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David M. Guptill Date

**EXPANDING THE SCOPE OF DONOR/ACCEPTOR**

**RHODIUM-CARBENE CHEMISTRY**

By

David M. Guptill
Doctor of Philosophy

Chemistry

_____

Huw M. L. Davies, Ph.D.
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Dean of the James T. Laney School of Graduate Studies

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Date

# EXPANDING THE SCOPE OF DONOR/ACCEPTOR RHODIUM-CARBENE CHEMISTRY

By

David M. Guptill

B.A., Gustavus Adolphus College, 2009

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

An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
in Chemistry
2014

## Abstract

EXPANDING THE SCOPE OF DONOR/ACCEPTOR

RHODIUM-CARBENE CHEMISTRY

By David M. Guptill

The reactions of donor/acceptor rhodium-carbenes have been studied widely for the last 25 years, and a variety have become widely accepted. These include, most notably, cyclopropanation and C–H insertion reactions. This work attempts to address some of the outstanding challenges in field of donor/acceptor rhodium-carbene chemistry. In particular, this work focuses on expanding the scope of C–H functionalization reactions by carbene induced C–H insertion.

The first part of this thesis describes work attempting to apply the combined cyclopropanation/Cope rearrangement (CPCR) to the total synthesis of (–)-Pseudolaric Acid B. The synthetic route relied on two sequential rhodium-carbene reactions to install the core of the natural product. Unfortunately, the CPCR reaction led to a product that was diastereomeric relative to the desired product, and this could not be overcome but altering the substrate. A second approach attempted to avoid this issue, but reached other roadblocks as well. Nevertheless, an interesting kinetic resolution was developed, in which a racemic substrate could be converted to a single enantiomer using the rhodium-catalyzed CPCR.

The second part of this thesis describes the application of 2-(trialkylsilyl)ethyl aryl- and styryldiazoacetates to the synthesis of *Z*-allylsilanes. The reaction is believed to proceed through an intramolecular C–H insertion to give a β-lactone, which then stereospecifically extrudes $CO_2$ under mild conditions to give the observed allylsilane products.

The third part of this thesis describes the application of 2,2,2-trichloroethyl aryldiazoacetates to the site-selective C–H functionalization of benzylic methyl groups and methyl ethers. The unique ester is believed to reduce the propensity of the intermediary rhodium-carbenes to undergo both destructive intramolecular C–H insertion chemistry as well as intermolecular dimerization reactions.

Finally, the application of the novel 2-(trimethylsilyl)ethyl and 2,2,2-trichloroethyl aryldiazoacetates to asymmetric cyclopropanation reactions is described. These esters are capable of being removed selectively under mild conditions, giving the synthetic chemist a variety of options for deprotection of cyclopropylcarboxylic acids.

# EXPANDING THE SCOPE OF DONOR/ACCEPTOR RHODIUM-CARBENE CHEMISTRY

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*For Lisa*

*and our future children*

## Acknowledgments

Perhaps it is to be expected, but when I began my graduate studies, I was completely unaware of just how challenging it would be to obtain this degree. Though I had been warned by my college professors, I realize now that it is not something you can fully appreciate until you have tried. Of course, the degree is not the goal in itself, but merely the acknowledgement that the goal has been achieved. Without a doubt none of us achieves anything alone, so it is important that I acknowledge those people who have played an important role in this part of my life.

First, I wish to acknowledge my advisor, Professor Davies. Science is logical and calculated, but it is also creative. Professor Davies allows his students the freedom to explore chemistry and their projects on their own terms, while also giving feedback to keep things "on track." This flexibility has given me the chance to be self-motivated and grow and mature as a scientist.

My committee members, Professors Frank McDonald and Fred Menger, have played an important role in my development as a scientist as well. Though the committee generally only meets once a year, I received valuable feedback on my research progress. I thank them for their guidance and support. Additionally, I wish to acknowledge Professor Simon Blakey, who served on my proposal defense committee, and has been a strong advocate for me at Emory in many ways.

Many people have said the Emory chemistry department is a special place, in no small part because of the support staff. Especially I wish to acknowledge Dr. Wu and Dr. Wang in the NMR center, from whom I learned a great deal during my time as an NMR service instructor. Thanks to my friends in the stockroom, Patti and Steve, not only for

their support, but their friendship over the last 5 years. All the other support staff including Dr. Strobel in the mass spec center, and Dr. Bacsa in the X-ray crystallography center have been important to the completion of this work as well. And finally, I must acknowledge Ann Dasher for her tireless efforts to make graduate student life a little more bearable. She is exceptional at what she does, and is an instrumental part of every PhD the chemistry department awards.

One cannot spend all day, every day with the same people and not develop some friendships. Especially I wish to acknowledge Jen Bon and Brett McGuire. Their ability to make me laugh and take my mind off of chemistry when I needed it has been most appreciated. Additionally, all the members of the Davies lab, past and present, including those who have mentored me, and those whom I have mentored, have all played an important role in obtaining this degree. Especially I wish to acknowledge a few postdocs who were especially influential: Dan Morton, Austin Smith, and Damien Valette. Their guidance and laughter made a huge difference.

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Finally, my family: my parents, sister, and in-laws have all been an enormous supportive force. Their help during this time has been monumental. Most importantly, however, has been the support of my wife, Lisa. We have often joked that, in a way, we *both* have gone through graduate school the last five years. Her love and support made it all bearable.

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## List of Figures

## List of Schemes

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## List of abbreviations

| | |
|---|---|
| **Ac** | acetyl |
| **APCI** | atmospheric pressure chemical ionization |
| **Ar** | aryl |
| **Bn** | benzyl |
| **Bu** | butyl |
| **DBU** | 1,8-diazabicycloundec-7-ene |
| **COD** | 1,5-cyclooctadiene |
| **Cy** | cyclohexyl |
| **dba** | bis(dibenzylideneacetone) |
| **DCC** | *N*,*N*-dicyclohexylcarbodiimide |
| **1,2-DCE** | 1,2-dichloroethane |
| **DCM** | dichloromethane |
| **DIBAL-H** | diisobutylaluminum hydride |
| **DMAP** | *N*,*N*-4-(dimethylamino)pyridine |
| **DMB** | 2,2-dimethylbutane |
| **DMF** | dimethylformamide |
| **dppf** | 1,1’-bis(diphenylphosphino)ferrocene |
| **EDG** | electron-donating group |
| **EE** | 1-ethoxyethyl |
| **Et** | ethyl |
| **equiv.** | equivalents |
| **ESI** | electrospray ionization |

