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Elliot F. Hicks April 7, 2020

Synthetic Applications of Dirhodium(II) Catalysis

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An abstract of
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Abstract

Synthetic Applications of Dirhodium(II) Catalysis
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Dirhodium(II) catalyzed reactions have proven to be synthetically useful tools for transforming bonds that are traditionally difficult to functionalize. These atypical transformations allow for the rapid construction of molecules which would otherwise take many steps to build. This study showcases two applications of dirhodium(II) catalysis. The first application focuses on the functionalization of organosilicon compounds as a way to rapidly and selectively incorporate silicon, which has potential applications in the pharmaceutical industry. The second application focuses on performing one step in a sequence in an enantioselective fashion. The resulting enantiomerically enriched compounds could be carried forward to make enantiomerically enriched endoperoxides, which have applications in antimalarial drug discovery.

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Table of Contents

Figures and Tables

1.) Introduction

1.1) The Importance of Stereochemistry and Stereoselective Synthesis

Stereochemistry generally refers to the spatial arrangement of the atoms in a molecule. Many molecules have a non-superimposable, mirror image counterpart. A pair of such molecules are called "enantiomers." This idea is similar to how a left hand is the mirror image of a right hand; they look the same but cannot be superimposed. This concept is illustrated in Figure 1.1.1.

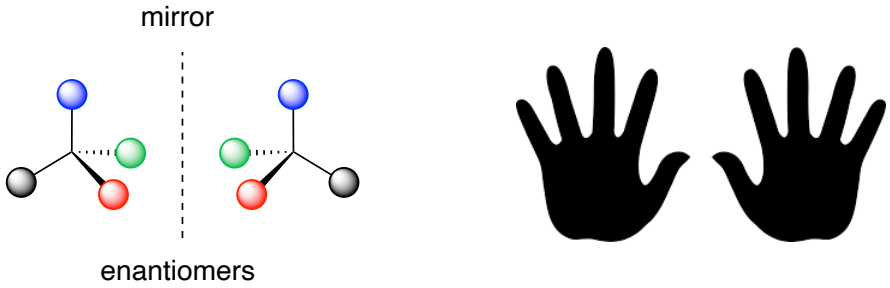


Figure 1.1.1: Visualization of chiral molecules (left) and comparison to left and right hand (right).

Molecules that have a non-superimposable, mirror image counterpart are said to be "chiral." Chirality and stereochemistry are important when synthesizing molecules. As seen in Figure 1.1.2, auereol, a representative natural product (secondary metabolites of plants or fungi), and Xarelto, a pharmaceutical agent, are chiral, with the chiral centers being indicated by the arrows.

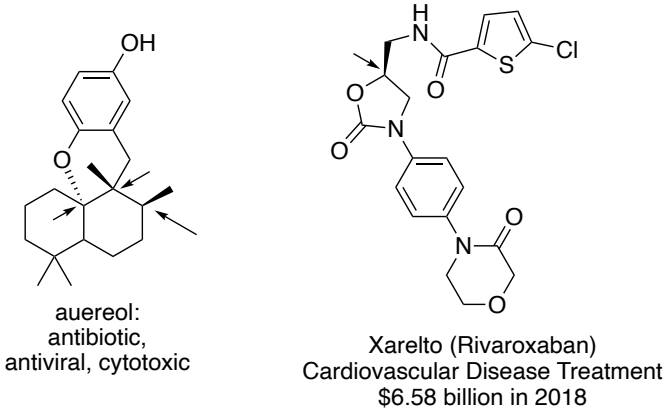


Figure 1.1.2: Representative chiral natural product and pharmaceutical agent

Chirality has extreme biological consequences. Although it may seem trivial, changing the spatial arrangement of the atoms, i.e. going from the left hand to right hand version of a molecule, can have drastic biological effects. One of the most famous examples of how drastically different the biological effects of two enantiomers can be is thalidomide, shown in Figure 1.1.3. One enantiomer of thalidomide has a sedative effect, while the other has a teratogenic effect.

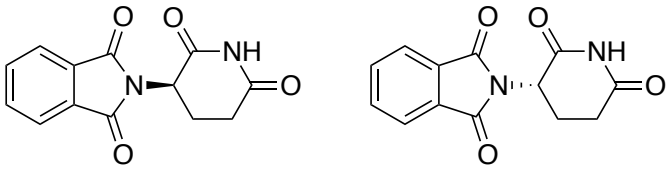


Figure 1.1.3: The two enantiomers of thalidomide and their biological effects

When synthesizing molecules, having control over the stereochemistry is therefore very important. One strategy to control the stereochemistry of the product(s) of a chemical reaction is to use a catalyst. In the Davies group, chiral dirhodium catalysts are used to control the stereochemistry of the products of the chemical reactions.

1.2) Rhodium Catalyzed Decomposition of Diazo Compounds

Carbenes are reactive species in which a carbon atom carries a lone pair and makes two bonds, leading to an overall neutral but electron deficient atom (Figure 1.2.1). Because of the carbon's electrophilicity and the relatively high energy of the lone pair, carbene compounds are able to perform reactions which cannot usually be performed through traditional functional group transformations.[1] These reactions include "X-H insertion reactions", where X can be C, O, or N; cyclopropanation reactions; and in some cases, rearrangement reactions. There are two sets of HOMO/LUMO interactions at play in these reactions. The HOMO of the carbene (lone pair

electrons) interact with the LUMO of the substrate. The HOMO of the substrate concurrently donates electron density to the LUMO of the electron deficient carbene. Through both sets of interactions, the carbon "inserts itself" into one bond of the substrate molecule. The inherent reactivity of a free carbene is such that it reacts normally in an unselective fashion because the carbene can react with any number of bonds that would typically not be reactive.[1]

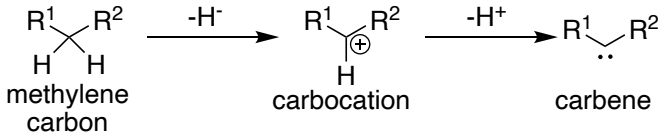


Figure 1.2.1: Depiction of a free carbene and its relation to other carbon species

Diazo compounds in conjunction with catalytic dirhodium catalysts, shown in the catalytic cycle in Figure 1.2.2, offer a robust way of generating these reactive carbene species while controlling their reactivity. In the diazonium compound shown in Figure 1.2.2, a significant amount of electron density is centered around the central carbon. These electrons are able to coordinate and form a complex with a dirhodium catalyst. Back-bonding of the rhodium complex facilitates the removal of nitrogen gas, an extremely good leaving group. This generates a rhodium-carbenoid complex.[2] The stability of this complex is governed by the R_1 and R_2 groups. The most commonly used diazo compounds by the Davies group tend to be so-called "donor-acceptor" compounds, in which R_1 is electron donating, usually an aromatic system, and R_2 is electron withdrawing, usually an ester. This combination helps create a stable carbenoid complex. The use of an "acceptor-acceptor" compound makes the carbene more electron deficient and more reactive. A "donor-donor" compound donates electron density to the electrophilic carbene. This stabilizes the carbene, making this species less reactive.[3] The "donor-acceptor" carbene has become the posterchild of the Davies group's chemistry and is often the

first type of diazo compounds to be used because they are easy to prepare, safe to handle, and still reactive enough to explore new types of reactions.

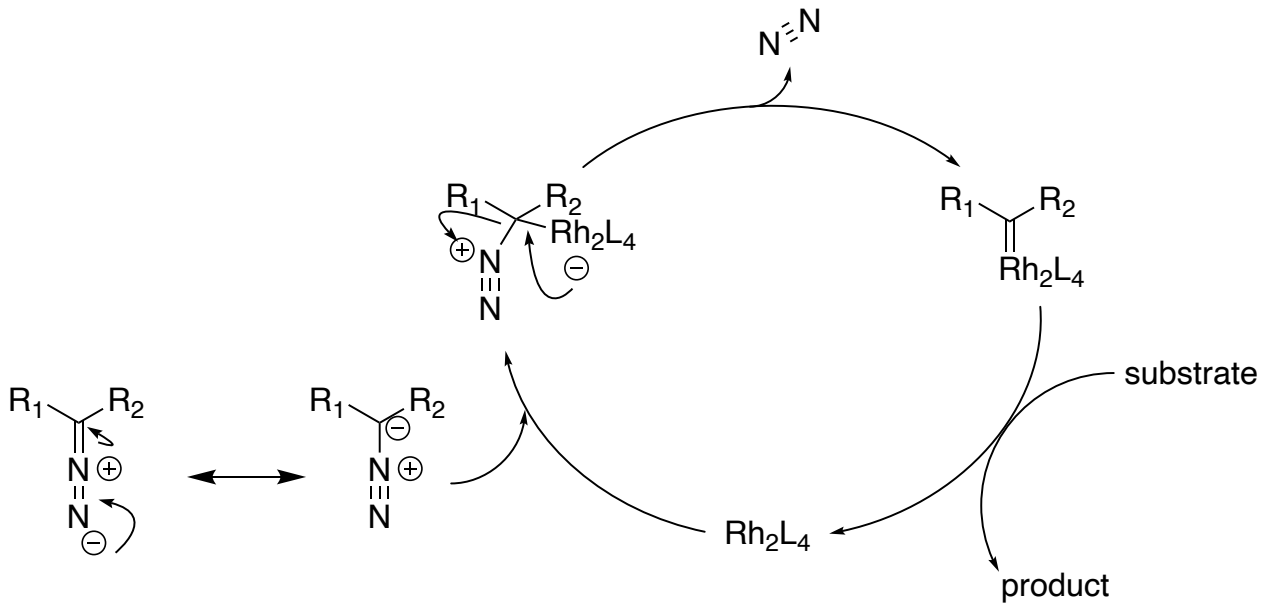


Figure 1.2.2: Typical catalytic cycle for Rh(II)-mediated decomposition of diazonium compounds

The stability of the carbenoid complex is of paramount importance when it comes to selectivity. Generation of a stable complex allows the substrate to approach the complex and the reaction to occur in a controlled fashion. If the complex is unstable, the reaction proceeds too easily and cannot be controlled. Chiral dirhodium catalysts need the substrate to approach in a controlled manner. This way the chirality of the catalyst has the ability to force the substrate to approach the complex in a specific orientation due to the steric requirements imposed by the chiral ligands.[4] Thus insertion into a bond can reliably occur via the same geometry each time resulting in a product that has a very well defined stereochemistry. As mentioned in Section 1.1 stereochemical control is critical when making molecules. Such stereochemical control is not possible using achiral catalysts or "free" carbenes. Because these "non-traditional" reactions can

be made to behave well, and the stereochemistry of the products can be so easily controlled, this type of chemistry has many applications for the pharmaceutical industry.

1.3) Synthetic Utility of Carbenes/Carbenoids & Davies Group Catalyst Development

The Davies group has developed an array of chiral dirhodium catalysts in an effort to control the reactivity of the carbenoid complex and impose different steric requirements to control the selectivity of the reactive species. Early developments in carbene chemistry demonstrated the unprecedented but often nonselective or non-stereospecific reactivity of carbenes.[5] For example, generating triplet carbenes often means that the reaction will proceed via a radical mechanism in which the stereochemistry will be difficult if not impossible to control because of bond rotation since the mechanism is not concerted.[2] Being able to control the stereochemistry and site selectivity of a carbene reaction is crucial.

The catalysts developed by the Davies group tend to target different bonds. C-H bonds are the most ubiquitous type of bond in almost every molecule. Because these bonds are so great in number, the reactivity of a free carbene is such that little to no control is possible when thinking about which C-H bond will react in any given molecule. Furthermore, if this C-H bond is at a prochiral site, there would be no way to control the stereochemistry at that site after the reaction.

The catalyst development in the Davies group is highly engineered to tackle the challenges presented above.[6] A selection of first, second, and third generation catalysts are shown in Figure 1.3. These catalysts have different reactivity and selectivity profiles, meaning they are best used in different reactions such as C-H insertion vs. cyclopropanation, or they target different bonds such as tertiary vs. primary C-H bonds. Many of the catalyst developments in the Davies group have come in differentiating between primary, secondary, and tertiary C-H

bonds.[4,7] The key to designing a new reaction lies in finding the correct catalyst for the desired transformation. The Davies group has attempted to create a library of catalysts which are capable of accessing any C-H bond in a given molecule by changing the steric environment of the chiral pocket of the dirhodium-carbene complex.

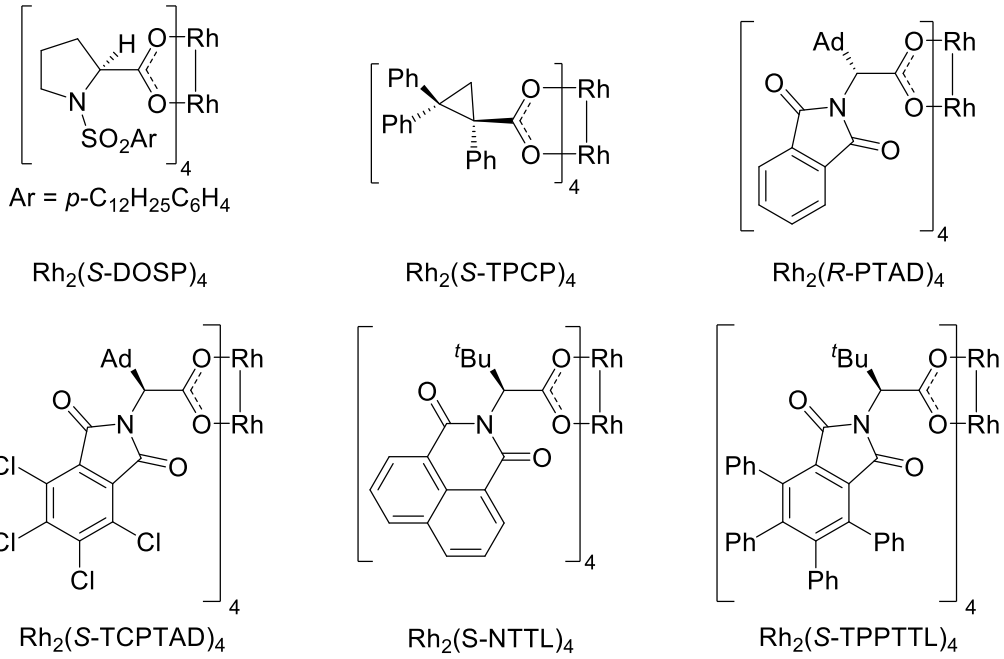


Figure 1.3: Representative catalysts developed by the Davies group

The library of catalysts is extensive, making the design of a new reaction much easier. The two projects presented are examples in which the group had previously shown the reactivity profile of certain catalysts, i.e. which bonds are most easily functionalized using those catalysts, and these projects were a matter of applying this knowledge to invent a new reaction. The success or failure of the reaction would either support the supposed reactivity or call this reactivity into question, both valuable outcomes when trying to understand how the catalysts control the reactivity and selectivity of the carbenoid complexes.

Based on the development of catalysts in the Davies group, both projects employ the use of a catalyst selected specifically for the desired reaction.

2.) First Application: C-H Functionalization of Cyclic Organoslianes

Previous work has shown that C-H insertion reactions of cyclic organosilicon molecules occur preferentially at the beta position relative to silicon.[8] This is rationalized by the beta-silicon effect. This effect states that orbital overlap form C-Si bonds can stabilize a positive charge at a position beta to silicon. This effect also has consequences for C-H insertion reactions of carbenes on organosilicon molecules. The overlap of the C-Si sigma bond with the antibonding orbital of the C-H bond beta to silicon, Figure 2.1, makes the hydrogen act more like hydride (H^-).

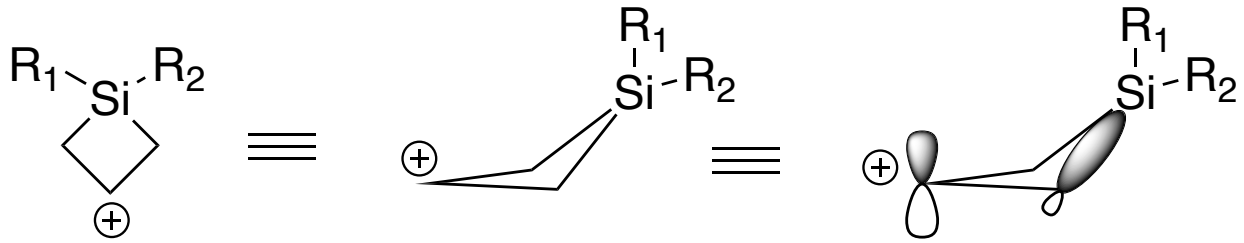


Figure 2.1: Demonstration of the beta-silicon effect. Orbital overlap stabilizes positive beta-position positive charge.

The lability of these beta-position hydrogens means that the C-H insertion reaction is more facile. In the mechanism shown in Figure 2.2, this reaction likely takes place in a way that resembles a hydride transfer, which is why a more labile hydride makes the reaction preferred.

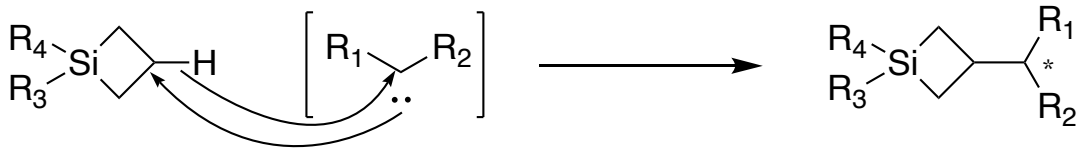


Figure 2.2: Possible mechanism for C-H insertion of rhodium carbene (shown as transient carbene, for clarity) and organosilicon compound.

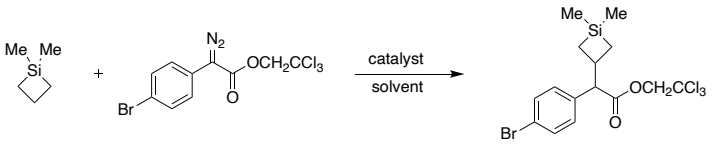
The prior study on the C-H insertion of organosilanes established the reaction using 1,2,3-triazoles as the carbene precursor. Methodology developed by the Davies group has shown that the catalyst Rh_2(S-NTTL)$_4$ is best suited for transformations involving triazole compounds, that is, the catalyst provides the highest levels of selectivity. However, in the paper, while many results give high enantiomeric excess, the substrate scope was relatively limited. The diazo compounds have decent diversity, but the silicon substrates used are limited to mostly four-membered rings. One glaring limitation is that the desymmetrization of the five-membered ring compounds showed low levels of diastereoselectivity.[8]

During this investigation, a new catalyst was concurrently developed in the Davies group, Rh_2(TPPTTL)$_4$. The big breakthrough with this catalyst was that it performed almost exclusively C-3 C-H insertion on substituted cyclohexane compounds with incredibly high levels of selectivity.[9] The motivation for revisiting the C-H functionalization of organosilanes was that this new catalyst could likely be paired with donor/acceptor diazo compounds and used to functionalize organosilicon molecules exclusively at the beta position. The beta-position is similar to the C3 position of cyclohexanes in that these positions are the same distance away from the reference point (carbon and silicon respectively). Therefore, the catalyst should give high levels of stereoselectivity for this transformation.

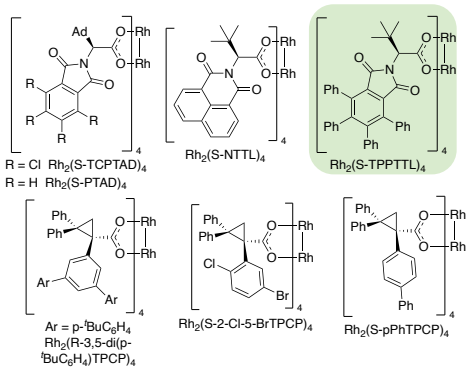
This hypothesis was tested by screening many different catalysts in a reaction with the silacyclobutane, shown in Figure 2.3. In this screening, the most important number is the enantiomeric excess. The reaction conditions can usually be further optimized (if desired) to improve yield, but under the same conditions the catalyst that performs the best should be the one selected, since the asymmetric induction cannot be changed as drastically by different reaction conditions as it can by choosing a different catalyst. From the table in Table 2.3,

$Rh_2(TPPTTL)_4$ clearly gives the highest stereoinduction, meaning that the initial hypothesis was correct.

