, 2H), 7.23-7.21 (m, 2H), 7.00-6.96 (m, 3H), 6.87-6.84 (m, 1H), 6.53-6.51 (m, 1H), 5.46 (dd, *J* = 5.5, 1.0 Hz, 1H), 4.73 (s, 2H), and 3.92 (d, *J* = 5.5 Hz, 1H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.6, 159.3, 134.1, 130.9, 128.6, 127.8, 125.6, 125.0, 121.7, 121.6, 110.0, 94.7, 74.3, 70.5, 37.8, and 30.4 ppm. **IR (neat)**: 2956, 1728, 1489 and 1209 cm^{-1}. **HR-MS (NSI)** *m/z*: calculated for $C_{18}H_{12}BrCl_3O_3H^+$ 459.9035, observed 460.9117. **(Chiralcel OD 0.5% i-PrOH/hexanes, 1.0 mL/min):** tR = 11.62 (minor), 15.01 (major) min. **$[\alpha]_D^{20}$** (c=0.59): -72.5.

2,2,2-trichloroethyl 6-(4-bromophenyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate



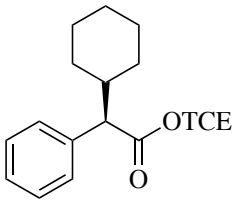
Following general procedure B using 2,3-dihydrofuran as a substrate, the desired cyclopropane was isolated as a clear oil (503mg, 91% yield, 0% ee). $\mathbf{R_f}$= 0.40 (SiO_2= 9:1 Hex:EtOAc). **^{1}H NMR (600 MHz; $CDCl_3$)** δ 7.52-7.49 (m, 2H), 7.25-7.23 (m, 2H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.60 (d, *J* = 11.9 Hz, 1H), 3.84 (dddd, *J* = 10.4, 8.8, 3.9, 1.3 Hz, 1H), 2.77 (t, *J* = 5.9 Hz, 1H), 2.54 (q, *J* = 8.8 Hz, 1H), 2.36-2.21 (m, 1H), and 1.86 (ddd, *J* = 13.0, 8.7, 3.8 Hz, 1H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$)** δ 168.9, 133.3, 131.7, 130.3, 122.1, 109.9, 94.9, 74.1, 70.2, 37.5, 32.9, and 26.1 ppm. **IR (neat)**: 2953, 2901, 1728 and 1488 cm^{-1}. **HR-MS (NSI)** *m/z*: calculated for $C_{14}H_{12}BrCl_3O_3H^+$ 412.9035, observed 412.9142. **(Chiralcel OD-H 1.0% i-PrOH/hexanes, 0.5 mL/min):** tR = 16.16, 18.06 min.

2,2,2-trichloroethyl (*R*)-2-(4-bromophenyl)-2-(cyclohexa-2,5-dien-1-yl)acetate



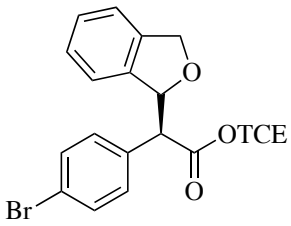
Following general procedure B using 1,4-cyclohexadiene as a substrate, the desired insertion product was isolated as a clear oil (605mg, 89% yield). $\mathbf{R_f}$= 0.42 (SiO_2= 9:1 Hex:EtOAc). **^{1}H NMR (500 MHz; $CDCl_3$)** δ 7.50-7.48 (m, 2H), 7.28-7.26 (m, 2H), 5.86-5.84 (m, 1H), 5.76 (m, 2H), 5.37-5.30 (m, 1H), 4.82 (d, *J* = 11.9 Hz, 1H), 4.72 (d, *J* = 11.9 Hz, 1H), 3.61-3.54 (m, 2H), and 2.63 (m, 2H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ 170.8, 134.7, 131.6, 130.5, 126.9, 126.7, 125.8, 124.9, 121.8, 94.7, 74.1, 57.5, 38.2, and 26.3 ppm. **IR (neat)**: 3030, 1749, 1487 and 1132 cm^{-1}. **HR-MS (NSI)** *m/z*: calculated for $C_{16}H_{14}BrCl_3O_2K^+$ 460.9243, observed 460.1432. **$[\alpha]_D^{20}$** (c=0.63): -17.6.