| | |
|---|---|
| **EWG** | electron-withdrawing group |
| **HMPA** | hexamethylphosphoramide |
| **HPLC** | high performance liquid chromatography |
| **HRMS** | high-resolution mass spectrometry |
| **Imid.** | Imidazole |
| **IR** | infrared spectroscopy |
| **L** | ligand |
| **LDA** | lithium diisopropylamide |
| ***m*-CPBA** | *meta*-chloroperbenzoic acid |
| **Me** | methyl |
| **Mes** | mesityl (2,4,6-trimethylphenyl) |
| **mmol** | millimoles |
| **MOM** | methoxymethyl |
| **NMR** | nuclear magnetic resonance |
| **N.R.** | no reaction |
| **NSI** | nanospray ionization |
| ***o*-NBSA** | *ortho*-nitrobenzenesulfonyl azide |
| ***p*-ABSA** | *para*-acetamidobenzenesulfonyl azide |
| **Ph** | phenyl |
| **Piv** | pivaloyl |
| **PMB** | *p*-methoxybenzyl |
| **por** | porphyrin |
| **Pr** | propyl |

| | |
|---|---|
| **RM** | reaction mixture |
| **TBAF** | tetrabutylammonium fluoride |
| **TBDPS** | *tert*-butyldiphenylsilyl |
| **TBME** | *tert*-butyl methyl ether |
| **TBS** | *tert*-butyldimethylsilyl |
| **TCE** | 2,2,2-trichloroethyl |
| **TEA** | triethylamine |
| **temp** | temperature |
| **Tf** | trifluoromethanesulfonyl |
| **THF** | tetrahydrofuran |
| **TIPS** | triisopropylsilyl |
| **TLC** | thin layer chromatography |
| **TMEDA** | *N*,*N*,*N'N'*-tetramethylethylenediamine |
| **TMS** | Trimethylsilyl |
| **TMSE** | 2-(trimethylsilyl)ethyl |
| **Ts** | tosyl |

# Chapter 1 –Introduction to Donor/Acceptor Rhodium-Carbene Chemistry

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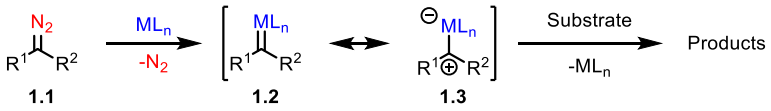
**Contents**

## 1.1 Introduction

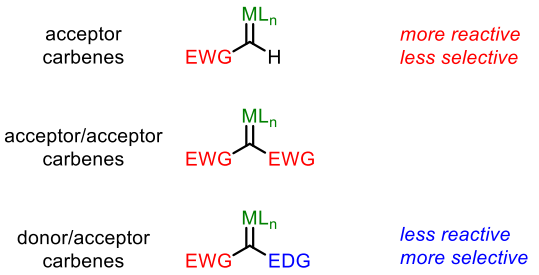
The quest for more efficient, selective, cost-effective reactions will likely be forever at the forefront of research in organic chemistry. One must identify chemical systems with enough energy to undergo a desired transformation, but not so much energy that the reaction occurs unselectively. One effective system has been to generate reactive carbene species from diazo compounds.[1] Most commonly, the carbenes are formed from diazo compounds **1.1** in the presence of a metal, which typically results in a transient metal-carbene (Eq. 1.1). Back-bonding from the metal stabilizes the carbene, and enables them to undergo selective reactions. Due to their greater ability for selective reactions, metal-carbenes have become widely used in organic chemistry.[2–6]




(Eq. 1.1)

Metal-carbenes have been classified according to the substituents surrounding the carbene center (Scheme 1.1).[6,7] Acceptor carbenes are so named because they contain one electron-withdrawing group and one hydrogen on either side of the carbene, while the acceptor/acceptor carbenes have two electron-withdrawing groups. Donor/acceptor carbenes, on the other hand, have one withdrawing group and one donor group, where the donor is an aryl, vinyl, or heteroaryl group. It can be seen from the resonance structure of the metal-carbene intermediate (**1.3**, Eq. 1.1) that a group with the ability to donate electrons by resonance would stabilize this intermediate. As a result, donor/acceptor carbenes tend to be more selective than their counterparts, in particular with regards to intermolecular reactions.[6]

**Scheme 1.1** Classification of metal-carbenes




Electron withdrawing group (EWG) = $CO_2R$, COR, CN, $PO_3R_2$, $SO_2R$, $NO_2$, $CF_3$
Electron donating group (EDG) = aryl, vinyl, heteroaryl

Dirhodium(II) tetracarboxylate catalysts (Figure 1.1) have been established for some time as excellent catalysts for decomposing diazo compounds to form the corresponding rhodium-carbenes. The prototypical catalyst is $Rh_2(OAc)_4$ which has been used for a variety of transformations.[8] The catalyst framework allows for a great deal of flexibility in ligand design, as theoretically any carboxylic acid could be installed around the dirhodium core.

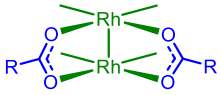



**Figure 1.1** Dirhodium(II) tetracarboxylate (two carboxylate ligands omitted for clarity)

Perhaps most interestingly, one could imagine the use of chiral ligands to impart a sense of asymmetric induction on the reactions of the rhodium-carbene intermediate. One important class of rhodium catalysts for donor/acceptor carbenes is the arylsulfonylprolinates, developed by McKervey,[9–11] which includes $Rh_2$(*S*-BSP)$_4$ (Figure 1.2). Later, Davies expanded these catalysts to include, among others, the more hydrocarbon soluble $Rh_2$(*S*-DOSP)$_4$[12] and the bridging catalyst $Rh_2$(*S*-bi-TISP)$_4$.[13]

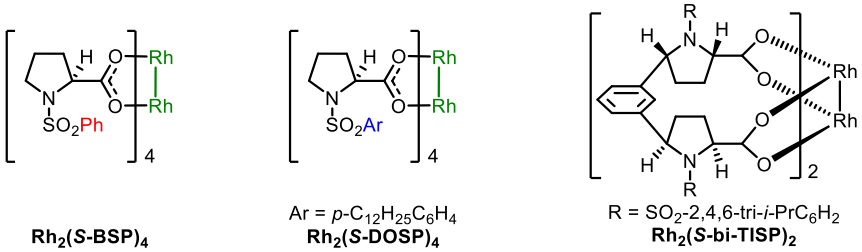



**Figure 1.2** Dirhodium catalysts derived from proline

Another class of dirhodium catalysts is composed of the *N*-phthalimidyl amino acid-derived catalysts utilized by Hashimoto.[14–16] Perhaps the most common of these catalysts is $Rh_2$(*S*-PTTL)$_4$ (Figure 1.3). A second generation catalyst in this family, $Rh_2$(*S*-PTAD)$_4$, was prepared and reported by Davies.[17]