Table 2.3: Optimization of the catalyst with structures of screened catalysts

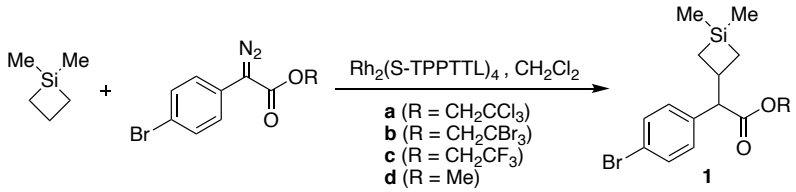


entry	catalyst	solvent	yield (%)	ee (%)
1	Rh_2(S-DOSP)$_4$	CH_2Cl_2	55	58
2	Rh_2(R-3,5-di(*p*-^{t}BuC_6H_4)TPCP)$_4$	CH_2Cl_2	67	-62
3	Rh_2(S-pPhTPCP)$_4$	CH_2Cl_2	45	72
4	Rh_2(S-NTTL)$_4$	CH_2Cl_2	70	38
5	Rh_2(S-PTAD)$_4$	CH_2Cl_2	59	-40
6	Rh_2(S-TCPTAD)$_4$	CH_2Cl_2	57	88
7	Rh_2(S-TPPTTL)$_4$	CH_2Cl_2	74	96



The next step in the optimization was to find the best acceptor group. This became a determination of which ester group gave the highest levels of enantiomeric excess using the catalyst that was already shown to perform best. The variation was a study of using tribromoethyl, tricholoroethyl, trifluoroethyl, and methyl ester groupings. The best ester group, based on enantioselectivity was the tricholoroethyl group (Table 2.4). This was expected as many recent studies in the Davies group have found that the trichloroethyl ester tends to outperform all other ester groups.

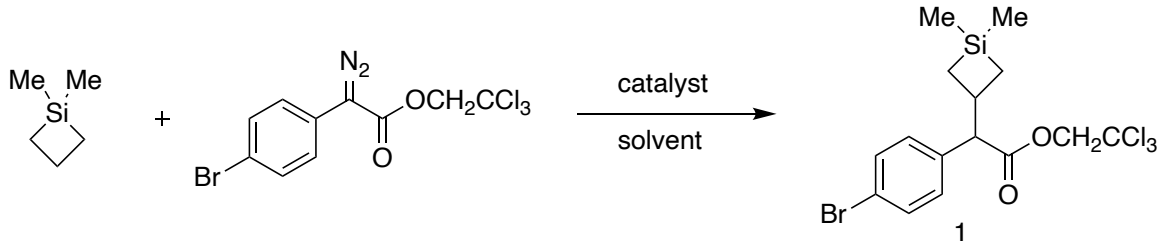
Table 2.4: Optimization of acceptor group.



entry	catalyst	product	yield (%)	ee (%)
1	Rh_2(S-TPPTTL)$_4$	**1a**	74	96
2	Rh_2(S-TPPTTL)$_4$	**1b**	67	88
3	Rh_2(S-TPPTTL)$_4$	**1c**	54	92
4	Rh_2(S-TPPTTL)$_4$	**1d**	68	93

After finding the best catalyst and ester group, the reaction conditions were probed to achieve the highest yield and enantiomeric excess possible, using reasonable conditions. Several reaction conditions were screened, varying solvents commonly used in these reactions, temperature, and stoichiometry of diazonium and silane substrates. The best conditions were found to be using three equivalents of silane substrate, and trifluorotoluene as solvent, conducting the reaction at room temperature (Table 2.5). It is also important to note that using extreme excess of the silane is wasteful and while it may have been able to marginally increase yield or enantioselectivity, the level of enantioselectivity was very high without an unreasonable excess of the silane. Using more than three equivalents of silane was not explored for this reason.

Table 2.5: Optimization of reaction conditions.

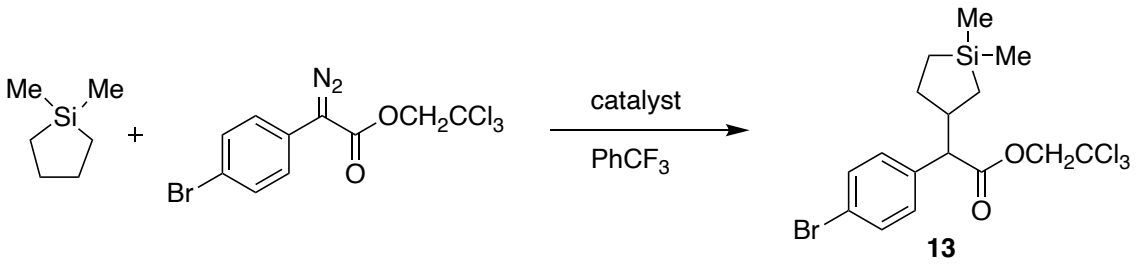


entry	catalyst	solvent	yield (%)	ee (%)
1	Rh_2(S-TPPTTL)$_4$	CH_2Cl_2	74	96
2[a]	Rh_2(S-TPPTTL)$_4$	CH_2Cl_2	72	94
3	Rh_2(S-TPPTTL)$_4$	$CHCl_3$	61	94
4	Rh_2(S-TPPTTL)$_4$	DCE[b]	64	95
5	Rh_2(S-TPPTTL)$_4$	TFT[c]	69	98

General reaction conditions: 3 equivalents of silane substrate (1M), 1 equivalent diazo (0.17M) added over 3h. [a] Reaction conducted at reflux. [b]1,2-dichloroethane. [c]*a,a,a*-trifluorotoluene.

One of the limitations of the previous study was a lack of diastereoselectivity in the desymmetrization reaction of the five-membered dimethyl-silacyclopentane. Thus another screening was performed using this five-membered substrate pushing the Rh_2(TPPTTL)$_4$ catalyst to see if it still was the best catalyst for the reaction (Table 2.6). In this screening the most important numbers were the diastereomeric ration (d.r.) as determined from crude ^{1}H NMR analysis. Because the system was being desymmetrized, the catalyst that performed with the highest ratio of one diastereomer to the other should be the one chosen. It also follows that this catalyst would give the highest levels of enantioselectivity for the diastereomers. The Rh_2(NTTL)$_4$ catalyst gave levels of diastereoselectivity similar to those in the previous study. The Rh_2(TPPTTL)$_4$ ratio more than double the ratio with Rh_2(NTTL)$_4$.

Table 2.6: Desymmetrization study.



entry	catalyst	combined yield (%)	d.r.
1	Rh_2(S-DOSP)$_4$	50	1.9:1
2[a]	Rh_2(S-pPh-TPCP)$_4$	56	1.5:1
3	Rh_2(R-PTAD)$_4$	72	2:1
4	Rh_2(R-TCPTAD)$_4$	73	2.2:1
5	Rh_2(S-NTTL)$_4$	33	4:1
6	Rh_2(S-TPPTTL)$_4$	56	14:1

Following this screening, the reaction was fully optimized and the substrate scope was expanded. The reactions of the four-membered substrate with various diazo compounds were the next steps to expand the scope of the reaction, shown in Figure 2.7. The diazo compounds with para substitution all gave greater than 90% enantiomeric excess. Substrates with ortho and meta substitution performed with reasonable enantiomeric excess as well. The drop in selectivity for the ortho-chloro compound may be explained by the fact that the ortho substitution does not cause as significant a level of steric crowding in the chiral pocket of the catalyst compared to meta- and para-substituted compounds. The heterocyclic compounds all performed very well with only a moderate drop in enantioselectivity for the thiophene compound. Stereochemistry of the products were assigned by analogy based on the crystal structure of compound **6** (see Experimental).

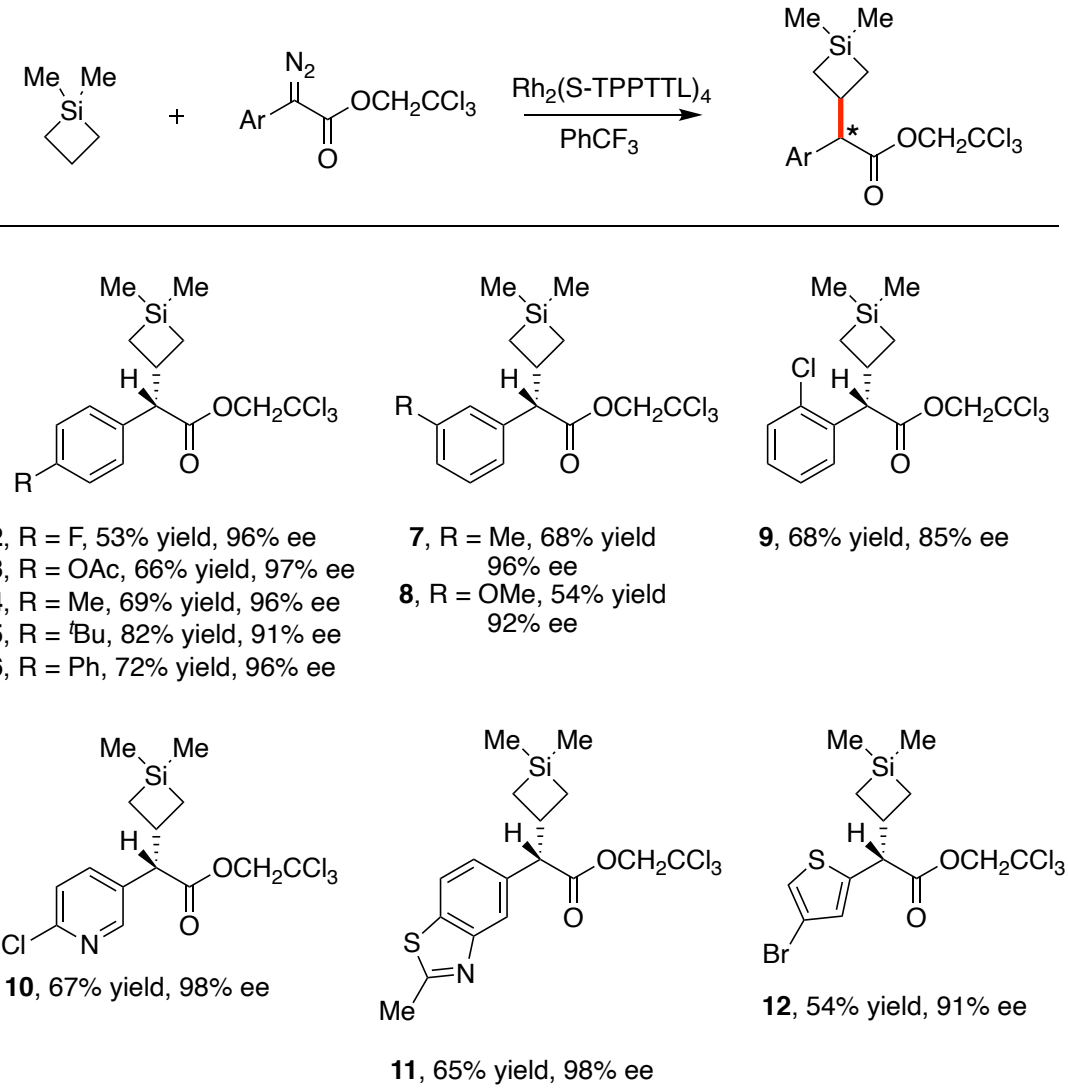


Figure 2.7: Expansion of diazonium scope using the four-membered organosilane.

The highlight of this study was the drastic improvement when using the five-membered organosilane. This was the silane compound that in the original study gave only limited selectivity both in terms of diastereomeric ratio and enantiomeric excess. As was the case in the previous optimization in Table 2.6, the $Rh_2(TPPTTL)_4$ was much better than the previous best catalyst, $Rh_2(NTTL)_4$. The diazo-compound scope was also expanded slightly; however, only para-substituted diazo compounds were used. As a further proof of concept, the reaction of the five-membered oragnosilane with the methyl-ester diazoacetate compound gave a significantly

lower diastereomeric ratio and yield (Figure 2.8). Stereochemistry of the products was assigned based on NMR experiments supported by previous work.[8]

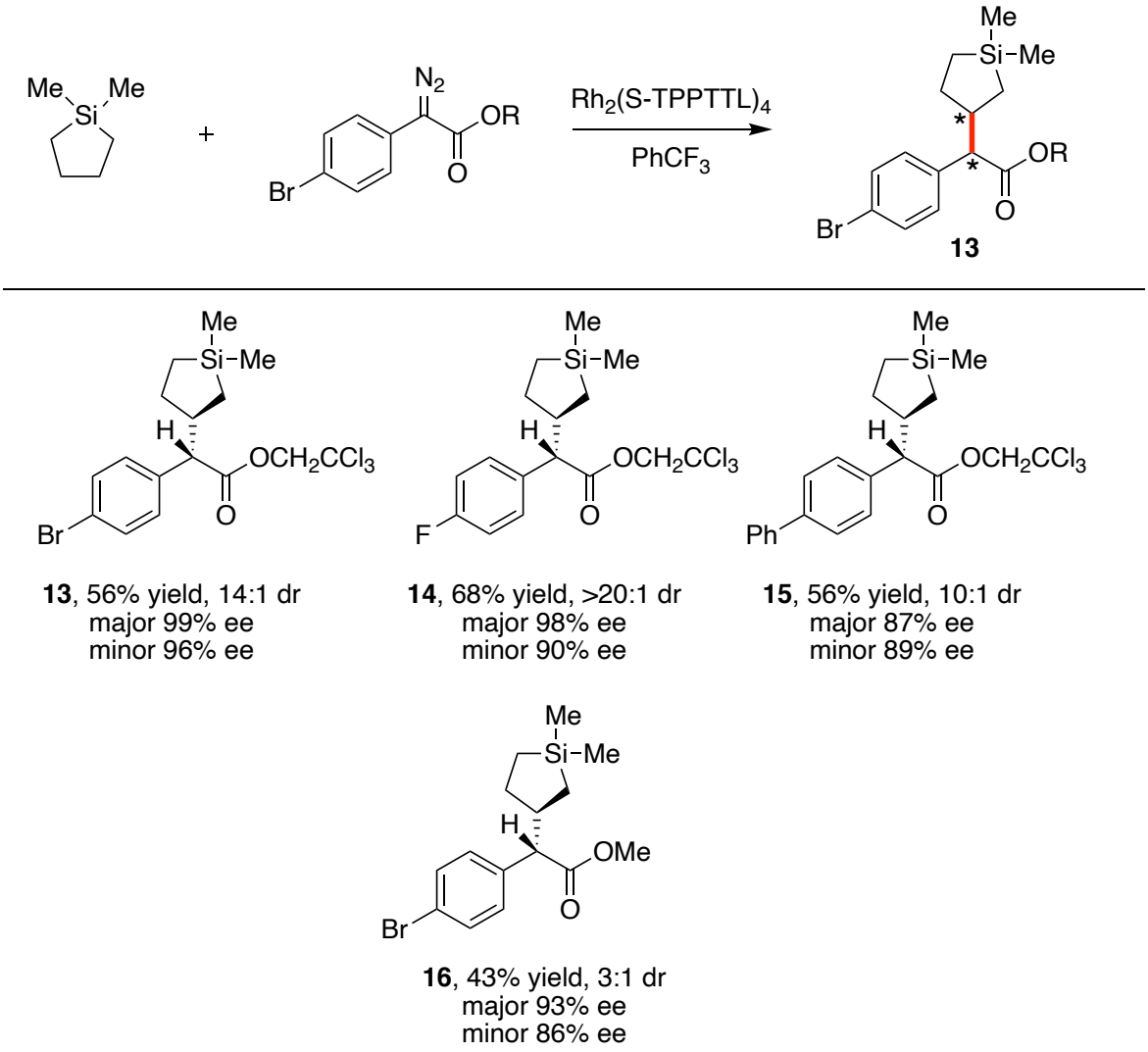


Figure 2.8: Diazo-substrate scope expansion with the five-membered oragnosilane.

Another interesting outcome of this study was the comparison of the para-substituted phenyl-silacyclobutanes shown in Figure 2.9. This was interesting because the sterics are basically the same for both but the electronics are different. However, the d.r. and ee appear to change based on the electronic properties. The relatively more electron rich ^{t}butyl substituted

compound had a slightly lower yield but displayed much higher levels of diastereo- and enantioselectivity. Stereochemistry was tentatively assigned by analogy to compound **6**.

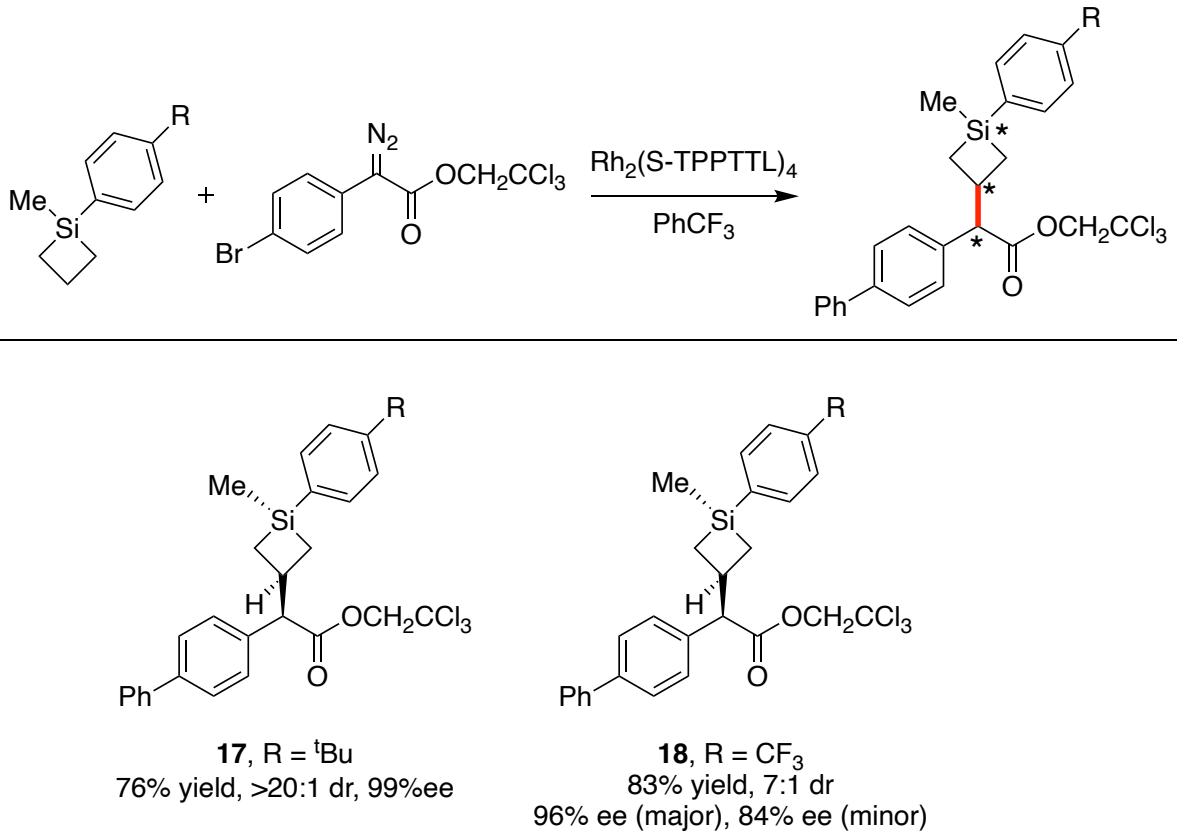


Figure 2.9: Higher stereoselectivity exhibited by the less electron withdrawing phenyl substitution.