2,2,2-trichloroethyl (*R*)-2-cyclohexyl-2-phenylacetate



To a flame-dried round bottom flask was added Pd/C (10 mol%) and 2,2,2-trichloroethyl (*R*)-2-(4-bromophenyl)-2-(cyclohexa-2,5-dien-1-yl)acetate (100 mg, 0.24 mmole, 1 equiv.). Methanol (8 mL) was then added and the flask went through vacuum/hydrogen cycles a couple times. The reaction was stirred for 6 hours and concentrated down by rotary evaporation. It was purified by column chromatography (silica gel, hexanes/EtOAc = 9:1) to give an oil (60 mg, 60% yield, 75% ee). $\mathbf{R_f}$= 0.69 (SiO_2= 9:1 Hex:EtOAc). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40-7.23 (m, 5H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 3.38 (d, *J* = 10.8 Hz, 1H), 2.10 (qt, *J* = 11.0, 3.4 Hz, 1H), 1.94-1.83 (m, 1H), 1.80-1.71 (m, 1H), 1.63 (dtt, *J* = 7.1, 5.5, 2.7 Hz, 2H), 1.42-1.25 (m, 2H), 1.24-1.05 (m, 3H) and 0.78 (ddd, *J* = 24.5, 12.2, 3.5 Hz, 1H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 172.3, 137.0, 128.9, 128.7, 127.6, 95.0, 74.2, 58.9, 40.9, 32.1, 30.4, 26.4, 26.0 and 26.0 ppm; **IR (neat):** 2925, 1732, 1510, 1248 and 1152 cm^{-1}. **HR-MS (EI)** *m/z* calculated for $C_{16}H_{20}Cl_3O_2^+$ 349.0523 observed 349.0526. **(Chiralcel OD-R 0.0% i-PrOH/hexanes, 0.25 mL/min):** tR = 17.61 (major), 19.69 (minor) min. **$[\alpha]_D^{20}$** (c=0.49): +6.4.

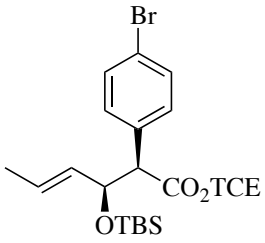
2,2,2-trichloroethyl (*S*)-2-(4-bromophenyl)-2-((*R*)-1,3- dihydroisobenzofuran-1-yl) acetate



Following general procedure B using phthalan as a substrate, the desired insertion product was isolated as a clear oil (326mg, 70% yield, 73% ee, d.r. 1:1). $\mathbf{R_f}$= 0.43 (SiO_2= 9:1 Hex:EtOAc). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.50 (dd, *J* = 8.6, 0.9 Hz, 2H), 7.29 -7.23 (m, 4H), 7.20 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.04 (td, *J* = 7.4, 1.0 Hz, 1H), 6.25 (d, *J* = 7.7 Hz, 1H, diasteromer A), 5.83 (dd, *J* = 9.4, 2.5 Hz, 1H, diastereomer B), 5.16 (dd,

J = 12.4, 2.7 Hz, 1H), 5.08 (d, *J* = 12.3 Hz, 1H), 4.80 (d, *J* = 11.9 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 1H), and 3.88 (d, *J* = 9.3 Hz, 1H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$):** δ 169.80, 139.56, 138.46, 132.62, 131.87, 131.07, 128.22, 126.94, 122.51, 122.39, 121.05, 94.69, 84.68, 74.31, 72.76, and 57.59 ppm. **IR (neat):** 2860, 1750, 1488, 1275 and 1136 cm^{-1}; **HR-MS (NSI)** *m/z* calculated for $C_{18}H_{14}BrCl_3O_3H^+$ 462.9192 observed 462.9273. **(Chiralcel OD 1.0% i-PrOH/hexanes, 1.0 mL/min):** tR = 8.52 (minor), 9.83 (major) min. **$[\alpha]_D^{20}$** (c=0.65): -32.6.

2,2,2-trichloroethyl (2*R*,3*S*,*E*)-2-(4-bromophenyl)-3-((*tert*-butyldimethylsilyl) oxy) hex-4-enoate



Following general procedure B using (*E*)-(but-2-en-1-yloxy)(*tert*-butyl) dimethylsilane as a substrate, the desired insertion product was isolated as a clear oil (517mg, 61% yield). **R_f**= 0.75 (SiO_2= 9:1 Hex:EtOAc). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.44 (m, 2H), 7.30 (d, 2H), 5.70 (dqd, *J* = 15.4, 6.5, 0.8 Hz, 1H), 5.42 (ddq, *J* = 15.3, 7.9, 1.6 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.54 (t, *J* = 8.0 Hz, 1H), 3.71 (d, *J* = 8.3 Hz, 1H), 1.65 (dd, *J* = 6.5, 1.7 Hz, 3H), 0.69 (s, 9H), -0.12 (s, 3H), and -0.27 (s, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.9, 134.5, 131.6, 131.2, 131.1, 128.8, 121.6, 94.6, 75.7, 74.2, 58.9, 25.5, 17.7, -4.3, and -5.4 ppm. **IR (neat):** 2954, 2856, 1751, 1488 and 1143 cm^{-1}. **HR-MS (NSI)** *m/z* calculated for $C_{20}H_{28}BrCl_3O_3SiH^+$ 529.0129 observed 529.0139. **$[\alpha]_D^{20}$** (c=1.16): +10.5.