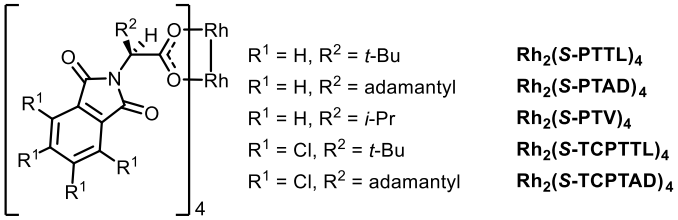



**Figure 1.3** Dirhodium catalysts derived from *N*-phthalimidyl amino acids

A third, more recently developed, class of catalysts is based on a chiral cyclopropane carboxylate ligand (Figure 1.4). This class includes the originally reported $Rh_2$(*R*-BTPCP)$_4$,[14] and the next generation $Rh_2$(*R*-BPCP)$_4$ and $Rh_2$(*R*-TPCP)$_4$.[18] Considered to be exceptionally bulky, these catalysts have been shown to give results that differ wildly from $Rh_2$(DOSP)$_4$ and $Rh_2$(PTAD)$_4$.[19]

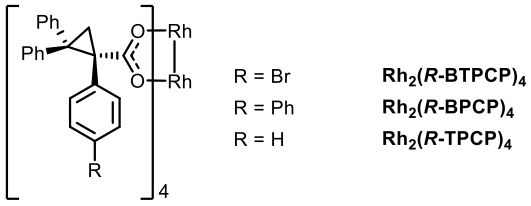
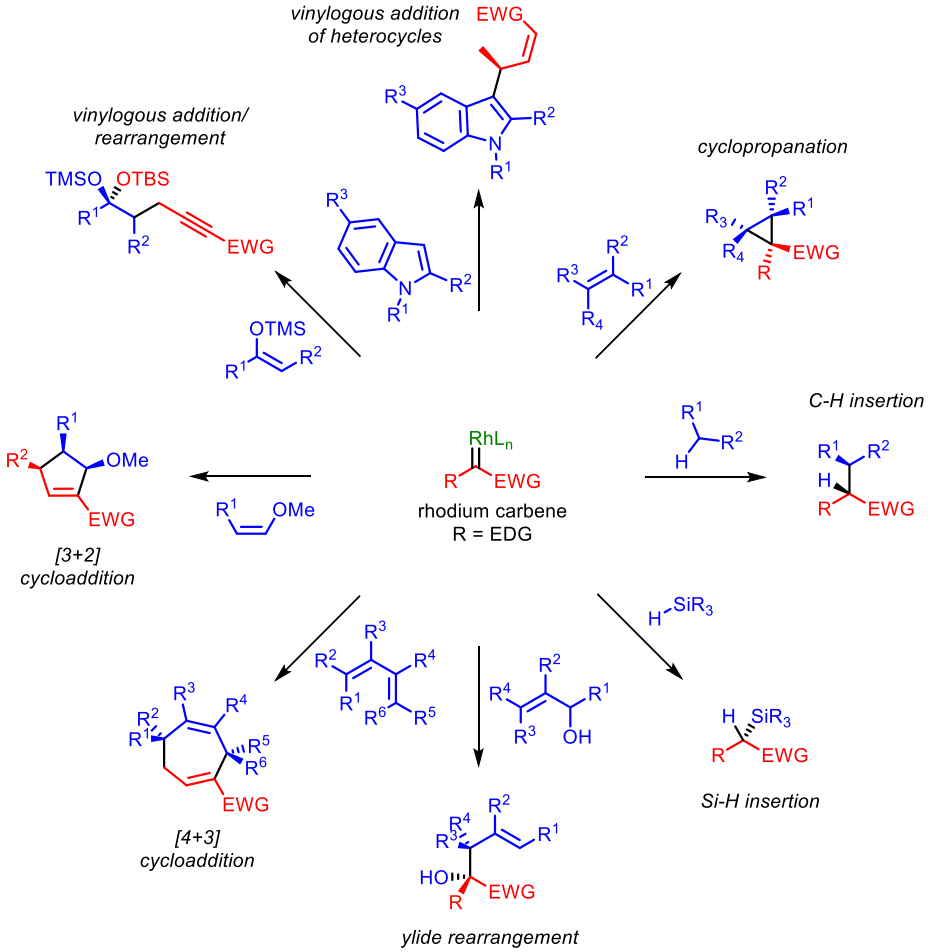



**Figure 1.4** Some triarylcyclopropane carboxylate catalysts

With these catalysts, a wide variety of asymmetric transformations are possible with donor/acceptor carbenes. Included among these are the classic reactions of carbenes: cyclopropanation and C–H insertion. However, donor/acceptor carbenes are also capable of undergoing Si–H insertion,[20] ylide formation/[2,3]-sigmatropic rearrangement,[21,22] [4+3] cycloaddition,[23–26] [3+2] cycloaddition,[27,28] vinylogous addition,[29] and vinylogous addition/rearrangement[30] reactions as well. For the cycloaddition and vinylogous addition reactions, vinylcarbenes are required, as this group participates directly in the reaction.

**Scheme 1.2** Some reactions of donor/acceptor carbenes

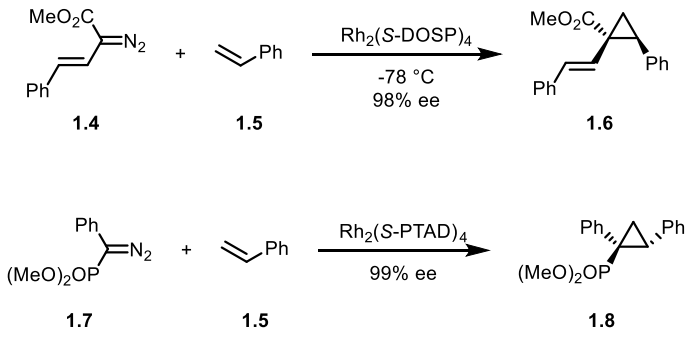


A brief introduction to both the cyclopropanation and C–H insertion reactions will be given in this chapter. More detailed introductions to these topics will be covered in later chapters as necessary. Introductions to other reactions shown in Scheme 1.2 will also be given as necessary in later chapters.