One rationalization for this difference in selectivity could be from the relative labilities of the hydrides. Rationally speaking, a more reactive substrate would exhibit lower levels of selectivity. If a species is very reactive, the facial selectivity of the hydride transfer and corresponding C-H insertion will likely be low since the reactivity is high, meaning there is nothing that differentiates the reaction at one face compared to the reaction of the other. In essence if the hydride of one compound is more labile than the hydride of the other, that compound will be more reactive. Logically this compound would exhibit a lower level of stereoselectivity.

The para-CF_3 group inductively removes electron density from the silicon. Under normal circumstances, carbon is more electronegative than silicon, polarizing C-Si bond toward carbon. With the inductive pulling of the CF_3 the relative electronegativity of Si increases because of the electron deficiency around silicon. Thus the C-Si bond becomes more nonpolar. Therefore the C-Si electron density is more available to donate into the C-H antibonding orbital, which makes the hydride more labile, making this substrate more reactive.

The ′butyl substrate does not inductively pull electron density away from silicon to the same extent, so the bond is more polarized toward carbon and the electron density donated by the C-Si bond is less, decreasing the relative lability of the hydride. Additionally, the sterics of a tertiary butyl grouping *are* slightly more demanding than a CF_3 group, meaning that the substrate has to approach in a more particular stereochemical orientation than the CF_3 substrate. In effect, both sterics and electronics work constructively to favor

In conclusion, using a rational catalyst selection process, it has been shown that $Rh_2(TPPTTL)_4$ is the best catalyst for this type of transformation. Because this is a new reaction for this catalyst, it was first proved that the catalyst was indeed the best for this transformation before proceeding to fill out the substrate scope. Further investigations to challenge this catalyst would be by using larger ring substrates, linear substrates, and substrates that include both a linear and cyclic chain.

3.) Second Application: Kinetic Resolution via Cyclopropanation of 2-phenyl-2,3-dihydrofuran

The second application of dirhodium(II) catalysis comes in the form of cycloproanation reactions. Instead of insertion into a C-H bond, the only new bonds formed are C-C bonds.

However the same principles apply for stereoselectivity, and stereochemically enriched products can easily be formed.

The Reiser group has developed a method which uses a sequential dirhodium catalyzed cyclopropanation followed by photochemical ring opening under an atmosphere of oxygen to yield endoperoxides (Figure 3.1). These endoperoxides are known for their antimalarial activity,[10] and these compounds were tested for their activity. As shown in the paper, the biological activity was moderate for most compounds.[11] However, the major limitation is that all products generated are racemic. The first step in the sequence is mediated by rhodium acetate, a racemic catalyst. The reaction gives one diastereomer, which should be expected because one face of the dihydrofuran is more accessible than the other due to the steric impediment imposed by the phenyl substitution at the 2-position. In this scheme all diastereomers are present in equal amounts because the catalyst is achiral.

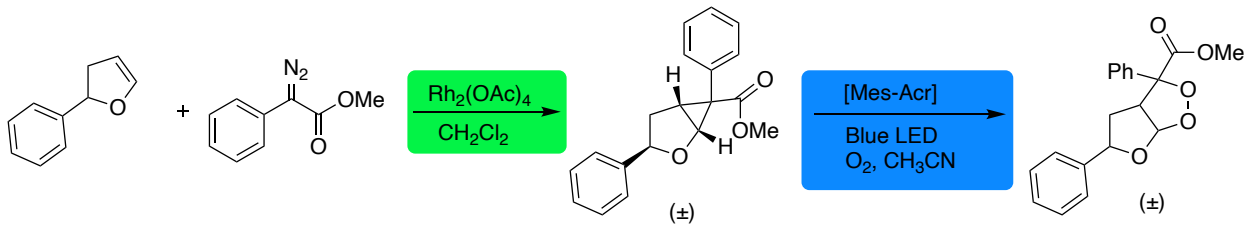


Figure 3.1: Sequential rhodium and photocatalytic process to generate endoperoxides

Biologically, it is possible that one enantiomer is more active than the other, or that the one enantiomer is entirely inactive. This is the case for many drug molecules in which one enantiomer causes a desired effect while the other is inactive or toxic.[12] The famous example of the latter behavior is thalidomide, in which one enantiomer had a desired effect and the other a deleterious, teratogenic effect.

Additionally, if the product of the cylclopropanation reaction could be generated as an enantioenriched product, this would allow for further investigations into whether the

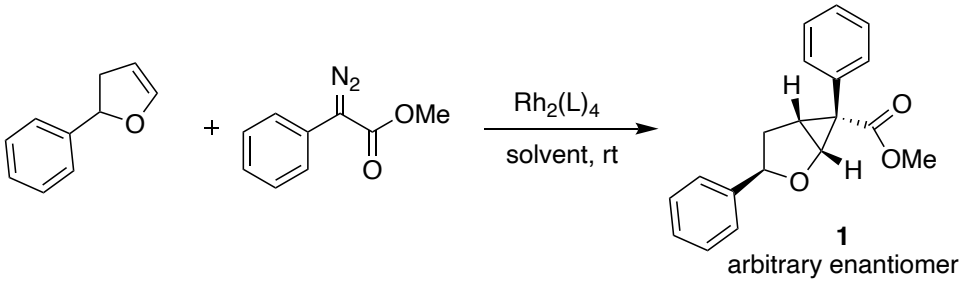
photocatalytic process preserves the level of enantioselectivity. Thus an investigation into whether this reaction can be performed asymmetrically is warranted, and could provide to be valuable if it were desired to further test these compounds for antimalarial activity.

The substrate appears to be very activated, due to the conjugation of the lone pairs of oxygen with the pi bond of the dihydrofuran. This electronically activates this bond, which should make cyclopropanation a more facile reaction. As previously mentioned, though, being too activated can be detrimental when it comes to stereoinduction.

This investigation began with a screen of different catalysts. As before, certain catalysts are known to perform well in cyclopropanation reactions. Thus it was hypothesized that $Rh_2(DOSP)_4$, $Rh_2(PTAD)_4$, and $Rh_2(TCPTAD)_4$ would be the most likely candidates for best catalyst in this reaction. But other catalysts were also tested so as to have a full picture of the reactivity profile.

Because this study only used the methyl ester diazoacetate compound with an unsubstituted phenyl group as the donating group, the screening for the enantioselective reaction began using this diazo compound. The catalysts were screened at room temperature, shown in Table 3.2. The results were very surprising. Almost no enantioenrichment was observed. This made very little sense because the substrate seemed so activated and well-suited for an enantioselective transformation, especially given that only one diastereomer is observed for an achiral catalyst.

Table 3.2: Initial screen of catalysts.

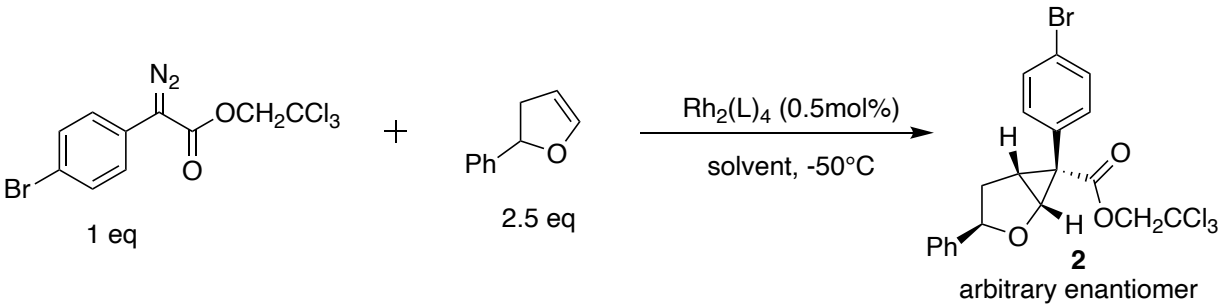


entry	catalyst	solvent	yield (%)	ee (%)	compound
1	Rh_2(S-TCPTAD)$_4$	CH_2Cl_2	73	2	1a
2	Rh_2(S-DOSP)$_4$	pentane	69	-34	1b
3	Rh_2(S-PTAD)$_4$	CH_2Cl_2	11	33	1c
4	Rh_2(S-TCPTTL)$_4$	CH_2Cl_2	68	9	1d

The diazo compound used was then changed to the tricholoroethyl diazoacetate tested in the silane project. This diazo tends to perform better than the methyl diazoacetate. Because the dihydrofuran substrate is so electronically active, this increased reactivity was hypothesized to be destroying the catalyst's selectivity. In other words, because the substrate is so reactive, the energy difference between reacting in one orientation compared to the other orientation was almost negligible. At room temperature, the energy barrier was easy to overcome for both orientations, and as a result, little to no enantioinduction occurred. It was then hypothesized that significantly lowering the temperature of the reaction would greatly favor an enantioselective reaction. At a lower temperature, the kinetic energy is greatly decreased, as the molecule is much more likely to follow the pathway that involves the lowest activation energy. The temperature chosen was -50°C, achieved using dry ice in acetonitrile.

A more extensive list of catalysts were screened at this lower temperature. This time many of the results were much more promising, seen in Table 3.3. $Rh_2(PTAD)_4$ was clearly the best performing catalyst. However the ligands of $Rh_2(PTAD)_4$ are flexible, meaning that the choice of solvent drastically affects the selectivity of the catalyst. Dichloromethane has slightly Lewis basic chlorine atoms which can coordinate to the rhodium and affect the chiral environment of the catalyst pocket. For that reason, pentane was used as the solvent, which drastically increased the enantiomeric excess of the reaction.

Table 3.3: Catalyst screening at -50°C using a new diazoacetate compound.



entry	catalyst	solvent	yield	ee	compound
1	$Rh_2(OAc)_4$	CH_2Cl_2	74%	0%	2a
2	$Rh_2(R\text{-}TCPTAD)_4$	CH_2Cl_2	73%	5%	2b
3	$Rh_2(S\text{-}DOSP)_4$	pentane	75%	34%	2c
4	$Rh_2(S\text{-}pBr\text{-}TPCP)_4$	CH_2Cl_2	69%	24%	2d
5	$Rh_2(S\text{-}PTAD)_4$	CH_2Cl_2	71%	62%	2e
6	$Rh_2(S\text{-}PTAD)_4$	pentane	72%	77%	2f
7	$Rh_2(R\text{-}2Cl\text{-}5Br\text{-}TPCP)_4$	CH_2Cl_2	76%	10%	2g
8	$Rh_2(S\text{-}TCPTTL)_4$	CH_2Cl_2	70%	-6%	2h
9	$Rh_2(S\text{-}TPPTTL)_4$	CH_2Cl_2	71%	5%	2i
10	$Rh_2(R\text{-}PTTL)_4$	CH_2Cl_2	81%	-32%	2j

In order to have a thorough screening and thorough control, the diazo group was changed back to the original diazo compound. Because the change went from methyl diazo at room

temperature to trichloroethyl diazo at -50°C, there is no definitive way of saying that the improvement was not simply due to the change in diazonium compound. The methyl diazo was also tested under the new conditions, and as expected it performed much better than originally, but it still did not perform as well as the trichloroethyl (Figure 3.4).

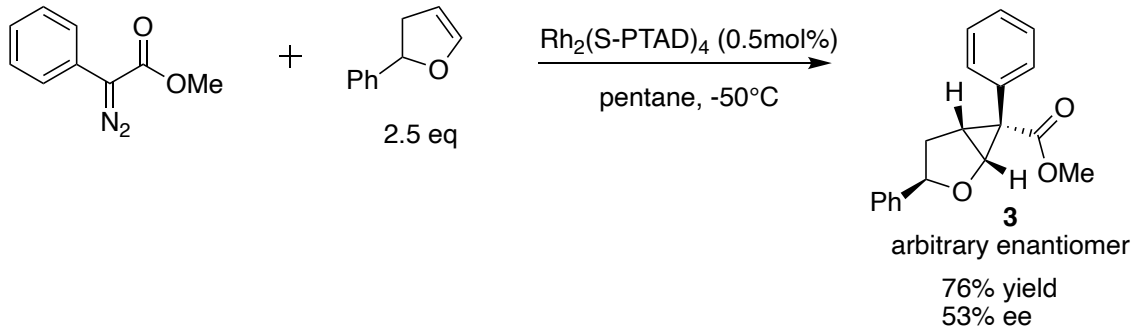


Figure 3.4: Test reaction using the original diazonium compound.

Because the methyl ester compound did not perform better, it was reasonable to assume that this was the best the set of reaction conditions. The final test was to use more equivalents of the 2,3-dihydrofuran to further improve the enantioselectivity. By using more equivalents of the dihydrofuran substrate, the highest enantiomeric excess achieved was 82% (Figure 3.5).

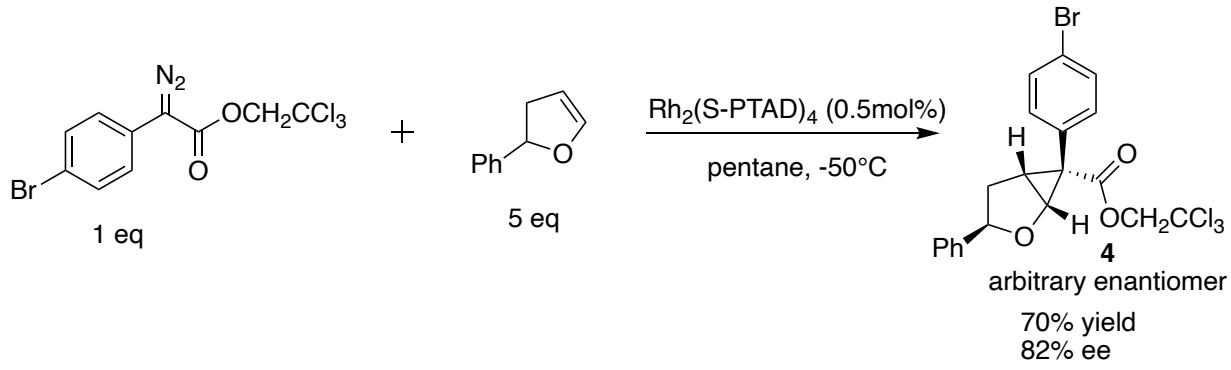


Figure 3.5: Highest enantiomeric excess achieved using five equivalents of 2,3-dihdrofuran

This is still only a moderate enantiomeric excess, especially given that the "traditional" cyclopropanation catalysts are capable of achieving enantiomeric excess greater than 99%.[13]

However, a more careful analysis of the stereochemistry of the reactants and products should explain why this transformation is still impressive.

With an achiral cyclopropanation substrate like styrene, the catalyst only differentiates between one approach of the substrate and another. As a result, generating only one product, in other words >99% enantiomeric excess, is a much simpler process. The sterics of the catalyst will dictate that only one approach is possible, and so the favored product will have a much lower activation energy (Figure 3.6).

However, with a chiral substrate, the situation is different. The one enantiomer of the product results from reaction with one of the substrate enantiomers. The other product enantiomer is the result of the reaction with the other enantiomer of the substrate (Figure 3.6). This means that the catalyst is not only differentiating between different orientations of the molecules, it is also differentiating between two stereochemically different versions of the molecule. Because the minor enantiomer, regardless of which of the compounds shown above it is, is formed from the reaction of the other enantiomer of the starting material, as the reaction proceeds, the relative concentration of preferred substrate decreases. In the catalyst screen scheme the equivalents of dihydrofuran used are 2.5. This means that effectively there are 1.25 equivalents of preferred substrate, and 1.25 equivalents of the other enantiomer of substrate which leads to the minor enantiomer of the product. Hypothetically, if only the preferred substrate reacted for the first half of the reaction, at the halfway point there would be 1.64 times the amount of minor substrate than major substrate. This means that near the end of the reaction, the differentiation between enantiomers is rendered more difficult because of the relative amounts of each substrate.

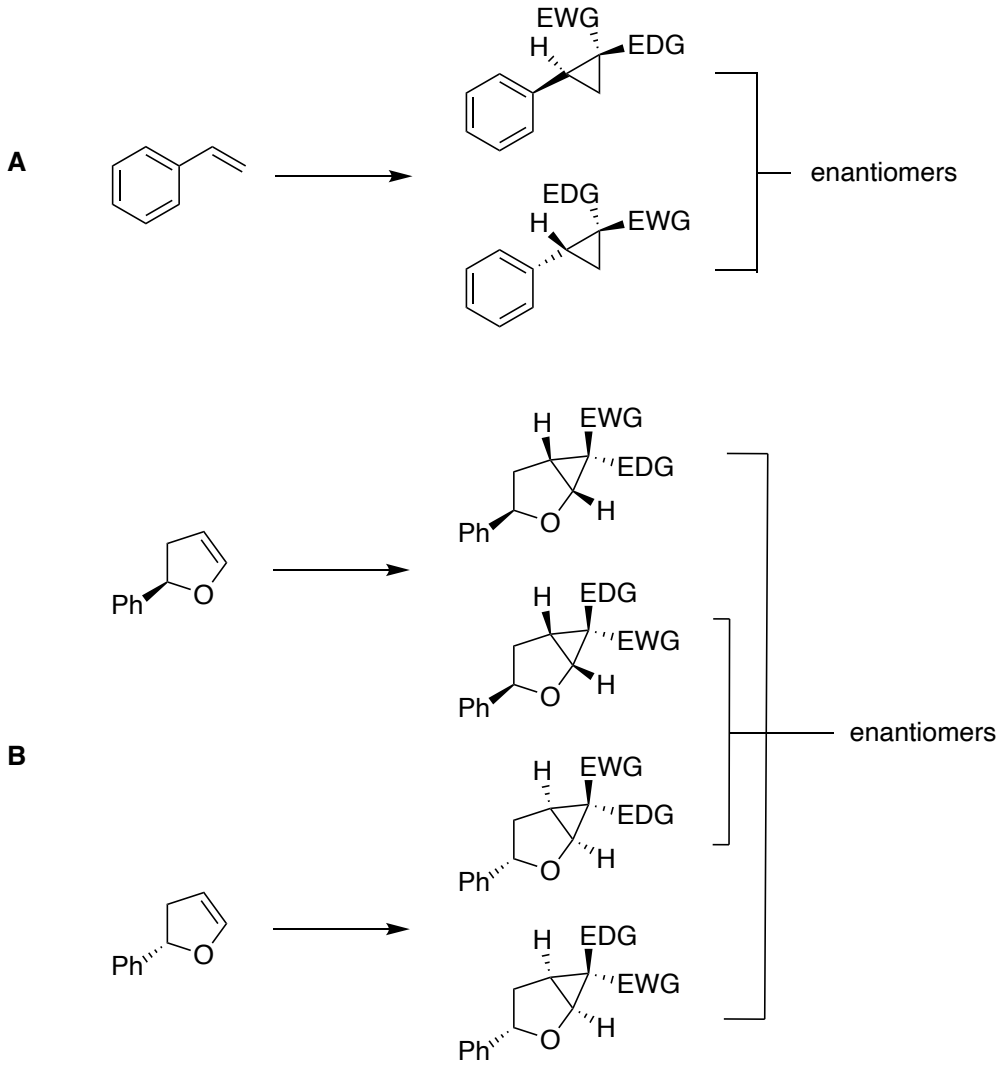


Figure 3.6: Depiction of different diastereomers of styrene cyclopropanation vs dihydrofuran relationship of enantiomers.

Based on the experiments at room temperature, this substrate is very reactive, and the selectivity between the two possible reactions (one enantiomer or the other) is very low, and for some catalysts nearly nonexistent at room temperature. At lower temperatures, the difference in energy between the two reaction pathways is more difficult to overcome, but given the constantly increasing amount of slightly disfavored substrate, the probability that this reaction occurs will steadily increase as the reaction proceeds. Overall, 82% is still moderate

enantioselectivity, but in the context of a kinetic resolution at relatively low catalyst loading, this is still a good result.

This experiment challenged the catalysts developed by the Davies group. At room temperature the catalysts could only marginally differentiate between the two enantiomers of the substrate. Thus the temperature was lowered so that the difference in energy was exacerbated to help influence the reaction with only one of the enantiomers. The $Rh_2(PTAD)_4$ catalyst performed with the highest level of enantioselectivity. Under optimized conditions a moderate enantiomeric excess of 82% was achieved.

4.) Conclusions

Dirhodium catalysis can be used in a variety of different ways. In the organosilane project, the use of dirhodium catalysis to facilitate C-H functionalization for stereospecific insertion onto organosilicon molecules makes for the rapid incorporation of silicon into a molecule. This type of chemistry has potential applications in the pharmaceutical industry. It is often desirable to be able to incorporate silicon for "sila-substitution," replacing a carbon with a silicon to exploit the different chemical properties of silicon compared to carbon. Additionally, pharmaceutical companies often derivatize drugs, meaning late stage modifications to drug molecules. The chemistry here shows that organosilicon drug molecules can be selectively functionalized and thereby derivatized using Rh(II) catalysis.

In the context of the endoperoxide work, dirhodium catalysis is also crucial. Asymmetric dirhodium catalysis could also prove to be invaluable in furthering the biological activity of the endoperoxides. To make an enantioenriched endoperoxide, the photocatalytic reaction would also have to be shown not to disrupt the stereochemistry. Because the cyclopropane ring opening reaction involves a breakage of the ring, there is always a chance for a change in

stereochemistry. However, because the cyclopropane was one diastereomer, and the resulting endoperoxide was also only one diastereomer, there is reason to believe that the stereochemistry is preserved in this reaction, and that the same level of enantiomeric excess should be observed after the reaction when the starting cyclopropane is an enantioenriched mixture. In terms of biological activity, if one enantiomer of the an endoperoxide is more active than another, using an enantioenriched mixture of the endoperoxide should still yield a net increase (or decrease depending on which enantiomer is more active) in activity if one enantiomer is more active than the other. If this is the case, this study is particularly useful. Although the reaction did not reach a full 99% enantiomeric excess, recrystallization techniques could lead to a product that is essentially only one enantiomer. By making an enantioenriched cyclopropane, less material would be wasted in the recrystallization process, which is desirable.

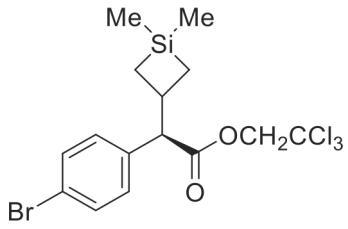
Overall asymmetric dirhodium catalysis should be seen as an invaluable tool that is still trying to be understood. The applications of this type of catalysis that are presented are still rooted in methodological development, but with the purpose of developing a method for a particular function. In the case of organosilicon molecules this methodology offers the potential for the incorporation of silicon or for the diversification of pre-existing organosilicon molecules to be tested for pharmacological effects. For the dihydrofurans, employing asymmetric catalysis offers the possibility of generating enantioenriched endoperoxides, which could be more effective than purely racemic endoperoxides as far as antimalarial activity is concerned.

5.) Experimental

5.1) General Procedure 1 for C–H Functionalization Reactions.

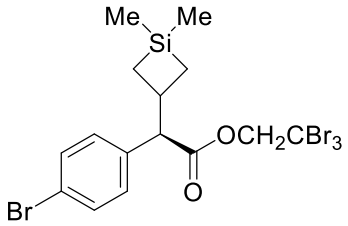
An oven-dried round bottom flask was equipped with stir bar and cooled under vacuum. A second

oven-dried round bottom flask was cooled under vacuum. After cooling to room temperature, the flask with the stir bar was loaded with Rh catalyst (0.5 mol% or 1 mol%), silane (3 equiv) and solvent (1 mL per mmol silane). Diazo compound (1 equiv) was added to the second flask and dissolved in solvent (6 mL per mmol diazo compound). The solution of diazo compound was added to the first solution of catalyst and silane dropwise via syringe pump over 3 hours. The reaction mixture was allowed to stir at least 2h after the addition was complete (the reaction can be allowed to stir overnight without product decomposition or ee erosion), and then the residual solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography. The General Procedure 1 was used to accomplish the reactions in Table 2.3, the optimization of the catalyst and solvent.

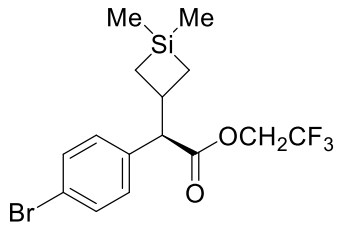


(*R*)-2,2,2-trichloroethyl 2-(4-bromophenyl)-2-(1,1-dimethylsiletan-3-yl)acetate (3a). The general procedure 1 was employed for the C–H functionalization of 1,1-dimethylsiletane (150 mg, 1.5 mmol) by reaction of 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (186 mg, 0.5 mmol) using Rh_2(*S*-TPPTTL)$_4$ as catalyst (6.2 mg, 0.5 mol%) and α,α,α-trifluorotoluene as solvent. After flash chromatography (gradient 0 -> 5% diethyl ether / hexanes) the title compound (134 mg, 61%) was obtained as a colorless oil: $[\alpha]^{23}_D$ -17.4 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 3.46 (d, *J* = 10.6 Hz, 1H), 2.92–2.75 (m, 1H), 1.36–1.27 (m, 1H), 0.91–0.78 (m, 2H), 0.52 (dd, *J* = 14.3, 10.8 Hz, 1H), 0.28 (s, 3H), 0.27 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ

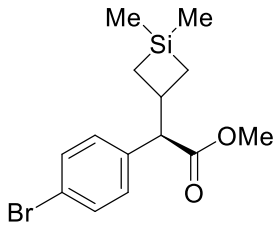
171.6, 136.4, 131.7, 130.3, 121.5, 95.0, 74.2, 62.1, 35.7, 20.7, 19.8, 1.5, -1.9; IR (film) 2959, 1750, 1488, 1249, 1122, 1012, 827, 807, 761, 721 cm^{-1}. MS (APCI+) 442.93964 (442.93978 calcd for $C_{15}H_{19}O_2BrCl_3Si$, M + H^+). The enantiopurity was determined to be 98.8:1.2 er by chiral HPLC analysis (Regis Technologies (*R*,*R*)-Whelk, 25 cm x 4.6 mm, 3% IPA/Hexanes, 1.00 mL/min, λ 210 nm, RT= 4.2 and 4.5 min).



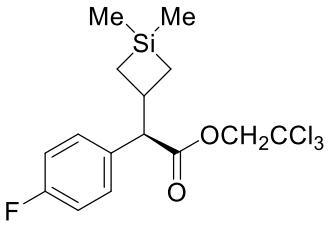
2,2,2-Tribromoethyl (*R*)-2-(4-bromophenyl)-2-(1,1-dimethylsiletan-3-yl)acetate (3b). The general procedure 1 was employed for the C–H functionalization of 1,1-dimethylsiletane (75 mg, 0.75 mmol) by reaction of 2,2,2-tribromoethyl 2-(4-bromophenyl)-2-diazoacetate (126 mg, 0.25 mmol) using Rh_2(*S*-TPPTTL)$_4$ as catalyst (6.2 mg, 1 mol%) and dichloromethane as solvent. This procedure afforded the title compound (97 mg, 67%) as a colorless oil: $[\alpha]^{23}_D$ +5.4 (*c* 0.25, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45–7.42 (m, 2H), 7.28–7.26 (m, 2H), 4.93 (d, *J* = 12.3 Hz, 1H), 4.83 (d, *J* = 12.3 Hz, 1H), 3.49 (d, *J* = 10.6 Hz, 1H), 2.88 (qt, *J* = 10.6, 8.0 Hz, 1H), 1.39–1.32 (m, 1H), 0.92–0.81 (m, 2H), 0.53 (dd, *J* = 14.2, 10.8 Hz, 1H), 0.29 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 136.3, 131.6, 130.3, 121.4, 77.1, 62.1, 35.5, 35.4, 20.7, 19.7, 1.4, -2.0; IR (film) 2960, 1746, 1488, 1407, 1366, 1248, 1216, 1182, 1120, 1073, 1011, 890, 871, 808, 718 cm^{-1}. MS (APCI+) 574.78917 (574.78823 calcd for $C_{15}H_{19}O_2Br_4Si$, M + H^+). The enantiopurity was determined to be 94:6 er by chiral HPLC analysis (Regis Technologies (*R*,*R*)-Whelk, 25 cm x 4.6 mm, 3% IPA/Hexanes, 1.00 mL/min, λ 210 nm, RT= 4.6 and 5.2 min).



2,2,2-Trifluoroethyl (*R*)-2-(4-bromophenyl)-2-(1,1-dimethylsiletan-3-yl)acetate (3c). The general procedure 1 was employed for the C–H functionalization of 1,1-dimethylsiletane (75 mg, 0.75 mmol) by reaction of 2,2,2-trifluoroethyl 2-(4-bromophenyl)-2-diazoacetate (81 mg, 0.25 mmol) using Rh_2(*S*-TPPTTL)$_4$ (6.2 mg, 1 mol%) as catalyst and dichloromethane as solvent. This procedure afforded the title compound (53 mg, 54%) as a colorless oil: $[\alpha]^{23}_D$ -8.1 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46–7.42 (m, 2H), 7.23–7.19 (m, 2H), 4.53 (dq, *J* = 12.7, 8.5 Hz, 1H), 4.34 (dq, *J* = 12.7, 8.4 Hz, 1H), 3.42 (d, *J* = 10.5 Hz, 1H), 2.78 (qt, *J* = 10.7, 8.0 Hz, 1H), 1.27 (dddd, *J* = 14.0, 7.9, 4.9, 1.0 Hz, 1H), 0.85 (dddd, *J* = 13.0, 8.1, 5.5, 1.1 Hz, 1H), 0.79 (dd, *J* = 14.0, 10.6 Hz, 1H), 0.52 (dd, *J* = 14.2, 10.9 Hz, 1H), 0.28 (s, 3H), 0.27 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.7, 136.3, 131.8, 130.1, 123.04 (q, *J* = 277.3 Hz), 121.6, 61.7, 60.44 (q, *J* = 36.6 Hz), 36.0, 20.3, 19.9, 1.5, -1.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ -73.72 (t, *J* = 8.4 Hz); IR (film) 2966, 1753, 1489, 1408, 1275, 1250, 1167, 1124, 1074, 1012, 979, 891, 871, 935, 808760, 721 cm^{-1}. MS (APCI+) 395.02849 (395.02843 calcd for $C_{15}H_{19}O_2BrF_3Si$, M + H$^+$). The enantiopurity was determined to be 96:4 er by chiral HPLC analysis (Chiralpak AS-H, 25 cm x 4.6 mm, 1% IPA/Hexanes, 0.5 mL/min, λ 254 nm, RT= 7.3 and 7.5 min).

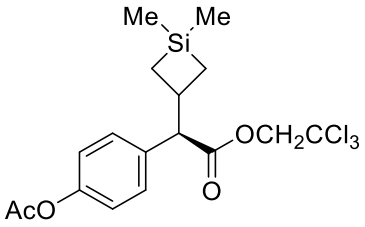


Methyl (*R*)-2-(4-bromophenyl)-2-(1,1-dimethylsiletan-3-yl)acetate (3d). The general procedure 1 was employed for the C–H functionalization of 1,1-dimethylsiletane (150 mg, 1.5 mmol) by reaction of methyl 2-(4-bromophenyl)-2-diazoacetate (128 mg, 0.50 mmol) using Rh_2(*S*-TPPTTL)$_4$ as catalyst (6.2 mg, 0.5 mol%) and α,α,α-trifluorotoluene as solvent. After flash chromatography (gradient 0 -> 5% diethyl ether / hexanes) the title compound (112 mg, 68%) was obtained as a colorless oil: $[\alpha]^{23}_D$ -38.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.39 (m, 2H), 7.23–7.18 (m, 2H), 3.65 (s, 3H), 3.32 (d, *J* = 10.6 Hz, 1H), 2.76 (qt, *J* = 10.6, 8.0 Hz, 1H), 1.31–1.22 (m, 1H), 0.85–0.78 (m, 1H), 0.76 (dd, *J* = 14.0, 10.6 Hz, 1H), 0.48 (dd, *J* = 14.0, 11.0 Hz, 1H), 0.27 (s, 3H), 0.26 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 137.3, 131.6, 130.1, 121.2, 62.2, 52.0, 35.9, 20.5, 19.7, 1.5, -1.9; IR (film) 2952, 1733, 1488, 1434, 1248, 1202, 1163, 1128, 1073, 889, 849, 807 cm^{-1}. MS (NSI+) 327.04133 (327.04105 calcd for $C_{14}H_{20}O_2BrSi$, M + H^+). The enantiopurity was determined to be 96.3:3.7 er by chiral HPLC analysis (Chiralpak ADH, 25 cm x 4.6 mm, 0.5% IPA/Hexanes, 0.5 mL/min, λ 210 nm, RT= 13.3 and 14.4 min).



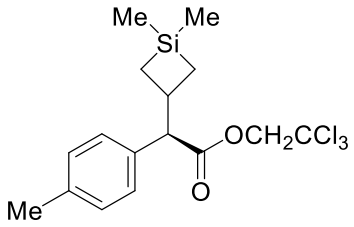
2,2,2-Trichloroethyl (*R*)-2-(1,1-dimethylsiletan-3-yl)-2-(4-fluorophenyl)acetate (4). The

general procedure 1 was employed for the C–H functionalization of 1,1-dimethylsiletane (150 mg, 1.50 mmol) by reaction of 2,2,2-trichloroethyl 2-(4-fluorophenyl)-2-diazoacetate (156, 0.5 mmol) using Rh_2(*S*-TPPTTL)$_4$ (6.2 mg, 0.5 mol%) as catalyst and α,α,α-trifluorotoluene as solvent. After flash chromatography (gradient 0 -> 5% diethyl ether / hexanes) the title compound (102 mg, 53%) as a colorless solid, mp 63–65 °C: $[\alpha]^{23}_D$ -3.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) □ 7.35–7.30 (m, 2H), 7.02–6.98 (m, 2H), 4.78 (d, *J* = 12.7 Hz, 1H), 4.63 (d, *J* = 12.7 Hz, 1H), 3.49 (d, *J* = 10.7 Hz, 1H), 2.91–2.79 (m, 1H), 1.36–1.29 (m, 1H), 0.90–0.78 (m, 2H), 0.53 (dd, *J* = 14.2, 10.7 Hz, 1H), 0.28 (s, 3H), 0.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 162.3 (d, *J* = 246 Hz) , 133.16 (d, *J* = 3.3 Hz), 130.10 (d, *J* = 7.9 Hz), 115.4 (d, *J* = 21.5 Hz) 95.1, 74.2, 61.9, 35.8, 20.6, 19.8, 1.5, -1.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.27; IR (film) 2960, 1750, 1605, 1508, 1248, 1224, 1120, 831, 802, 756, 718 cm^{-1}. MS (NSI+) 383.02009 (383.01984 calcd for $C_{15}H_{18}Cl_3FO_2Si$, M + H^+). The enantiopurity was determined to be 97.8:2.2 er by chiral HPLC analysis (Regis Technologies (*R*,*R*)-Whelk, 25 cm x 4.6 mm, 0.5% IPA/Hexanes, 0.5 mL/min, λ 230 nm, RT= 9.6 and 10.8 min).



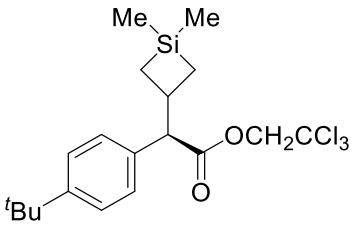
(*R*)-2,2,2-trichloroethyl-2-(4-acetoxyphenyl)-2-(1,1-dimethylsiletan-3-yl)acetate (5). The general procedure 1 was employed for the C–H functionalization of 1,1-dimethylsiletane (150 mg, 1.5 mmol) by reaction of 2,2,2-trichloroethyl 2-(4-acetoxyphenyl)-2-diazoacetate (176 mg, 0.50 mmol) using Rh_2(*S*-TPPTTL)$_4$ (6.2 mg, 0.5 mol%) as catalyst and α,α,α-trifluorotoluene as

solvent. This procedure afforded the title compound (140 mg, 66%) as a colorless oil: $[\alpha]^{23}_{D}$ -28.3 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39–7.35 (m, 2H), 7.06–7.01 (m, 2H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 3.51 (d, *J* = 10.6 Hz, 1H), 2.86 (qt, *J* = 10.6, 8.0 Hz, 1H), 2.29 (s, 3H), 1.33 (dddd, *J* = 13.9, 7.9, 4.9, 1.0 Hz, 1H), 0.89 (dddd, *J* = 14.1, 8.1, 4.9, 1.1 Hz, 1H), 0.83 (dd, *J* = 14.2, 10.7 Hz 1H), 0.54 (dd, *J* = 14.2, 10.7 Hz 1H), 0.28 (s, 3H), 0.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 169.5, 150.1, 134.9, 129.5, 121.6, 95.1, 74.2, 62.1, 35.8, 21.3, 20.6, 19.9, 1.5, -1.8; IR (film) 2960, 1751, 1506, 1369, 1249, 1197, 1121, 1018, 910, 835, 807, 752, 719 cm^{-1}. MS (APCI+) 423.03498 (423.03475 calcd for $C_{17}H_{22}O_4Cl_3Si$, M + H^+). The enantiopurity was determined to be 98.3:1.7 er by chiral HPLC analysis (Regis Technologies (*R*,*R*)-Whelk, 25 cm x 4.6 mm, 1% IPA/Hexanes, 1.00 mL/min, λ 230 nm, RT= 18.9 and 19.8 min).



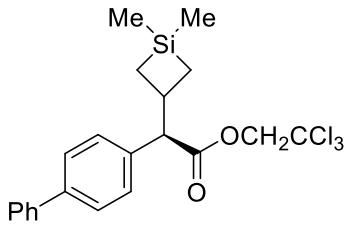
2,2,2-Trichloroethyl (*R*)-2-(1,1-dimethylsiletan-3-yl)-2-(*p*-tolyl)acetate (6). The general procedure 1 was employed for the C–H functionalization of 1,1-dimethylsiletane (150 mg, 1.5 mmol) by reaction of 2,2,2-trichloroethyl 2-diazo-2-(p-tolyl)acetate (154 mg, 0.50 mmol) using Rh_2(*S*-TPPTTL)$_4$ (6.2 mg, 0.5 mol%) as catalyst and α,α,α-trifluorotoluene as solvent. This procedure afforded the title compound (131 mg, 69%) as a colorless oil: $[\alpha]^{23}_{D}$ -23.9 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27–7.24 (m, 2H), 7.14–7.11 (m, 2H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 3.48 (d, *J* = 10.6 Hz, 1H), 2.89 (qt, *J* = 10.6, 8.1 Hz, 1H), 2.33

(s, 3H), 1.34 (dddd, J = 14.0, 8.0, 4.9, 1.1 Hz, 1H), 0.92–0.86 (m, 1H), 0.83 (dd, J = 14.0, 10.4 Hz, 1H), 0.56 (dd, J = 14.2, 10.8 Hz, 1H), 0.28 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.2, 137.2, 134.4, 129.3, 128.4, 95.2, 74.2, 62.4, 35.6, 21.2, 20.6, 19.8, 1.5, -1.8; IR (film) 2961, 2903, 1749, 1366, 1248, 1203, 1153, 1113, 912, 890, 874, 851, 828, 805, 769, 751, 718 cm^{-1}. MS (APCI+) 379.04513 (379.04492 calcd for $C_{16}H_{22}O_2Cl_3Si$, M + H^+). The enantiopurity was determined to be 98.1:1.9 er by chiral HPLC analysis (Regis Technologies (*R*,*R*)-Whelk, 25 cm x 4.6 mm, 1% IPA/Hexanes, 1.00 mL/min, λ 230 nm, RT= 4.0 and 5.2 min).