## 1.2 Cyclopropanation

Donor/acceptor rhodium-carbenes react with electron-rich olefins to give cyclopropanes. The reaction is routinely highly diastereoselective, even in the absence of a catalyst.[31] With chiral catalysts, the reaction can be highly enantioselective as well (Scheme 1.3).[12,17,32,33]

**Scheme 1.3** Enantioselective cyclopropanations with donor/acceptor rhodium-carbenes




It is generally accepted that the reaction goes through a concerted-asynchronous transition state, a view that was supported by recent theoretical studies by the Davies group.[34] The calculated bond lengths and bond orders (shown in Figure 1.5) were consistent with this mechanism.

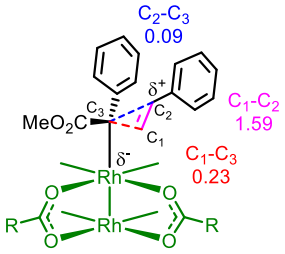



**Figure 1.5** Calculated transition state for donor/acceptor rhodium carbene cyclopropanation; Calculated bond orders shown.

A model has been proposed for $Rh_2(DOSP)_4$ catalyzed reactions (including cyclopropanations) to explain/predict the stereochemistry of the resulting products (Figure 1.6).[35,36] In this model, the 4 arylsulfonyl groups of the catalyst are arranged in a $D_2$ symmetric orientation, and are considered to function as blocking groups. The ester, which is perpendicular to the Rh–C bond to minimize resonance destabilization of the carbene, blocks approach from the back (as drawn). The substrate is considered to approach from the front, over the donor group. This predictive model works well for cyclopropanation reactions of aryl and vinyldiazoacetates with $Rh_2(S\text{-DOSP})_4$.

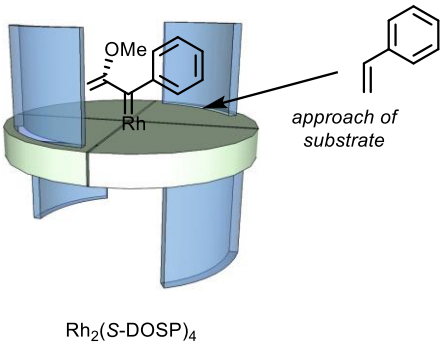



**Figure 1.6** Predictive model for $Rh_2(S\text{-DOSP})_4$ catalyzed cyclopropanation.

## 1.3 C–H Insertion

C–H insertion with donor/acceptor carbenes has become a major area of interest in the Davies group. This introduction will focus on the fundamentals of intermolecular C–H insertion reactions. The C–H insertion event is considered to be initiated by a hydride transfer that ultimately forms a new C–C bond.[34] In their theoretical studies, Davies and co-workers found that the calculated transition states for C–H insertion showed evidence for considerable hydride transfer (Figure 1.7). For 1,4-cyclohexadiene, the transition state was calculated to be early, with a higher degree of C–H bond formation/breaking than C–C bond formation (new C–H bond order = 0.36, old C–H bond order 0.51). With cyclopentane, a later transition state was calculated, with a bond order for the new C–H bond of 0.69. Though the C–C bond was more fully formed in the transition state for cyclopentane relative to 1,4-cyclohexadiene, the C–C bond order was still relatively low compared to the degree of C–H bond formation/breaking. These results support the generally accepted "pseudo hydride-transfer" mechanism for rhodium carbene C–H insertion.

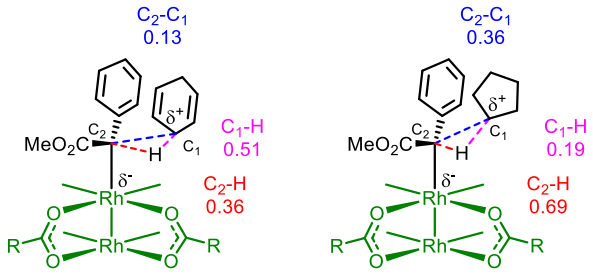



**Figure 1.7** Calculated transition states for C–H insertion with 1,4-cyclohexadiene and cyclopentane. Calculated bond orders shown.

Until very recently, intermolecular C–H insertion with donor/acceptor rhodium carbenes had been conducted almost exclusively with $Rh_2(DOSP)_4$. The factors

influencing selectivity in these reactions has been reviewed.[36] Because of the high degree of hydride transfer character involved in C–H insertion reactions, the electronic nature of the C–H bond is important. Those best able to stabilize a carbocation are most reactive (Figure 1.8). Therefore, in an electronic sense, the order of reactivity from most to least reactive is tertiary > secondary > primary. However, rhodium-carbene complexes are sterically demanding. Therefore, the steric environment of the C–H bond is also important, and from this perspective, the order of reactivity is primary > secondary > tertiary.

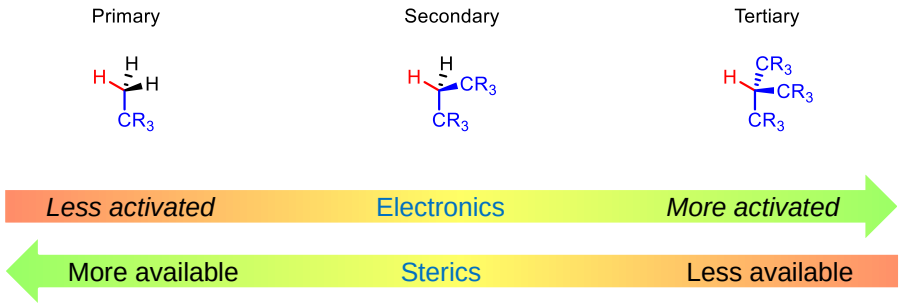


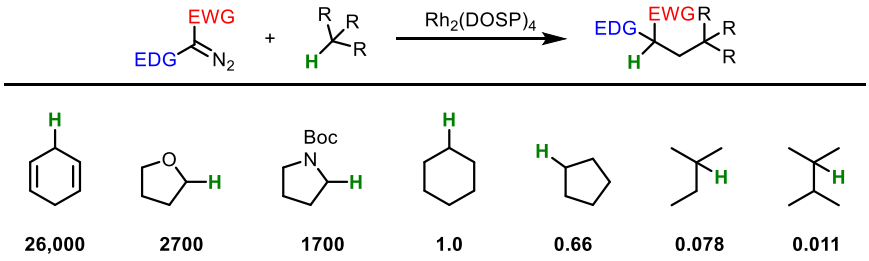

**Figure 1.8** Electronic vs steric requirements of C–H bonds

As a result, C–H insertion with $Rh_2(DOSP)_4$ has typically taken place preferentially at secondary sites. These C–H bonds are believed to provide the best balance of electronic activation without being too sterically crowded. However, this can be changed by altering the steric environment of the catalyst. A demonstration of this concept can be seen with the use of the bulky triarylcyclopropane carboxylate catalysts to effect primary C–H functionalization.[19] This topic will be discussed in more detail in Chapter 4.