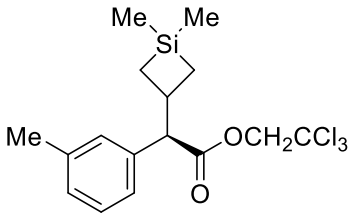
2,2,2-Trichloroethyl (*R*)-2-(4-(*tert*-butyl)phenyl)-2-(1,1-dimethylsiletan-3-yl)acetate (7). The general procedure 1 was employed for the C–H functionalization of 1,1-dimethylsiletane (150 mg, 1.5 mmol) by reaction of 2,2,2-trichloroethyl 2-(4-(tert-butyl)phenyl)-2-diazoacetate (175 mg, 0.50 mmol) using Rh_2(*S*-TPPTTL)$_4$ (6.2 mg, 0.5 mol%) as catalyst and α,α,α-trifluorotoluene as solvent. This procedure afforded the title compound (172 mg, 82%) as a colorless oil: $[\alpha]^{23}_D$ -23.9 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.29 (m, 4H), 4.82 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 12.0 Hz, 1H), 3.50 (d, J = 10.7 Hz, 1H), 2.90 (qt, J = 10.5, 8.0 Hz, 1H), 1.37–1.33 (m, 1H), 1.31 (s, 9H), 0.95–0.88 (m, 1H), 0.85 (dd, J = 14.0, 10.4 Hz, 1H), 0.58 (dd, J = 14.3, 10.8 Hz, 1H), 0.29 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.2, 150.3, 134.3, 128.1, 125.4, 95.2, 74.2, 62.3, 35.7, 34.6, 31.5, 20.6, 20.0, 1.5, -1.8; IR (film) 2957, 1749, 1513, 1370, 1285, 1248, 1214, 1152, 1118, 1045, 912, 890, 872, 849, 807, 750, 718 cm^{-1}. MS (APCI+) 421.09218

(421.09187 calcd for $C_{19}H_{28}O_2Cl_3Si$, M + H^+). The enantiopurity was determined to be 95.4:4.6 er by chiral HPLC analysis (Regis Technologies (*R*,*R*)-Whelk, 25 cm x 4.6 mm, 0.5% IPA/Hexanes, 0.5 mL/min, λ 230 nm, RT= 8.8 and 9.2 min).

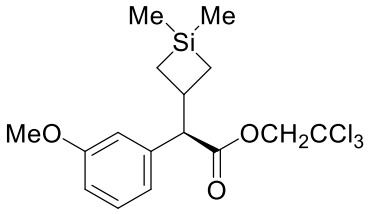


2,2,2-Trichloroethyl (*R*)-2-([1,1'-biphenyl]-4-yl)-2-(1,1-dimethylsiletan-3-yl)acetate (8). The general procedure 1 was employed for the C–H functionalization of 1,1-dimethylsiletane (150 mg, 1.5 mmol, 3 equiv) by reaction of 2,2,2-trichloroethyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (184 mg, 0.50 mmol, 1 equiv) using Rh_2(*S*-TPPTTL)$_4$ (6.2 mg, 0.5 mol%) as catalyst and α,α,α-trifluorotoluene as solvent. After flash chromatography (gradient 0 -> 5% diethyl ether / hexanes) the title compound (160 mg, 72%) was obtainedas a colorless solid, mp 69–70 °C: $[\alpha]^{23}_D$ -22.7 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.52 (m, 4H), 7.43 (t, *J* = 8.2 Hz, 4H), 7.34 (t, *J* = 7.7 Hz, 1H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 3.56 (d, *J* = 10.6 Hz, 1H), 2.94 (qt, *J* = 10.5, 8.1 Hz, 1H), 1.40–1.33 (m, 1H), 0.94 (ddd, *J* = 13.4, 8.0, 5.0 Hz, 1H), 0.87 (dd, *J* = 14.0, 10.4 Hz, 1H), 0.61 (dd, *J* = 14.0, 10.4 Hz, 1H), 0.30 (s, 3H), 0.29 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 140.8, 140.4, 136.5, 129.0, 128.9, 127.4, 127.3, 127.2, 95.1, 74.2, 62.4, 35.7, 20.7, 19.9, 1.5, -1.8; IR (film) 3030, 2959, 2927, 1750, 1486, 1449, 1411, 1371, 1248, 1153, 1121, 1047, 1009, 914, 891, 873, 832, 806, 750, 721, 698 cm^{-1}. MS (APCI+) 441.06081 (441.06057 calcd for $C_{21}H_{24}O_2Cl_3Si$, M + H^+). The enantiopurity was determined to be 98.2:1.8 er by chiral HPLC analysis (Regis Technologies (*R*,*R*)-Whelk, 25 cm x 4.6 mm, 3% IPA/Hexanes,

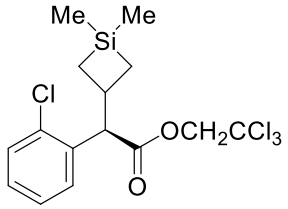
1.00 mL/min, λ 210 nm, RT= 5.5 and 6.1 min). The absolute configuration of this compound was determined by X-ray crystallographic analysis as described below.



2,2,2-Trichloroethyl (*R*)-2-(1,1-dimethylsiletan-3-yl)-2-(*m*-tolyl)acetate (9). The general procedure 1 was employed for the C–H functionalization of 1,1-dimethylsiletane (150 mg, 1.5 mmol, 3 equiv) by reaction of 2,2,2-trichloroethyl 2-diazo-2-(m-tolyl)acetate (154 mg, 0.50 mmol, 1 equiv) using Rh_2(*S*-TPPTTL)$_4$ (6.2 mg, 0.5 mol%) as catalyst and α,α,α-trifluorotoluene as solvent. After flash chromatography (gradient 0 -> 5% diethyl ether / hexanes) the title compound (129 mg, 68%) was obtained as a colorless oil: $[\alpha]^{23}_D$ -23.2 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (p, *J* = 7.6 Hz, 4H), 7.07 (d, *J* = 7.5 Hz, 1H), 4.82 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 3.47 (d, *J* = 10.7 Hz, 1H), 2.89 (qt, *J* = 10.6, 8.0 Hz, 1H), 2.34 (s, 3H), 1.38–1.30 (m, 1H), 0.94–0.78 (m, 2H), 0.56 (dd, *J* = 14.1, 10.9 Hz, 1H), 0.29 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 138.1, 137.3, 129.2, 128.4, 128.3, 125.6, 95.2, 74.2, 62.8, 35.6, 21.6, 20.7, 19.8, 1.5, -1.8; IR (film) 2958, 2924, 1751, 1607, 1489, 1370, 1163, 1205, 1120, 888, 857, 834, 803, 743, 717 cm^{-1}. MS (APCI+) 379.04511 (379.04492 calcd for $C_{16}H_{22}O_2Cl_3Si$, M + H^+). The enantiopurity was determined to be 89.4:10.6 er by chiral HPLC analysis (Regis Technologies (*R*,*R*)-Whelk, 25 cm x 4.6 mm, 1% IPA/Hexanes, 1.00 mL/min, λ 210 nm, RT= 4.0 and 5.5 min).

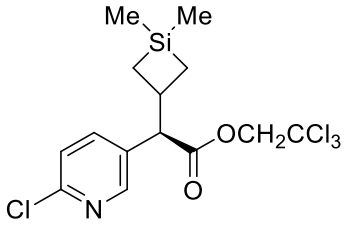


2,2,2-Trichloroethyl (*R*)-2-(1,1-dimethylsiletan-3-yl)-2-(3-methoxyphenyl)acetate (10). The general procedure 1 was employed for the C–H functionalization of 1,1-dimethylsiletane (150 mg, 1.5 mmol) by reaction of 2,2,2-trichloroethyl 2-diazo-2-(3-methoxyphenyl)acetate (162 mg, 0.5 mmol) using Rh_2(*S*-TPPTTL)$_4$ (6.2 mg, 0.5 mol%) as catalyst and α,α,α-trifluorotoluene as solvent. After flash chromatography (gradient 0 -> 5% diethyl ether / hexanes) the title compound (108 mg, 54%) as a colorless oil: $[\alpha]^{23}_D$ -26.9 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.9 Hz, 1H), 6.97–6.91 (m, 2H), 6.83–6.78 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 3.80 (s, 3H), 3.48 (d, *J* = 10.7 Hz, 1H), 2.88 (qt, *J* = 10.6, 8.0 Hz, 1H), 1.33 (ddd, *J* = 13.8, 8.2, 5.3 Hz, 1H), 0.89 (ddd, *J* = 14.0, 7.6, 5.0 Hz, 1H), 0.82 (dd, *J* = 13.9, 10.5 Hz, 1H), 0.57 (dd, *J* = 14.2, 10.8 Hz, 1H), 0.28 (s, 3H), 0.27 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 159.7, 138.9, 129.5, 121.1, 114.2, 112.9, 95.1, 74.2, 62.8, 55.4, 35.7, 20.7, 19.8, 1.5, -1.8; IR (film) 2958, 1750, 1600, 1585, 1491, 1263, 1120, 1049, 891, 857, 834, 807, 746, 717 cm^{-1}. MS (NSI+) 395.03998 (395.03983 calcd for $C_{16}H_{22}O_3Cl_3Si$, M + H$^+$). The enantiopurity was determined to be 96.2:3.8 er by chiral HPLC analysis (Regis Technologies, Inc. (R,R)-Whelk-01, 25 cm x 4.6 mm, 0.5% IPA/Hexanes, 0.5 mL/min, λ 210 nm, RT= 11.9 and 19.5 min).



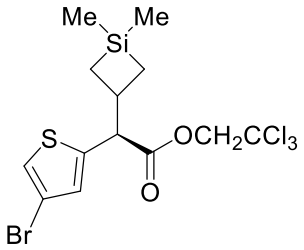
2,2,2-Trichloroethyl (*R*)-2-(2-chlorophenyl)-2-(1,1-dimethylsiletan-3-yl)acetate (11). The

general procedure 1 was employed for the C–H functionalization of 1,1-dimethylsiletane (150 mg, 1.5 mmol) by reaction of 2,2,2-trichloroethyl 2-(2-chlorophenyl)-2-diazoacetate (165 mg, 0.50 mmol) using Rh_2(*S*-TPPTTL)$_4$ (6.2 mg, 0.5 mol%) as catalyst and α,α,α-trifluorotoluene as solvent. After flash chromatography (gradient 0 -> 5% diethyl ether / hexanes) the title compound (125 mg, 63%) was obtained as a colorless oil: $[\alpha]^{23}_D$ -18.2 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.38 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.26–7.22 (m, 1H), 7.18 (td, *J* = 7.7, 1.7 Hz, 1H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.28 (d, *J* = 10.6 Hz, 1H), 2.93 (tdd, *J* = 10.5, 8.2, 2.4 Hz, 1H), 1.40–1.33 (m, 1H), 0.99–0.84 (m, 2H), 0.63 (dd, *J* = 14.1, 10.8 Hz, 1H), 0.29 (s, 3H), 0.29 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 135.3, 134.8, 129.6, 129.3, 128.5, 127.1, 95.0, 74.2, 57.1, 35.5, 20.8, 19.4, 1.5, -1.7; IR (film) 2959, 2918, 1752, 1474, 1443, 1371, 1286, 1249, 1126, 1051, 1035, 914, 892, 871, 834, 807, 747, 719 cm^{-1}. MS (APCI+) 398.99097 (398.99029 calcd for $C_{15}H_{19}O_2Cl_4Si$, M + H^+). The enantiopurity was determined to be 92.5:7.5 er by chiral HPLC analysis (Regis Technologies, Inc. (R,R)-Whelk-01, 25 cm x 4.6 mm, 0.5% IPA/Hexanes, 0.25 mL/min, λ 210 nm, RT= 19.4 and 20.5 min).



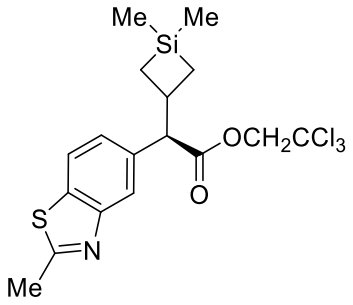
2,2,2-Trichloroethyl (*R*)-2-(6-chloropyridin-3-yl)-2-(1,1-dimethylsiletan-3-yl)acetate (15). The general procedure 1 was employed for the C–H functionalization of 1,1-dimethylsiletane (150 mg, 1.50 mmol, 3 equiv) by reaction of 2,2,2-trichloroethyl 2-(6-chloropyridin-3-yl)-2-diazoacetate using Rh_2(*S*-TPPTTL)$_4$ (6.2 mg, 0.5 mol%) as catalyst and α,α,α-trifluorotoluene as solvent. After flash chromatography (gradient 0 -> 5% diethyl ether / hexanes) the title compound

(133 mg, 67%) was obtained as a colorless oil: $[\alpha]^{23}_D$ -8.9 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 2.3 Hz, 1H), 7.73 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 3.52 (d, *J* = 10.5 Hz, 1H), 2.86–2.75 (m, 1H), 1.37–1.29 (m, 1H), 0.90–0.82 (m, 2H), 0.53 (dd, *J* = 14.0, 10.9 Hz, 1H), 0.28 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 150.8, 149.9, 138.5, 132.1, 124.3, 94.8, 74.4, 59.1, 36.0, 20.7, 19.9, 1.4, -2.0; IR (film) 2959, 1749, 1584, 1565, 1457, 1390, 1249, 1122, 1105, 832, 807 cm^{-1}. MS (NSI+) 399.98572 (399.98554 calcd for $C_{14}H_{18}O_2NCl_4Si$, M + H^+). The enantiopurity was determined to be 99.1:0.9 er by chiral HPLC analysis (Regis Technologies (*R*,*R*)-Whelk, 25 cm x 4.6 mm, 1% IPA/Hexanes, 1.00 mL/min, λ 210 nm, RT= 10.5 and 12.8 min). This reaction was also conducted at 3 mmol scale generating the title compound in 66% yield. The enantiopurity was determined to be 99.0:1.0 on this scale using the same conditions described above.



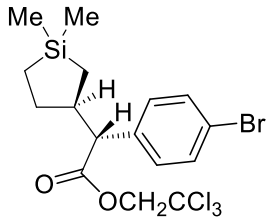
2,2,2-Trichloroethyl (*S*)-2-(4-bromothiophen-2-yl)-2-(1,1-dimethylsiletan-3-yl)acetate (17). The general procedure 1 was employed for the C–H functionalization of 1,1-dimethylsiletane (150 mg, 1.5 mmol) by reaction of 2,2,2-trichloroethyl 2-(4-bromothiophen-2-yl)-2-diazoacetate (189 mg, 0.50 mmol) using Rh_2(*S*-TPPTTL)$_4$ (6.2 mg, 0.5 mol%) as catalyst and α,α,α-trifluorotoluene as solvent. After flash chromatography (gradient 0 -> 5% diethyl ether / hexanes) the title compound (123 mg, 54%) was obtained as a colorless oil: $[\alpha]^{23}_D$ -13.1 (*c* 1.00, CH_2Cl_2); ^1H NMR

(500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 1.5 Hz, 1H), 6.93 (d, *J* = 1.5 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 11.9 Hz, 1H), 3.74 (d, *J* = 10.2 Hz, 1H), 2.78 (tdd, *J* = 10.5, 8.1, 2.4 Hz, 1H), 1.32–1.22 (m, 1H), 1.11–1.01 (m, 1H), 0.85 (dd, *J* = 13.9, 10.7 Hz, 1H), 0.67 (dd, *J* = 14.1, 10.9 Hz, 1H), 0.29 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 140.9, 128.8, 122.3, 109.2, 94.8, 74.5, 57.4, 37.1, 20.4, 20.2, 1.4, -1.9; IR (film) 2958, 1751, 1522, 1249, 1213, 1122, 829, 807, 741, 719 cm^{-1}. MS (APCI+) 448.89665 (448.89620 calcd for $C_{13}H_{17}O_2BrCl_3SSi$, M + H^+). The enantiopurity was determined to be 95.7:4.3 er by chiral HPLC analysis (Regis Technologies (*R*,*R*)-Whelk, 25 cm x 4.6 mm, 0.5% IPA/Hexanes, 0.5 mL/min, λ 210 nm, RT= 11.7 and 10.4 min).



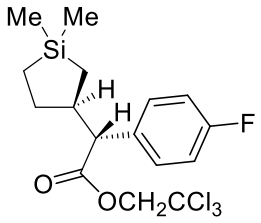
2,2,2-trichloroethyl (*R*)-2-(1,1-dimethylsiletan-3-yl)-2-(2-methylbenzo[*d*]thiazol-5-yl)acetate (19). The general procedure 1 was employed for the C–H functionalization of 1,1-dimethylsiletane (150 mg, 1.5 mmol) by reaction of 2,2,2-trichloroethyl 2-diazo-2-(2-methylbenzo[d]thiazol-5-yl)acetate (0.5 mmol, 182.3 mg) using Rh_2(*S*-TPPTTL)$_4$ (12.3 mg, 1.0 mol%) as catalyst and α,α,α-trifluorotoluene as solvent. After flash chromatography (10%, then 15% EtOAc in hexanes) the title compound (141 mg, 65%) was obtained as a colorless oil: $[\alpha]^{23}_D$ -26.3 (*c* 1.00, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.39 (d, *J* = 6.9 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 3.64 (d, *J* = 10.6 Hz, 1H), 3.03–2.90 (m, 1H), 2.83

(s, 3H), 1.37 (m, 1H), 0.91–0.83 (m, 2H), 0.57 (dd, *J* = 14.2, 10.8 Hz, 1H), 0.28 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 167.5, 153.7, 135.5, 134.7, 125.1, 122.3, 121.2, 94.9, 74.0, 62.3, 35.7, 20.6, 20.2, 19.7, 1.3, -2.0; IR (neat) 2858, 1750, 1526, 1249, 1120, 832, 807, 760, 718 cm^{-1}. MS (APCI+) 436.01288 (436.01224 calcd for $C_{17}H_{21}O_2NCl_3SSi$, M + H^+). The enantiopurity was determined to be 98.9:1.1 er by chiral HPLC analysis (Chiralpak IA-U, 10 cm x 3 mm, 1.6 μm, 10% IPA/Hexanes, 0.5 mL/min, λ 280 nm, RT= 1.5 and 1.8 min).



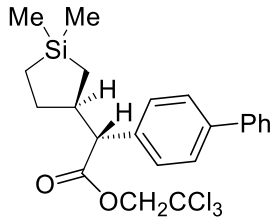
2,2,2-Trichloroethyl (*R*)-2-(4-bromophenyl)-2-((*R*)-1,1-dimethylsilolan-3-yl)acetate (20). The general procedure 1 was employed for the C–H functionalization of cyclotetramethylenedimethylsilane (171 mg, 1.5 mmol) by reaction of 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (186 mg, 0.50 mmol) using Rh_2(*S*-TPPTTL)$_4$ (6.2 mg, 0.5 mol%) as catalyst and α,α,α-trifluorotoluene as solvent. After flash chromatography (gradient 0 -> 5% diethyl ether / hexanes) the title compound (129 mg, 56%) was obtained as a yellow oil and as a 14:1 mixture of diastereomers as determined by ^{1}H NMR analysis by comparing the dd at 0.27 ppm and -0.06 ppm (when the same reaction is conducted with $Rh_2(OAc)_4$ as catalyst the dr is ~1.5:1). The NMR data is for the major diastereomer: $[\alpha]^{23}_D$ -8.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.42 (m, 2H), 7.27–7.22 (m, 2H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 3.34 (d, *J* = 10.4 Hz, 1H), 2.35–2.24 (m, 1H), 2.08 (dddd, *J* = 12.4, 8.4, 4.3, 2.2 Hz, 1H), 1.24–1.12 (m, 1H), 0.82 (ddd, *J* = 14.8, 7.0, 2.1 Hz, 1H), 0.62–0.45 (m, 2H), 0.08 (s, 3H), 0.06 (s, 3H), -0.05 (dd, J = 14.5, 11.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 137.2, 131.8, 130.4,

121.5, 95.0, 74.3, 59.1, 44.5, 32.4, 18.5, 12.8, -1.2, -1.3; IR (film) 2949, 2848, 1750, 1488, 1407, 1371, 1248, 1159, 1125, 1074, 1055. 1012, 842, 802, 762, 722 cm^{-1}. MS (ESI-) 454.94131 (454.94088 calcd for $C_{16}H_{19}O_2BrCl_3Si$, M - H^+). The enantiopurity was determined to be 99.3:0.7 er by chiral HPLC analysis for the major diastereomer (Chiralpak ADH, 25 cm x 4.6 mm, 0.1% IPA/Hexanes, 0.25 mL/min, λ 210 nm, RT= 38.6 and 40.5 min) and 97.8:2.2 for the minor diastereomer (Regis Technologies (*R*,*R*)-Whelk, 25 cm x 4.6 mm, 0.1% IPA/Hexanes, 0.25 mL/min, λ 210 nm, RT= 32.5 and 44.2 min).



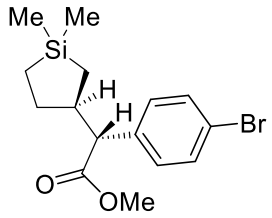
2,2,2-trichloroethyl (*R*)-2-((*R*)-1,1-dimethylsilolan-3-yl)-2-(4-fluorophenyl)acetate (21). The general procedure 1 was employed for the C–H functionalization of cyclotetramethylenedimethylsilane (171 mg, 1.5 mmol) by reaction of 2,2,2-trichloroethyl 2-(4-fluorophenyl)-2-diazoacetate (156 mg, 0.50 mmol) using Rh_2(*S*-TPPTTL)$_4$ (6.2 mg, 0.5 mol%) as catalyst and α,α,α-trifluorotoluene as solvent. After flash chromatography (gradient 0 -> 5% diethyl ether / hexanes) the title compound (136 mg, 68%) was obtained as a colorless oil and as a >20:1 mixture of diastereomers as determined by ^{1}H NMR analysis by comparing the dd at 0.29 ppm and -0.05 ppm. The NMR data is for the major diastereomer: $[\alpha]^{23}_D$ -13.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.31 (m, 2H), 7.04–6.97 (m, 2H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 11.9 Hz, 1H), 3.36 (d, *J* = 10.5 Hz, 1H), 2.36–2.25 (m, 1H), 2.09 (dddd, *J* = 12.4, 8.5, 4.4, 2.2 Hz, 1H), 1.24–1.13 (m, 1H), 0.82 (ddd, *J* = 14.7, 7.0, 2.2 Hz, 1H), 0.59–0.54 (m, 1H), 0.50 (ddd, *J* = 14.5, 6.1, 2.2 Hz, 1H), 0.08 (s, 3H), 0.07 (s, 3H), -0.05 (dd, *J* = 14.5, 11.7 Hz, 1H); ^{13}C

NMR (151 MHz, $CDCl_3$) δ 172.4, 162.3 (d, J = 245.8 Hz), 133.9 (d, J = 3.3 Hz), 130.2 (d, J = 7.9 Hz), 115.5 (d, J = 21.3 Hz), 95.0, 74.2, 58.9, 44.6, 32.4, 18.5, 12.8, -1.2, -1.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.24 – -115.36 (m); IR (film) 2950, 1750, 1605, 1508, 1226, 1160, 1124, 839, 801, 759, 720 cm^{-1}. MS (ESI-) 395.02120 (395.02094 calcd for $C_{16}H_{19}O_2Cl_3FSi$, M - H^+). The enantiopurity was determined to be 99:1 er by chiral HPLC analysis for the major diastereomer (Regis Technologies (*S*,*S*)-Whelk, 10 cm x 4.6 mm, 1.8 μm, 0.5% IPA/Hexanes, 0.5 mL/min, λ 230 nm, RT= 5.9 and 6.3 min) and 95:5 for the minor diastereomer (Regis Technologies (*S*,*S*)-Whelk, 10 cm x 4.6 mm, 1.8 μm, 0.5% IPA/Hexanes, 0.5 mL/min, λ 230 nm, RT= 5.3 and 7.1 min).



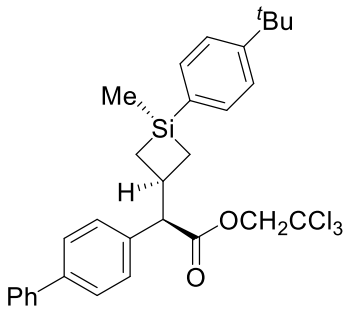
2,2,2-trichloroethyl (*R*)-2-([1,1'-biphenyl]-4-yl)-2-((*R*)-1,1-dimethylsilolan-3-yl)acetate (22). The general procedure 1 was employed for the C–H functionalization of cyclotetramethylenedimethylsilane (171 mg, 1.5 mmol) by reaction of 2,2,2-trichloroethyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (185 mg, 0.50 mmol) using Rh_2(*S*-TPPTTL)$_4$ (6.2 mg, 0.5 mol%) as catalyst and α,α,α-trifluorotoluene as solvent. After flash chromatography (gradient 0 -> 5% diethyl ether / hexanes) the title compound (127 mg, 56%) was obtained as a colorless oil and as a 10:1 mixture of diastereomers as determined by ^1H NMR analysis by comparing the dd at 0.34 ppm and 0.03 ppm. The NMR data is for the major diastereomer: $[\alpha]^{23}_D$ -10.3 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.61–7.53 (m, 4H), 7.47–7.41 (m, 4H), 7.37–7.32 (m, 1H), 4.83 (d, J = 12.0 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 3.43 (d, J = 10.5 Hz, 1H), 2.47–2.34 (m,

1H), 2.17–2.10 (m, 1H), 1.32–1.17 (m, 1H), 0.88–0.79 (m, 1H), 0.64–0.53 (m, 2H), 0.10 (s, 3H), 0.08 (s, 3H), 0.03 (dd, J = 14.5, 11.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 140.8, 140.4, 137.2, 129.1, 128.9, 127.4, 127.3, 127.2, 95.1, 74.3, 59.4, 44.6, 32.5, 18.6, 12.9, -1.1, -1.2; IR (film) 2948, 1749, 1488, 1411, 1371, 1248, 1159, 1122, 1055, 837, 803, 757, 723, 698 cm^{-1}. MS (NSI+) 455.07648 (455.07622 calcd for $C_{22}H_{26}O_2Cl_3Si$, M + H^+). The enantiopurity was determined to be 93.3:6.7 er by chiral HPLC analysis for the major diastereomer (Chiralpak ADH, 25 cm x 4.6 mm, 0.5% IPA/Hexanes, 0.25 mL/min, λ 210 nm, RT= 29.8 and 42.5 min) and 94.6:5.4 for the minor diastereomer (Chiralpak ADH, 25 cm x 4.6 mm, 0.5% IPA/Hexanes, 0.25 mL/min, λ 210 nm, RT= 26.2 and 33.6 min).



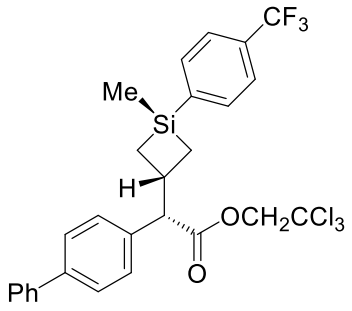
Methyl (*R*)-2-(4-bromophenyl)-2-((*R*)-1,1-dimethylsilolan-3-yl)acetate (23). The general procedure 1 was employed for the C–H functionalization of cyclotetramethylenedimethylsilane (171 mg, 1.5 mmol) by reaction of methyl 2-(4-bromophenyl)-2-diazoacetate (128 mg, 0.50 mmol) using Rh_2(*S*-TPPTTL)$_4$ (6.2 mg, 0.5 mol%) as catalyst and α,α,α-trifluorotoluene as solvent. After flash chromatography (gradient 0 -> 5% diethyl ether / hexanes) the title compound (74 mg, 43%) was obtained as a colorless oil and as a 3:1 mixture of diastereomers as determined by ^{1}H NMR analysis by comparing the d at 3.21 ppm and 3.18 ppm. The NMR data is for the major diastereomer: $[\alpha]^{23}_D$ -21.9 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.40 (m, 2H), 7.24–7.19 (m, 2H), 3.64 (s, 3H), 3.18 (d, J = 10.5 Hz, 1H), 2.31–2.15 (m, 1H), 1.99 (dddt, J = 10.2, 6.3, 4.4, 2.2 Hz, 1H), 1.13 (qd, J = 12.2, 7.1 Hz, 1H), 0.83–0.75 (m, 1H), 0.55 (ddd, J = 14.8,

12.1, 8.0 Hz, 1H), 0.45 (ddd, *J* = 14.5, 6.1, 2.1 Hz, 1H), 0.07 (s, 3H), 0.05 (s, 3H), -0.09 (dd, *J* = 14.5, 11.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 138.1, 131.7, 130.3, 121.2, 59.3, 52.0, 44.8, 32.5, 18.5, 12.8, -1.2, -1.3; IR (film) 2948, 1734, 1487, 1434, 1407, 1247, 1203, 1161, 1141, 1012, 840, 819, 800 cm^{-1}. MS (APCI+) 341.05708 (341.05670 calcd for $C_{15}H_{22}O_2BrSi$, M + H$^+$). The enantiopurity was determined to be 96.6:3.4 er by chiral HPLC analysis for the major diastereomer (Regis Technologies (*R*,*R*)-Whelk, 25 cm x 4.6 mm, 0.5% IPA/Hexanes, 0.25 mL/min, λ 210 nm, RT= 33.6 and 46.3 min) and 92.8:7.2 for the minor diastereomer (Regis Technologies (*R*,*R*)-Whelk, 25 cm x 4.6 mm, 0.5% IPA/Hexanes, 0.25 mL/min, λ 210 nm, RT= 32.3 and 36.9 min).



2,2,2-Trichloroethyl (*R*)-2-([1,1'-biphenyl]-4-yl)-2-((1*S*,3*s*)-1-(4-(*tert*-butyl)phenyl)-1-methylsiletan-3-yl)acetate (27). The general procedure 1 was employed for the C–H functionalization of 1-(4-(*tert*-butyl)phenyl)-1-methylsiletane (328 mg, 1.5 mmol, 3 equiv) by reaction of 2,2,2-trichloroethyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (184 mg, 0.50 mmol, 1 equiv) using Rh_2(*S*-TPPTTL)$_4$ (12 mg, 1.0 mol%) as catalyst and α,α,α-trifluorotoluene as solvent. This procedure afforded the title compound (212 mg, 76%) as a colorless solid and as a >20:1 mixture of diastereomers as determined by ^{1}H NMR analysis by comparing the dd at 0.93 ppm and 0.8 ppm and the s at 0.56 ppm and 0.53 ppm (the dr was ~3:1 when the reaction was conducted

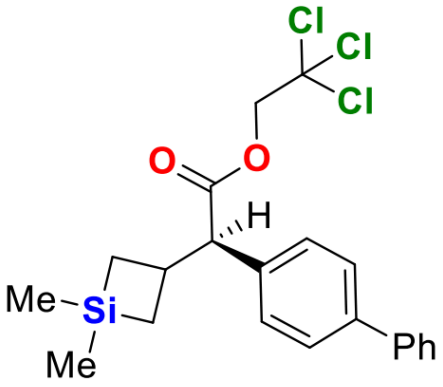
with $Rh_2(OAc)_4$). The NMR data is for the major diastereomer, mp 38–42 °C: $[\alpha]^{23}_D$ -104.6 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64–7.56 (m, 6H), 7.54–7.45 (m, 6H), 7.40–7.35 (m, 1H), 4.88 (d, *J* = 12.0 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 3.77–3.42 (d, *J* = 10.5 Hz, 1H), 3.12 (qt, *J* = 10.1, 8.0 Hz, 1H), 1.62–1.54 (m, 1H), 1.37 (s, 9H), 1.25 (dd, *J* = 14.1, 10.3 Hz, 1H), 1.20–1.11 (m, 1H), 1.00 (dd, *J* = 14.5, 10.7 Hz, 1H), 0.62 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.0, 153.1, 140.81, 140.5, 136.3, 134.2, 133.7, 129.0, 128.9, 127.4, 127.3, 127.2, 125.2, 95.1, 74.2, 62.2, 35.4, 34.9, 31.4, 20.4, 19.5, -3.9; IR (film) 3073, 3029, 2962, 2904, 2867, 1748, 1598, 1487, 1386, 1370, 1266, 1250, 1153, 1119, 1088, 868, 836, 822, 777, 739, 722, 697 cm^{-1}. MS (APCI+) 559.13941 (559.13882 calcd for $C_{30}H_{34}O_2Cl_3Si$, M + H^+). The enantiopurity was determined to be 99.3:0.7 er by chiral HPLC analysis (Regis Technologies (*R*,*R*)-Whelk, 25 cm x 4.6 mm, 1% IPA/Hexanes, 1.00 mL/min, λ 210 nm, RT= 8.6 and 10.1 min).

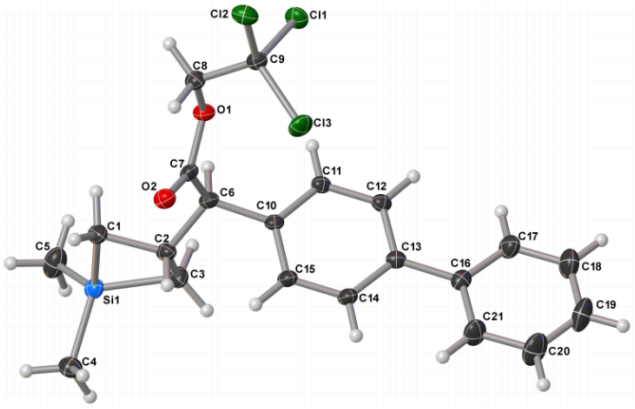


2,2,2-Trichloroethyl (*S*)-2-([1,1'-biphenyl]-4-yl)-2-((1*R*,3*s*)-1-methyl-1-(4-(trifluoromethyl)phenyl)siletan-3-yl)acetate (29). The general procedure 1 was employed for the C–H functionalization of 1-methyl-1-(4-(trifluoromethyl)phenyl)siletane (345 mg, 1.5 mmol) by reaction of 2,2,2-trichloroethyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (185 mg, 0.50 mmol) using Rh_2(*S*-TPPTTL)$_4$ (6.2 mg, 1.0 mol%) as catalyst and α,α,α,-trifluorotoluene as solvent. After flash chromatography (gradient 0 -> 5% diethyl ether / hexanes) the title compound (224 mg, 78%) was obtained as a colorless oil and as a 7:1 mixture of diastereomers as determined by ^{1}H NMR

analysis by comparing the dd at 0.97 ppm and 0.89 ppm. The NMR data is for the major diastereomer: $[\alpha]^{23}_{D}$ -76.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75–7.64 (m, 4H), 7.64–7.57 (m, 4H), 7.53–7.42 (m, 4H), 7.37 (t, *J* = 7.4 Hz, 1H), 4.88 (d, *J* = 12.0 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 3.68 (d, *J* = 10.5 Hz, 1H), 3.17 (m, 1H), 1.64 (ddd, *J* = 14.5, 8.0, 4.9 Hz, 1H), 1.31–1.16 (m, 2H), 1.00 (dd, *J* = 14.6, 10.6 Hz, 1H), 0.65 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 142.6, 140.72, 140.73, 136.0, 134.0, 131.8 (q, *J* = 32.3 Hz), 129.0, 128.9, 127.5, 127.4, 127.2, 124.7 (q, *J* = 3.6 Hz), 124.2 (q, *J* = 272 Hz), 95.1, 74.2, 62.0, 35.4, 20.1, 19.2, -3.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.00; IR (film) 1748, 1323, 1163, 1119, 1059, 1018, 827, 740, 722, 698 cm^{-1}. MS (NSI+) 511.2413 (511.2414 calcd for $C_{27}H_{25}O_2Cl_3F_3Si$, M + H^+). This reaction was also conducted using the same scale as described above with Rh_2(*R*-TPPTTL)$_4$ as catalyst generating the enantiomer of the title compound (238 mg, 83% yield) after flash chromatography (gradient 0 -> 5% diethyl ether / hexanes) and as a 7:1 mixture of diastereomers as determined by ^{1}H NMR analysis by comparing the dd at 0.97 ppm and 0.89 ppm. HPLC analysis was conducted on four reactions conducted with four different catalysts: $Rh_2(OAc)_4$, Rh_2(*R*/*S*-TPPTTL)$_4$, Rh_2(*S*-TPPTTL)$_4$ and Rh_2(*R*-TPPTTL)$_4$ (see HPLC traces below). The enantiopurity was determined most effectively from the reaction using Rh_2(*R*-TPPTTL)$_4$ because of unfavorable overlap between the diastereomers when Rh_2(*S*-TPPTTL)$_4$ was used as catalyst, and the result reported in the manuscript derives from the reaction with Rh_2(*R*-TPPTTL)$_4$. The enantiopurity was determined to be 98:2 er by chiral HPLC analysis for the major diastereomer (Regis Technologies (*S*,*S*)-Whelk, 10 cm x 4.6 mm, 1.8 μm, 0.5% IPA/Hexanes, 0.5 mL/min, λ 230 nm, RT= 22.4 and 29.3 min) and 92:8 for the minor diastereomer (Regis Technologies (*S*,*S*)-Whelk, 10 cm x 4.6 mm, 1.8 μm, 0.5% IPA/Hexanes, 0.5 mL/min, λ 230 nm, RT= 23.2 and 34.8 min).

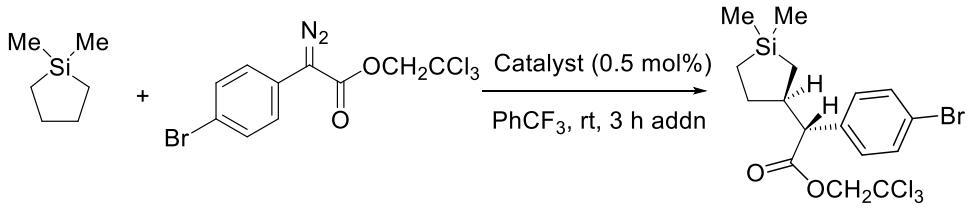
5.1.1) Crystal Structure of Compound 6





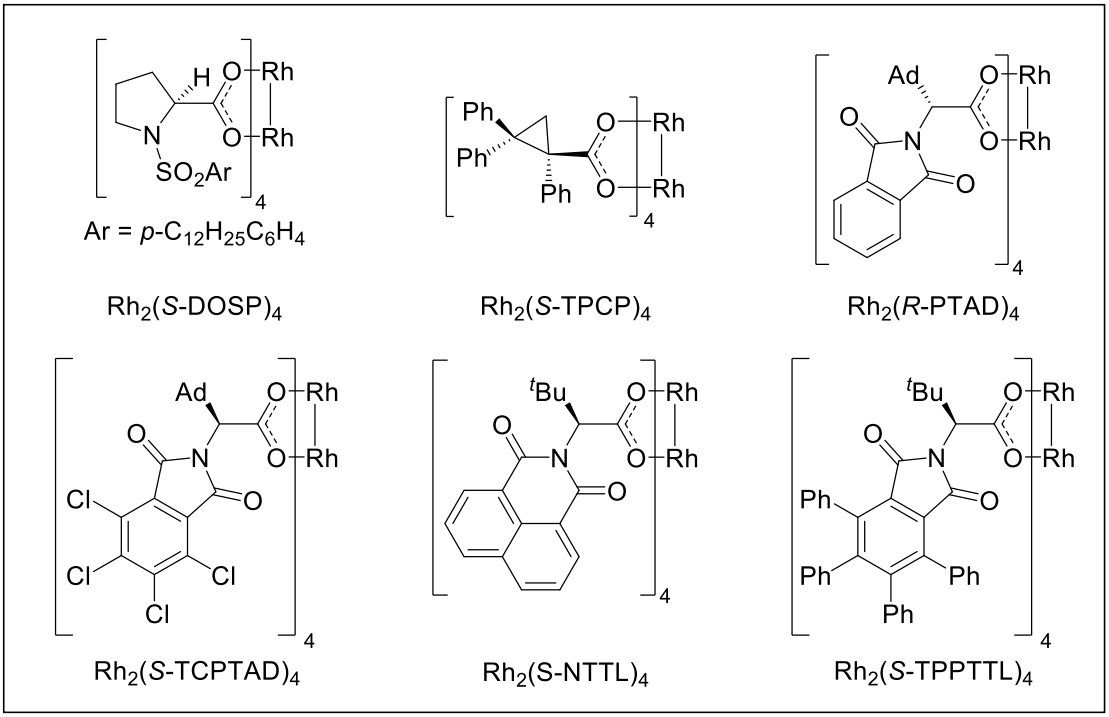
5.2) Catalyst Screen for Diastereoselective Reactions

A catalyst screen was conducted using General Procedure 1 to determine the best catalyst for achieving high diastereoselectivity for the C–H functionalization of 5 membered rings cyclotetramethylenedimethylsilane. The level of diastereoselectivity was examined by comparing the dd at 0.29 ppm (minor) with the dd at -0.05 ppm (major).