Not surprisingly, functional groups that can stabilize a carbocation enhance rhodium-carbene C–H functionalization as well. Relative rates of insertion into various C–H

bonds have been determined by competition studies (Scheme 1.4).[37] The effect of a vinyl or heteroatom group α to the C–H bond can be clearly seen. Additionally, the steric effect can also be seen when comparing cyclohexane and cyclopentane to 2-methylbutane and 2,3-dimethylbutane. Functionalization of the less electronically activated secondary C–H bonds of the cyclic hydrocarbons is preferred to the more electronically activated tertiary positions of the acyclic compounds, due to steric reasons.

**Scheme 1.4** Relative rates of C–H insertion with donor/acceptor rhodium carbenes




## 1.4 Conclusion

Despite a large volume of work with donor/acceptor rhodium carbenes, reactions of these intermediates have continued to evolve. The ever-increasing demand for specific, selective, and cost-effective transformations drives the interest in continuing to expand the chemistry. In the following chapters, I present my work with donor/acceptor rhodium-carbenes. Some of the challenges this work attempts to address include:

*1) Applying known and established reactions in new and complex settings*. Methodology studies often focus on showcasing a new reaction with substrates that work well. However, using natural products as inspiration for challenging those reactions further is of importance to discovering/expanding the true scope of a reaction. An

application of the Davies group's [4+3] cycloaddition methodology to the total synthesis of a natural product is investigated.

*2) Developing new methods for the preparation of important synthetic building blocks.* Many important synthetic building blocks can be prepared by a number of available methods. But with increasing importance and variety of uses comes an increased need for new, varied methods for their synthesis, however specific those might be. An application of C–H functionalization to the synthesis of *Z*-allylsilanes is discussed.

*3) Expanding the scope of site-selective C–H functionalization.* Despite the large amount of work with C–H functionalization, challenges remain in terms of selectivity. As mentioned, secondary C–H bonds are typically preferred. These challenges are partially addressed by utilization of a bulky new class of catalysts for selective primary C–H functionalization, together with a new robust class of diazo reagents.

*4) Expanding the scope of diazo reagents available for cyclopropanation*. As the cyclopropanation of olefins with donor/acceptor rhodium carbenes has become well-established, improving the scope of this transformation relative to the ester group of the diazo could be important to its continued adoption by the synthetic community. A brief study of asymmetric cyclopropanation with two new ester groups is discussed.

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# Chapter 2 – Reactions of Donor/Acceptor Rhodium-Carbenes with Electron-Deficient Dienes and Alkenes

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## Contents

# 2.1 Towards a Total Synthesis of Pseudolaric Acid

## 2.1.1 Introduction

### 2.1.1.1 Pseudolaric Acid B

Pseudolaric Acid B (**2.2**) is a member of a class of diterpenes, the most plentiful of which are Pseudolaric acids A and B (Figure 2.1). These natural products are harvested from the roots, or bark near the roots, of the golden larch, or *Pseudolarix kaempferi*.[1] In traditional Chinese medicine, the plant material was processed and dried to give a crude drug known as *tujingpi*, which was used to treat fungal skin infections. Not surprisingly, when *tujingpi* was analyzed, the main components, **2.1** and **2.2**, were found to have anti-fungal properties. All together, the natural products in this family boast a variety of anti-fungal, anti-fertility, cytotoxic, and anti-angiogenic properties.


Pseudolaric Acid A
**2.1**

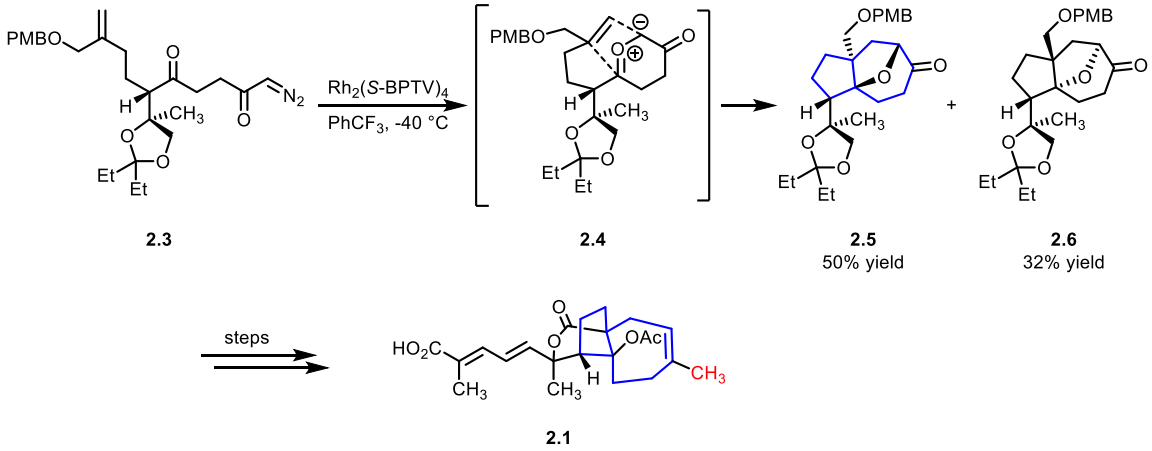
Pseudolaric Acid B
**2.2**

**Figure 2.1** Pseudolaric Acid B, with the core highlighted in blue

Key structural features include a congested tri-cyclic core, and an interesting dienoic acid side chain. The intriguing structure has caused Pseudolaric acids A and B to become the objects of much synthetic interest.[1–7] The first completed total synthesis was reported in 2006 by Chiu and coworkers, of Pseudolaric acid A.[4] This synthesis relied on a carbene cyclization-cycloaddition cascade (CCCC) reaction to install the perhydroazulene core (Scheme 2.1). In the event, linear precursor **2.3** was allowed to be decomposed by $Rh_2$(*S*-BPTV)$_4$, giving an intermediate rhodium carbene. The carbene was trapped by the pendant ketone, forming a 1,3-dipole intermediate, **2.4**, which then