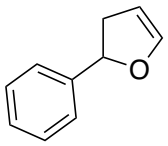
Catalyst	Combined Yield	dr
Rh_2(*S*-DOSP)$_4$	50%	1.9:1
Rh_2(*S*-*p*-Ph-TPCP)$_4$	56%	1.5:1
Rh_2(*R*-PTAD)$_4$	72%	2:1
Rh_2(R-TCPTAD)$_4$	73%	2.2:1
Rh_2(S-NTTL)$_4$	33%	4:1
Rh_2(S-TPPTTL)$_4$	56%	14:1

Catalyst Structures

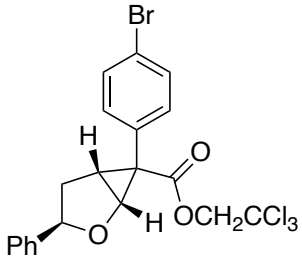


5.3) General Procedure 2 for Cyclopropanation Reactions

An oven-dried round bottom flask was equipped with stir bar and cooled under vacuum. A second oven-dried round bottom flask was cooled under vacuum. After cooling to room temperature, the flask with the stir bar was loaded with Rh catalyst (0.5 mol% or 1 mol%), dihydrofuran (2.5 equiv) and solvent (4.5 mL per mmol dihdrofuran) and cooled to -50°C. Diazo compound (1 equiv) was added to the second flask and dissolved in solvent (10 mL per mmol diazo compound). The solution of diazo compound was added to the first solution of catalyst and dihydrofuran dropwise via syringe pump over 2 hours. The reaction mixture was allowed to stir until the orange color of the solution had disappeared after the addition was complete, and then the residual solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography gradient (0->5%) ethyl acetate/hexanes. The General Procedure 2 was used to accomplish the reactions in Figure 3.3, the optimization of the catalyst and solvent.

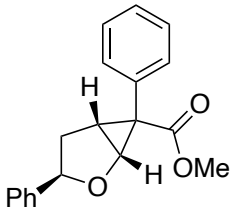


2-phenyl-2,3-dihydrofuran. 4Å molecular sieves, $^{n}Bu_4NCl$ (50 mmol, 2.5 equiv), and potassium acetate (40 mmol, 2.0 equiv) were added to 20 mL of dry N,N-dimethylformamide and stirred vigorously. Iodobenzene (20mmol, 1.0 equiv) was added to the vigorously stirred solution followed by 2,3-dihydrofuran (100 mmol, 5 equiv). Finally, palladium acetate (1 mmol, 5 mol%) was added to the solution, which was allowed to stir overnight. The solution was diluted with diethyl ether (75 mL) and allowed to stir before being filtered over a short silica plug, eluting with diethyl ether (100 mL). The filtrate was washed with water, washed again with saturated sodium chloride, dried over $MgSO_4$ and filtered. The filtrate was concentrated to afford the crude product. The crude product was purified by silica gel chromatography eluting with 3% ethyl acetate in hexanes. The collected fractions, which were visible by UV of the TLC and stained deep blue with cerium molybdate stain, were concentrated under reduced pressure to afford the product (1.95g, 65% yield) ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, 4H), 7.30 (m, 1H), 6.46 (q, 1H), 5.52 (dd, 1H), 4.97 (q, 1H), 3.08 (tt, 1H), 2.61 (qt, 1H).



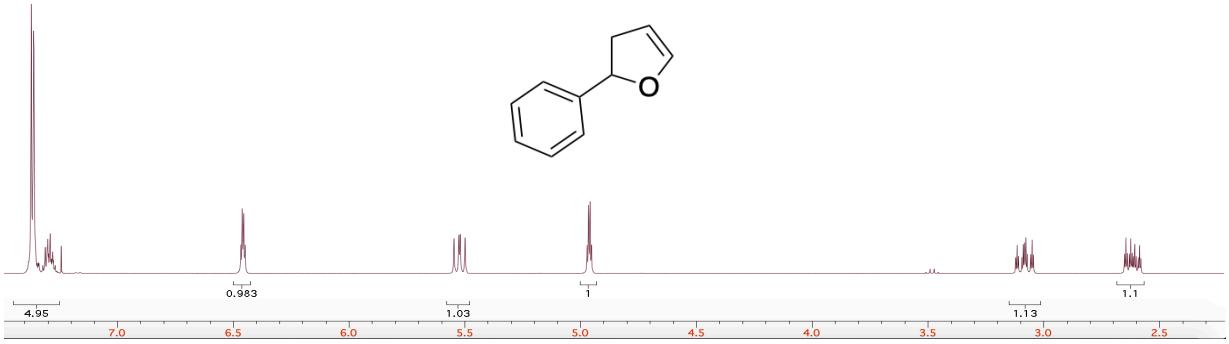
2,2,2-trichloroethyl 6-(4-bromophenyl)-3-phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate (2a-2j, 4). General Procedure 2 was employed using (dihydrofuran) and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate with the dirhodium catalysts listed in Figure 3.3 to afford the title

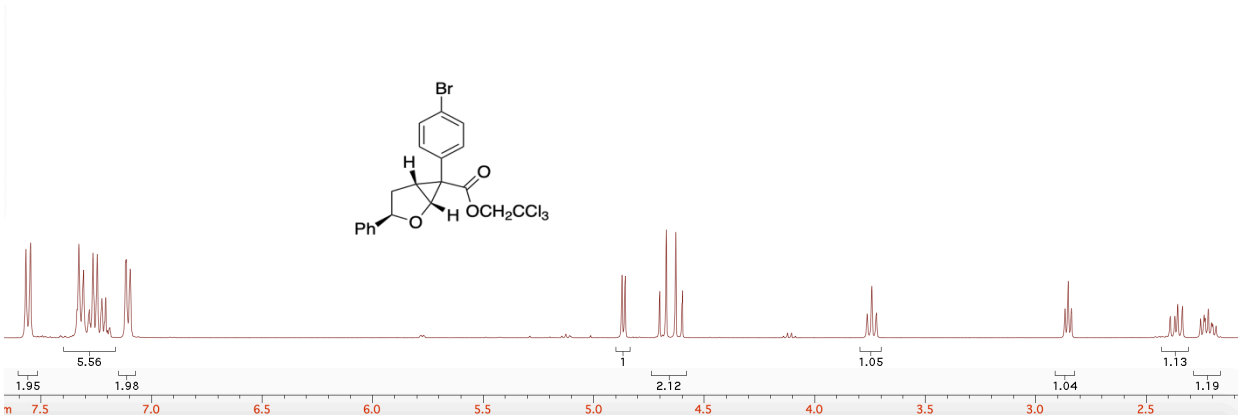
compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2H), 7.26 (m, 5H), 7.12 (d, 2H), 4.86 (d, 1H), 4.68 (dd, 2H), 3.74 (t, 1H), 2.86 (t, 1H), 2.36 (m, 1H), 2.23 (m, 1H). Chiral HPLC analysis was performed using a CHIRALCEL® OD-H column, 2% i-PrOH/hexanes, 0.5mL/min, λ 210nm, RT=17.04 and 19.85 min (racemic).

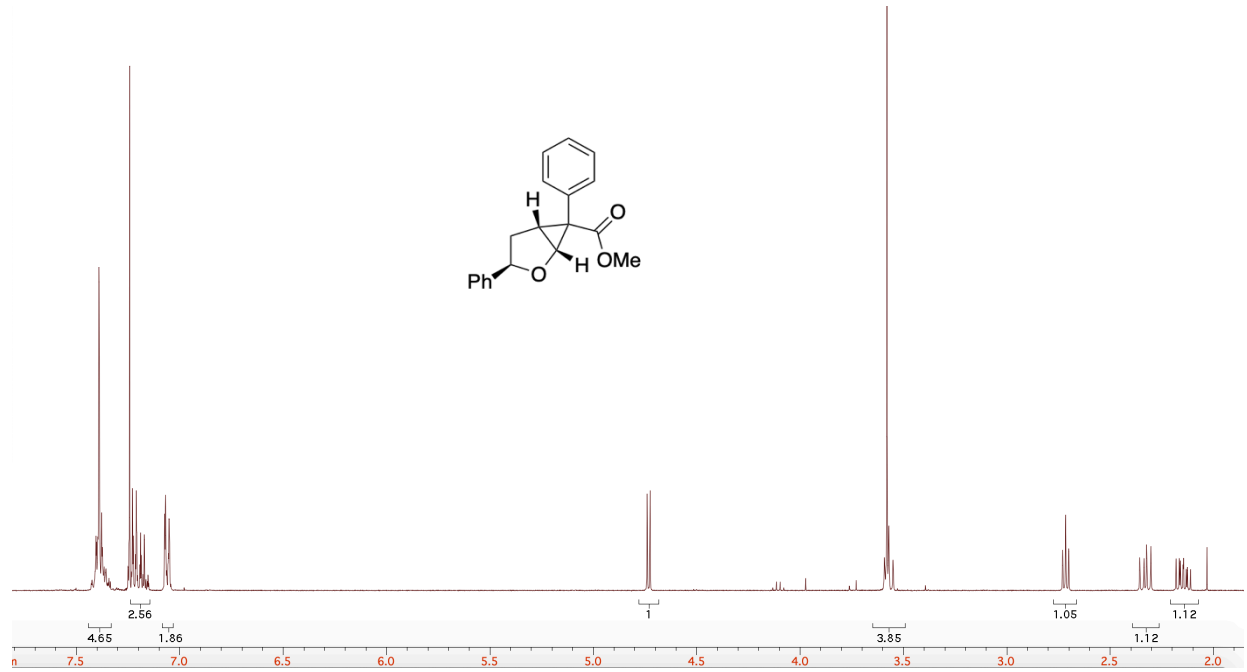


Methyl 3,6-diphenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate (1a-1d, 3). For compounds 1a-1d, General Procedure 2 was employed at room temperature using the catalysts listed in Figure 3.2. For compound 3, General Procedure 2 was employed using (dihydrofuran) and methyl 2-diazo-2-phenylacetate with Rh_2(S-PTAD)$_4$ as catalyst at the specified temperature. Purification by silica gel chromatography (0->5% gradient) ethyl acetate/hexanes afforded the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 5H), 7.20 (m, 3H), 7.05 (d, 2H), 4.73 (d, 1H), 3.55 (overlap of signals: s, 3H; t, 1H), 2.71 (t, 1H), 2.32 (m, 1H), 2.15 (m, 1H). The enantiopurity of the compounds in Figure 3.2 were determined using a Phenomenex Lux Cellulose-1 column, 4.6 x 250 nm, 5 μm, 10% i-PrOH/heptane, 0.5mL/min, λ 215nm, RT = 11.46 and 12.23 (racemic). The enantiopurity of compound **3** was shown to be 76.5:23.5 er by chiral HPLC analysis; CHIRALCEL® OD-H column, 2% i-PrOH/hexanes, 0.5mL/min, λ 210nm, RT=17.04 and 19.85 min (racemic).

5.3.1) Representative ^{1}H NMR Spectra



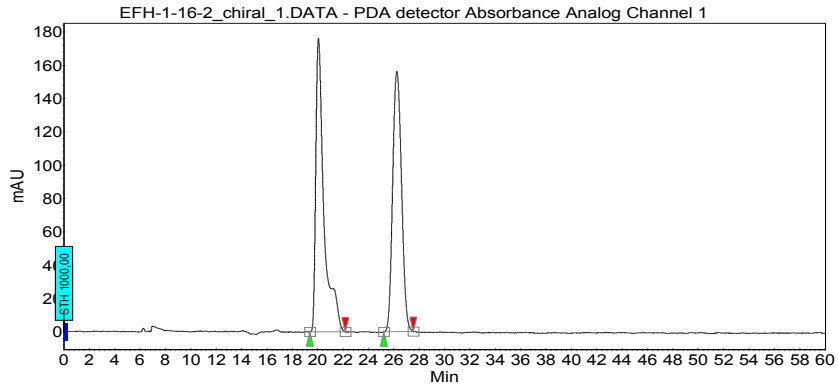




5.4) Dihydrofuran HPLC Traces

5.4.1) Traces Corresponding to Figure 3.2

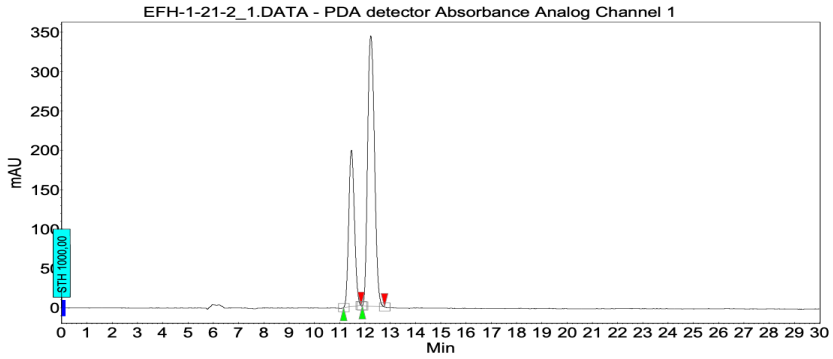
Compound 1a



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	20,06	51,02	176,4	132,2	51,019
2	UNKNOWN	26,24	48,98	156,5	126,9	48,981
Total			100,00	332,9	259,1	100,000

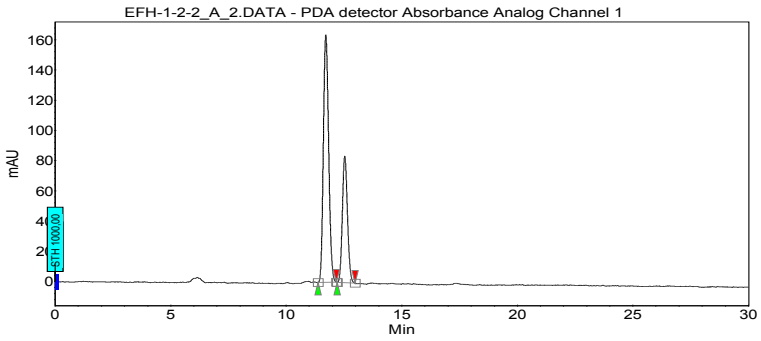
Compound 1b



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	11,46	32,59	198,9	52,4	32,591
2	UNKNOWN	12,23	67,41	343,4	108,3	67,409
Total			100,00	542,3	160,7	100,000

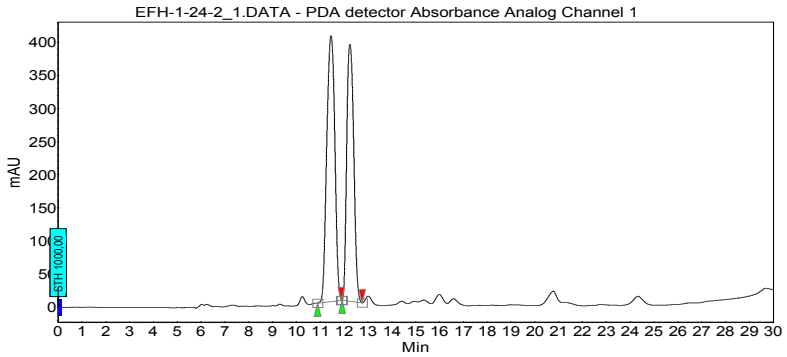
Compound 1c



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	11,71	66,99	164,0	43,6	66,988
2	UNKNOWN	12,53	33,01	83,9	21,5	33,012
Total			100,00	247,8	65,0	100,000

Compound 1d

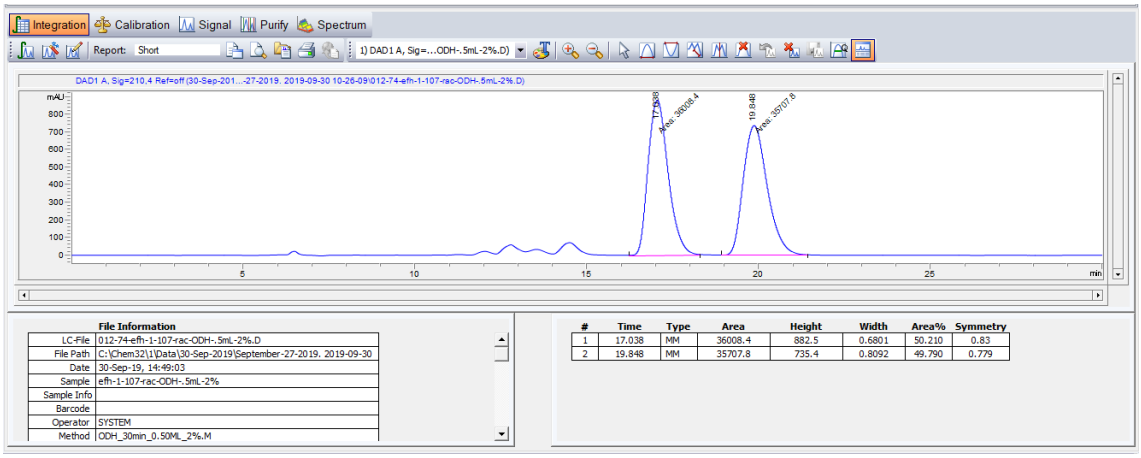


Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	11,45	54,27	401,5	157,5	54,265
2	UNKNOWN	12,24	45,73	387,8	132,7	45,735
Total			100,00	789,3	290,2	100,000

5.4.2) Traces Corresponding to Figure 3.3

Compound 2a

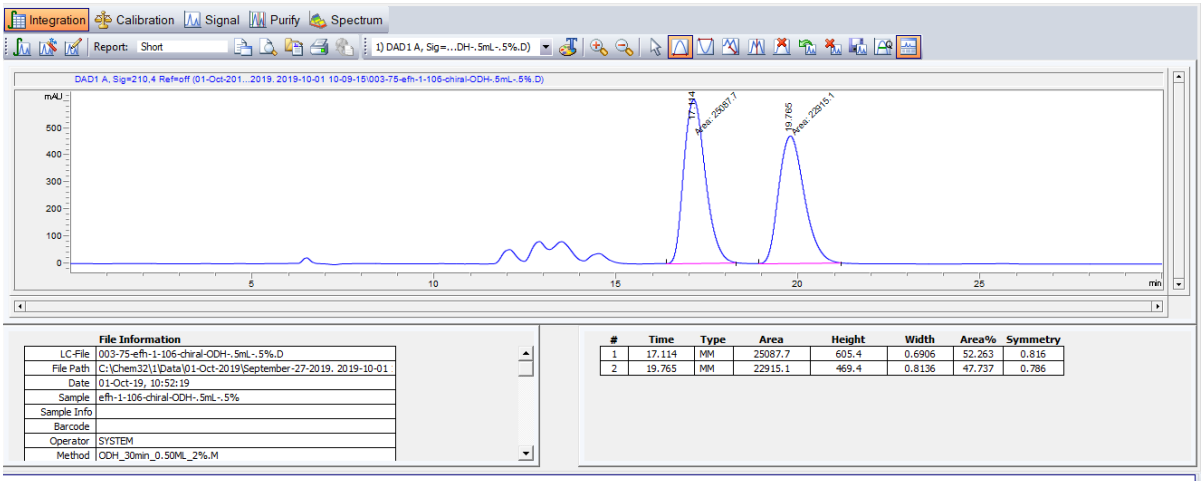


File Information

LC-File	012-74-efh-1-107-rac-ODH-.5mL-2%.D
File Path	C:\Chem32\1\Data\30-Sep-2019\September-27-2019. 2019-09-30
Date	30-Sep-19, 14:49:03
Sample	efh-1-107-rac-ODH-.5mL-2%
Sample Info	
Barcode	
Operator	SYSTEM
Method	ODH_30min_0.50ML_2%.M