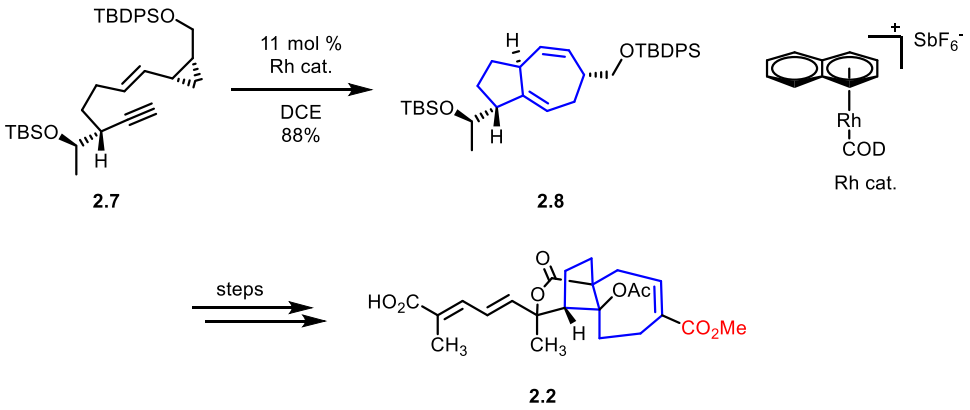
participated in a 1,3-dipolar cycloaddition with the nearby alkene to give diastereomers **2.5** and **2.6** in 50% and 32% yield, respectively. Though somewhat low selectivity was achieved in this step, it generated a substantial amount of complexity, forming two of the three rings contained within the natural product. The correct diastereomer, **2.5**, was then taken on to complete the total synthesis.

**Scheme 2.1** Key CCCC Reaction in Chiu's Synthesis of **2.1**




In 2007, Trost reported the first total synthesis of Pseudolaric Acid B using an asymmetric [5+2] cycloaddition as the key step (Scheme 2.2).[3] As in Chiu's synthesis, Trost began with a linear precursor, **2.7**. This participated in a [5+2] cycloaddition between the vinyl cyclopropane and the alkyne. The product **2.8** was then converted to the natural product.

**Scheme 2.2** Key [5+2] Cycloaddition in Trost's Synthesis of **2.2**

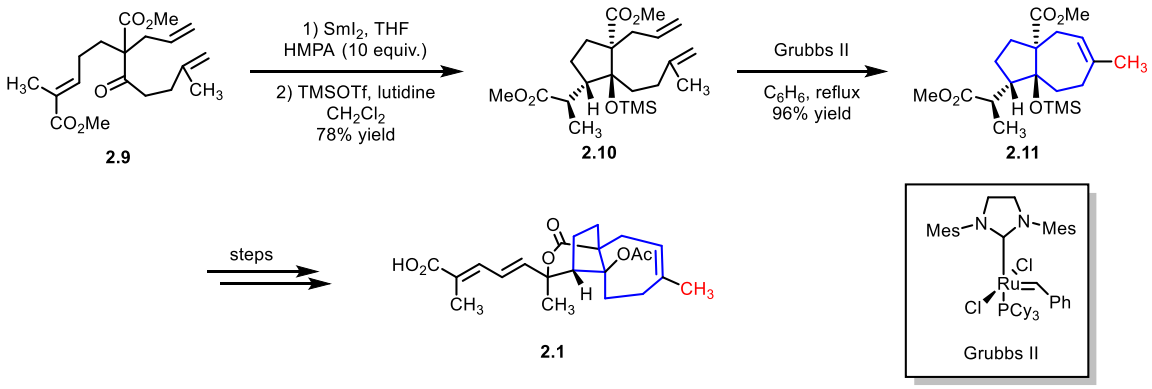



**2.7** **2.8** **2.2**

Despite the accomplishment of preparing Pseudolaric Acid B, and the impressive cycloaddition to generate the core, the rest of the Trost synthesis is arguably cumbersome. Only one of the two stereocenters generated during the [5+2] cycloaddition is present in the natural product itself. This stereocenter is ultimately destroyed and remade to install the quaternary chiral center at the same position. The dienoic acid side chain of **2.2** is also challenging to install, requiring several synthetic manipulations in the end game of the molecule.

Another synthesis of Pseudolaric acid A was reported in 2011, in this case as a racemate.[8] The key steps in this synthesis were a $SmI_2$ mediated cyclization followed by a ring-closing metathesis reaction to prepare the core of the natural product (Scheme 2.3). Perhaps most impressively, all four stereocenters were set in the cyclization reaction, as **2.9** was converted to **2.10** in good yield.

**Scheme 2.3** Two Key Steps in a Total Synthesis of **2.1**



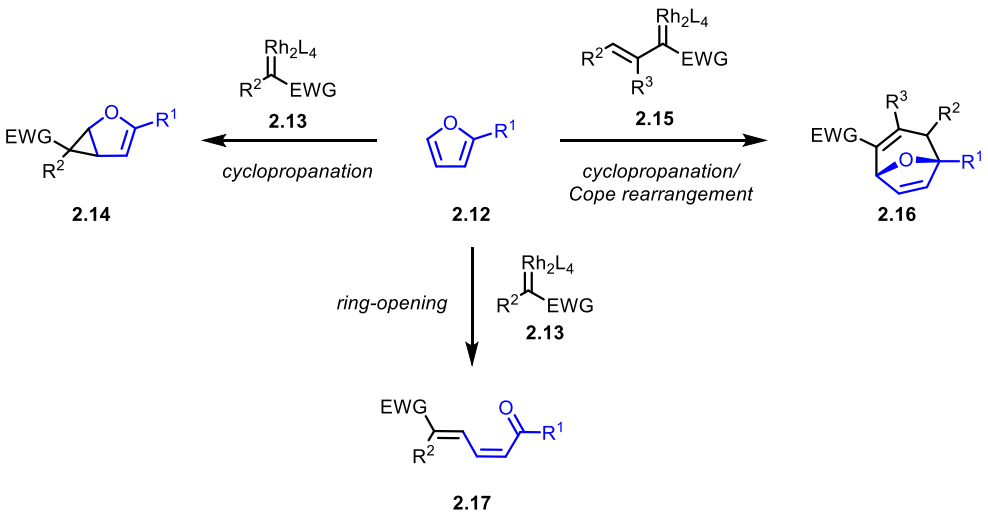

It is interesting to note that in each of these total syntheses, the dienoic acid side chain of the natural products was installed at or near the end of the synthesis. In each case, this seemingly small task was nothing but, requiring a tedium of small manipulations in the end game. Clearly this portion of the molecule has been a major challenge in preparing Pseudolaric acids A and B. A strategy that could avoid such an endgame, and replace it with one or two simple steps, would add elegance to the overall synthetic story of the Pseudolaric acids.

### 2.1.1.2 Reactions of Carbenes with Furans

Furans, as electron-rich heterocycles, react easily with electrophilic rhodium-carbenes. The nature of the products depends on the structure of both the carbene and the furan.[9,10] Several examples are shown in Scheme 2.4. Furans undergo cyclopropanation reactions with all types of carbenes **2.13** to generate furanylcyclopropane derivatives **2.14**.[11–13] One special case of cyclopropanation involves the use of vinylcarbene compounds, **2.15**.[14–16] After initial cyclopropanation, the divinylcyclopropane that is formed undergoes a Cope rearrangement to give cycloheptadienes **2.16** with predictable stereochemistry. This formal [4+3] cycloaddition will be discussed in more detail later,

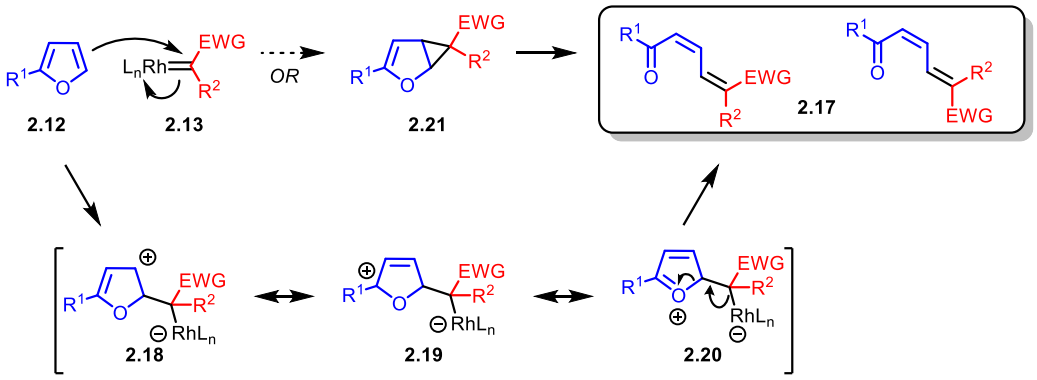
but for now it is sufficient to mention that furans are generally excellent substrates for this reaction.

**Scheme 2.4** Reactions of carbenes with furans



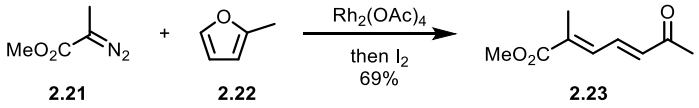

The ring-opening reaction of furans to give dienes **2.17**, however, often competes with cyclopropanation and cycloaddition pathways. This ring-opening pathway is favored with the incorporation of electron-donating groups into the furan, and disfavored with electron-withdrawing groups. It has been proposed that the diene products arise from a zwitterionic intermediate (Scheme 2.5, **2.18**-**2.20**) which collapses with loss of rhodium to form the diene products **2.17**.[9,11,13] Clearly an electron-donating substituent ($R^1$) on the furan would stabilize this intermediate. Indeed, when $R^1$ = OMe, only products arising from ring-opening are observed.[10] Nevertheless, a cyclopropane intermediate cannot be ruled out, as it has been observed that furanylcyclopropanes **2.21** can rearrange upon standing to give diene products as well.[11]

**Scheme 2.5** Possible mechanisms for ring-opening of furans




One important feature of the ring-opening reaction is the geometry of the double bonds. The alkene that was once a part of the furan is formed with the *Z* configuration in the final product due to the constraints imposed by the five-membered ring. The geometry of the second double bond is presumably related instead to the orientation of the atoms of **2.20** during the final elimination process.

Based on this picture, it is not surprising that an alkyl substituted furan also gives ring-opened products (Eq. 2.1). Wenkert and co-workers found that diazo compound **2.21**, in the presence of rhodium (II) acetate, caused the ring-opening of 2-methylfuran (**2.22**). The *Z* alkene was isomerized to form the *E* by treatment with iodine, giving the final product **2.23** in 69% yield.[17] It should be noted that in this reaction the furan **2.22** was used as solvent.



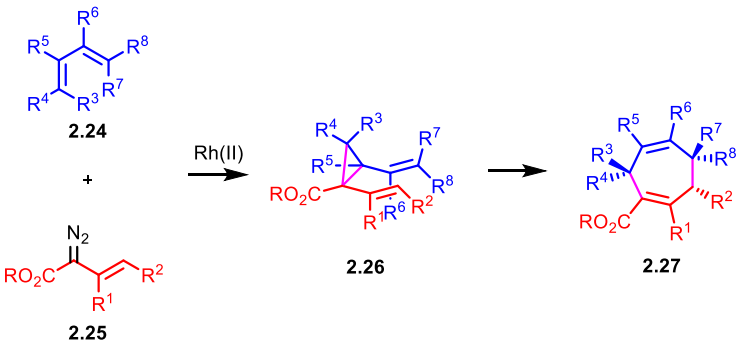

(Eq. 2.1)

### 2.1.1.3 The Cyclopropanation/Cope Rearrangement

Vinyl carbenes are known to undergo [4+3] cycloaddition reactions with dienes to give highly functionalized cycloheptadienes (Scheme 2.6).[14–16,18,19] With the use of chiral catalysts, this process can be highly enantioselective.[20] The reaction proceeds by a

tandem cyclopropanation/Cope rearrangement to give the [4+3] products **2.27**. This method is successful since rhodium carbenes are capable of undergoing diastereoselective cyclopropanations to give *cis*-divinylcyclopropane intermediates (**2.26**). The *cis* orientation is important, since only it can undergo the Cope rearrangement, while the *trans* isomer cannot. Additionally, due to the structural limitations of the cyclopropane, the rearrangement occurs in a stereodefined manner *via* a boat transition state.[21,22] As a result, the stereochemical outcome of the products **2.27** is predictable.