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	17.038	MM	36008.4	882.5	0.6801	50.210	0.83
2	19.848	MM	35707.8	735.4	0.8092	49.790	0.779

Compound 2b

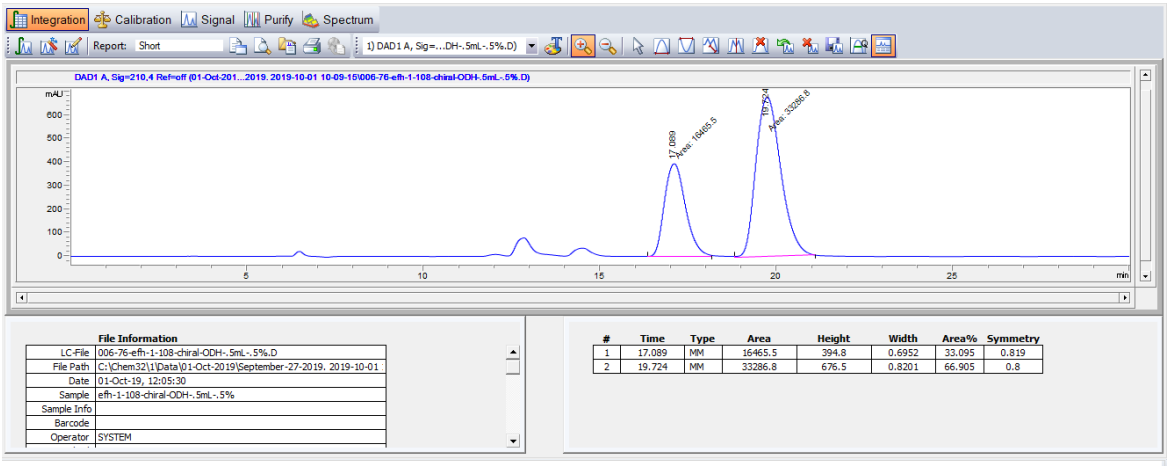


File Information

LC-File	003-75-efh-1-106-chiral-ODH-.5mL-.5%.D
File Path	C:\Chem32\1\Data\01-Oct-2019\September-27-2019. 2019-10-01
Date	01-Oct-19, 10:52:19
Sample	efh-1-106-chiral-ODH-.5mL-.5%
Sample Info	
Barcode	
Operator	SYSTEM
Method	ODH_30min_0.50ML_2%.M

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	17.114	MM	25087.7	605.4	0.6906	52.263	0.816
2	19.765	MM	22915.1	469.4	0.8136	47.737	0.786

Compound 2c

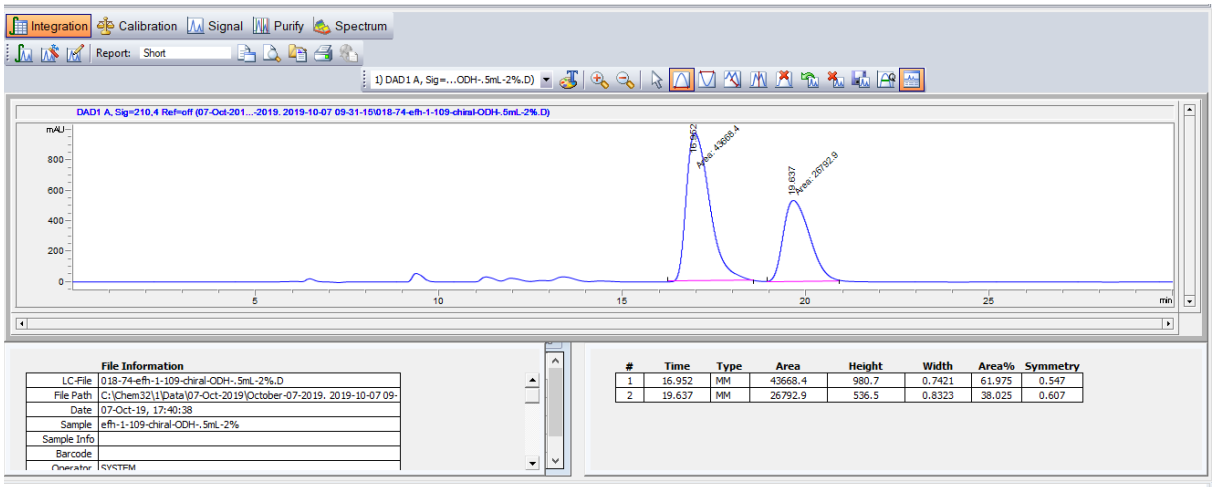


File Information

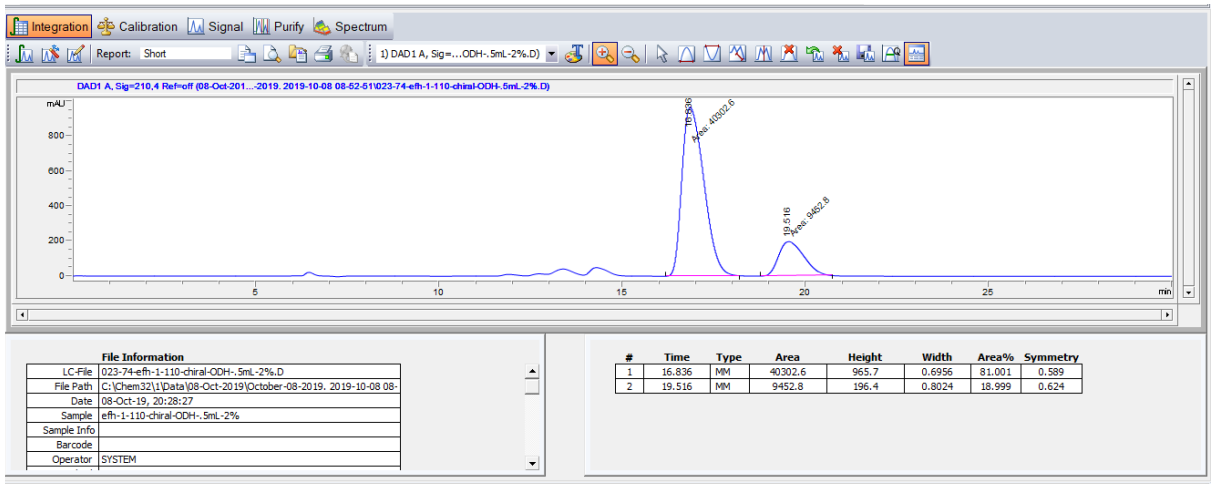
LC-File	006-76-efh-1-108-chiral-ODH-.5mL-.5%.D
File Path	C:\Chem32\1\Data\01-Oct-2019\September-27-2019. 2019-10-01
Date	01-Oct-19, 12:05:30
Sample	efh-1-108-chiral-ODH-.5mL-.5%
Sample Info	
Barcode	
Operator	SYSTEM

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	17.089	MM	16465.5	394.8	0.6952	33.095	0.819
2	19.724	MM	33286.8	676.5	0.8201	66.905	0.8

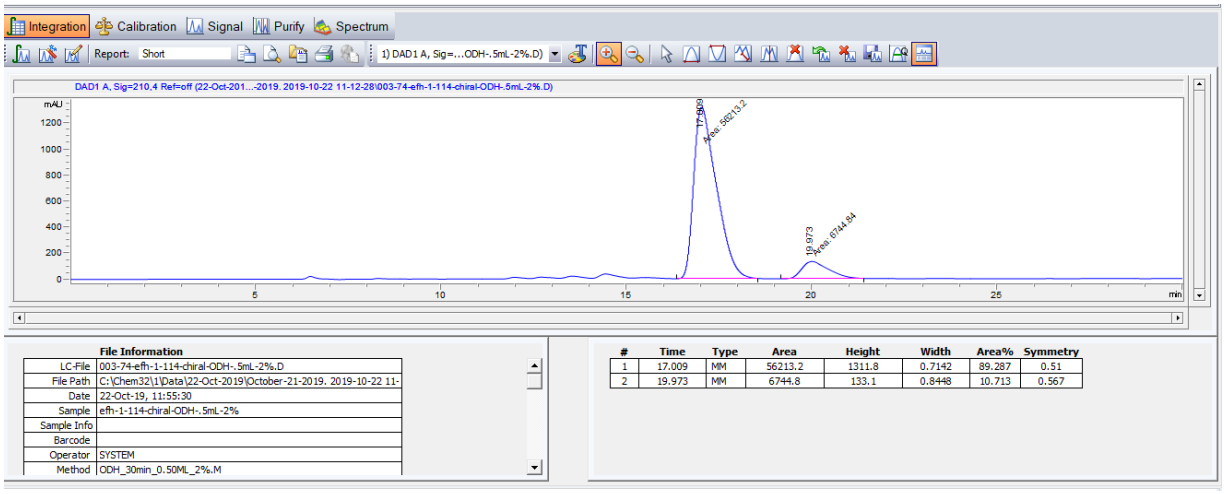
Compound 2d



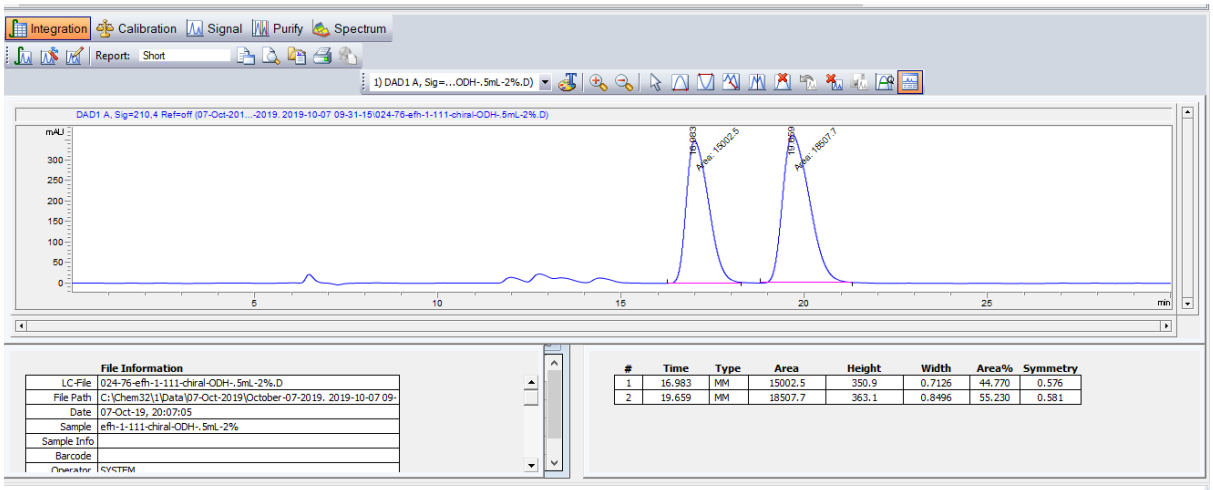
Compound 2e



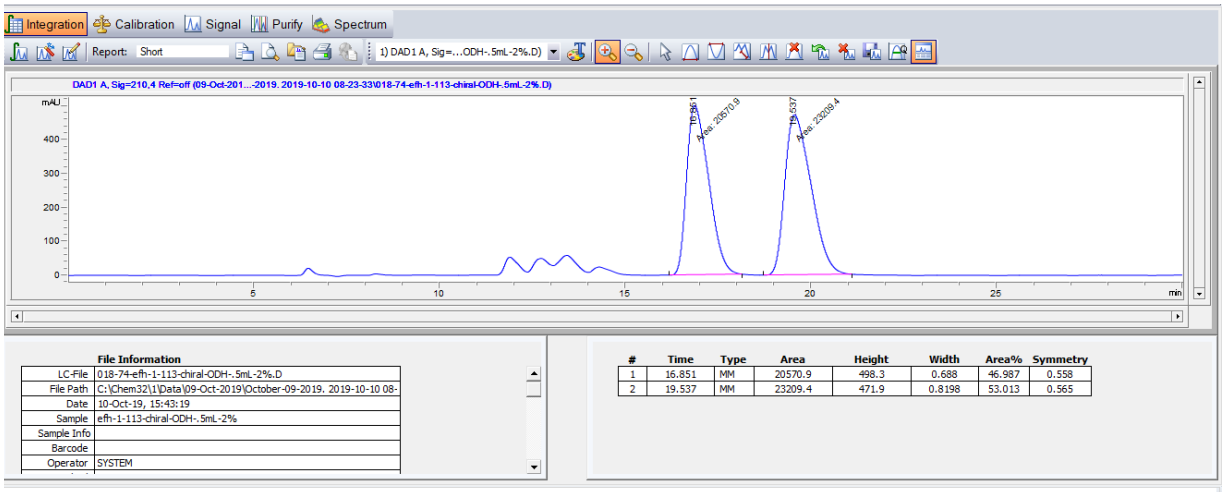
Compound 2f



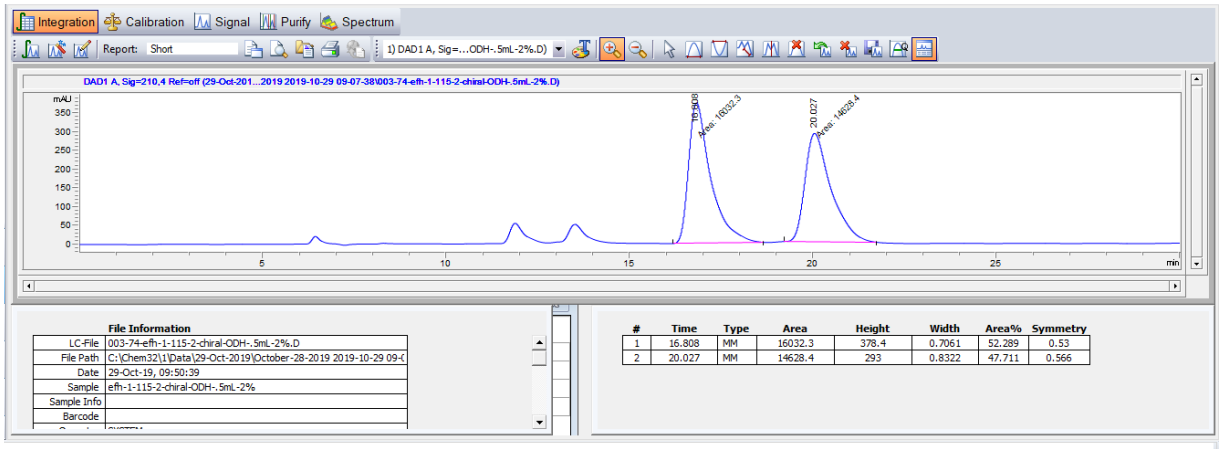
Compound 2g



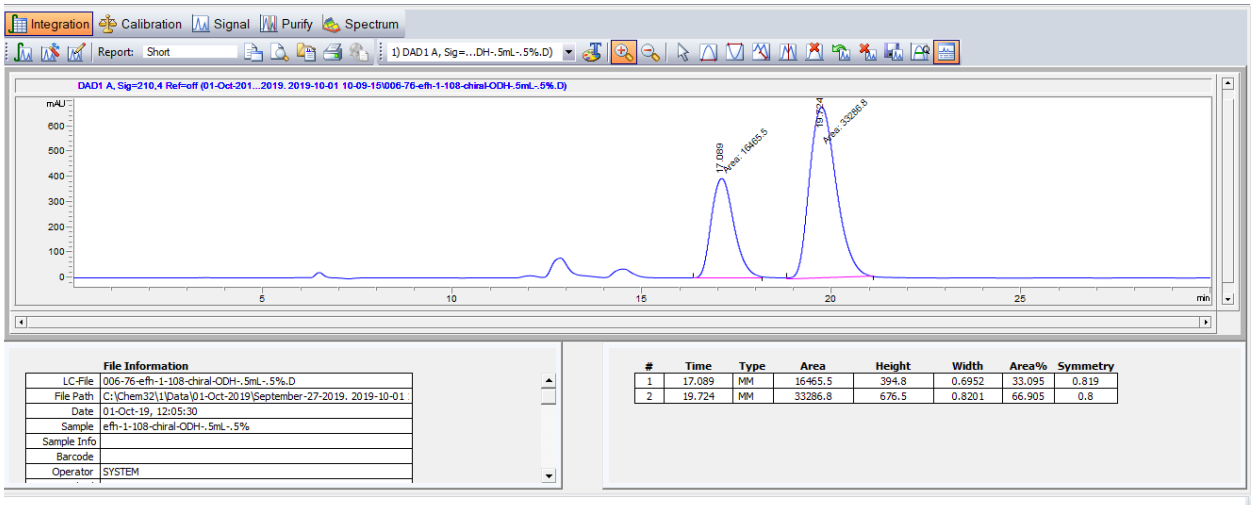
Compound 2h



Compound 2i

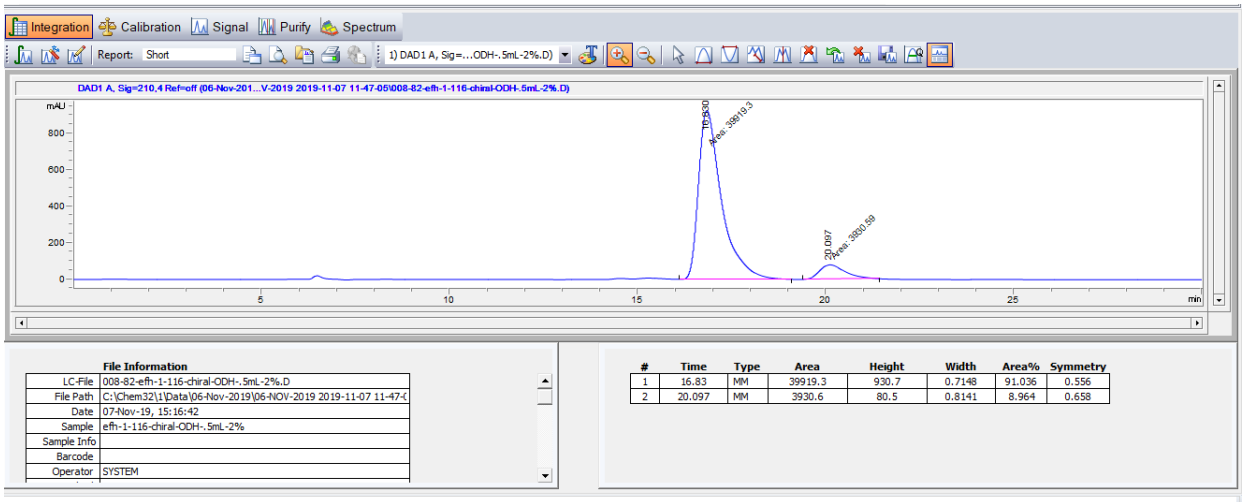


Compound 2j



5.4.3) HPLC Trace for Figure 3.5

Compound 4



6.) References

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