**Scheme 2.6** Cyclopropanation/Cope rearrangement

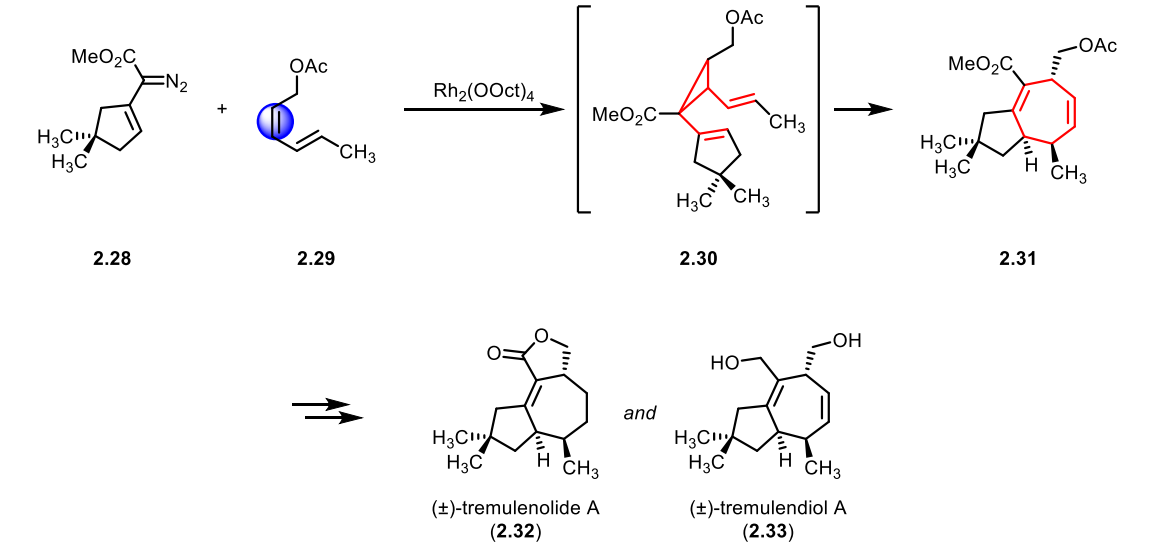


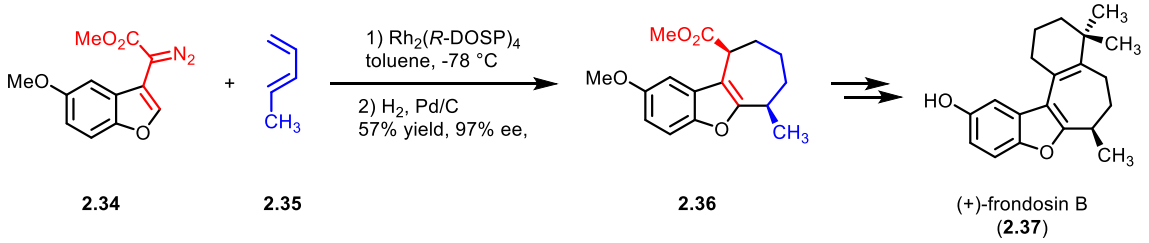

Clearly, the efficient, controlled, and predictable preparation of seven-membered rings is enormously powerful. The method has been used in multiple total syntheses,[23] two of which are shown in Scheme 2.7. The first is a total synthesis of two natural products, (±)-tremulenolide A (**2.32**) and (±)-tremulendiol A (**2.33**).[24] This application of the [4+3] cycloaddition is an impressive example of the regiocontrol that is possible in the cyclopropanation step. In the presence of rhodium(II) octanoate, diazo **2.28** reacts selectively with the *Z* olefin of **2.29** over the *E*, to give the *cis*-divinylcyclopropane **2.30**. This intermediate then undergoes a Cope rearrangement through the boat transition state as drawn to give the seven-membered ring **2.31** with the appropriate relative stereochemistry.

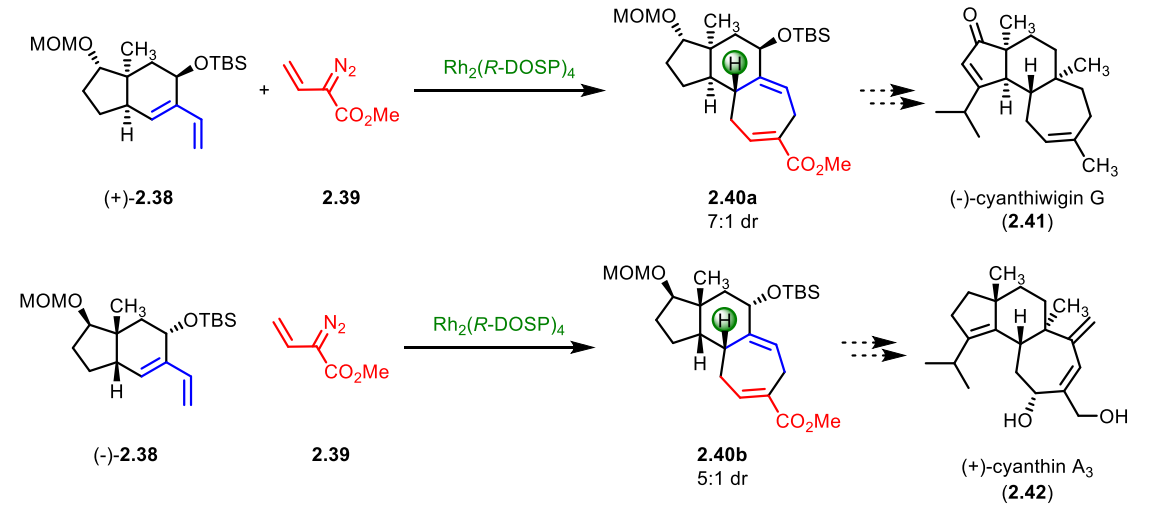
A second example highlights the range of vinyldiazo compounds that can participate in this chemistry. In this formal synthesis of (+)-frondosin B,[25] the benzofuranyl diazo **2.34** was allowed to react with diene **2.35** in the presence of $Rh_2$(*R*-DOSP)$_4$ to give the product resulting from a cyclopropanation/Cope rearrangement. Subsequent hydrogenation gave **2.36**, which was converted to an intermediate that has previously been used to prepare (+)-frondosin B.[26]

A final example comes from Sarpong, with an entry into the cyanthane and cyanthiwigin diterpenes.[27] This highlights the power of the rhodium catalyst to control the stereochemistry of the product despite using a chiral substrate. When using (+)-**2.38**, and $Rh_2$(*R*-DOSP)$_4$, the cycloaddition product **2.40a** was formed, with a 7:1 dr at the newly formed chiral center (green). With the opposite enantiomer of the substrate, but the same catalyst, a different diastereomer was formed, **2.40b**, with a 5:1 dr. These products were considered potential precursors to (–)-cyanthiwigin G (**2.41**) and (+)-cyanthin $A_3$ (**2.42**).

**Scheme 2.7** The [4+3] cycloaddition in synthetic settings

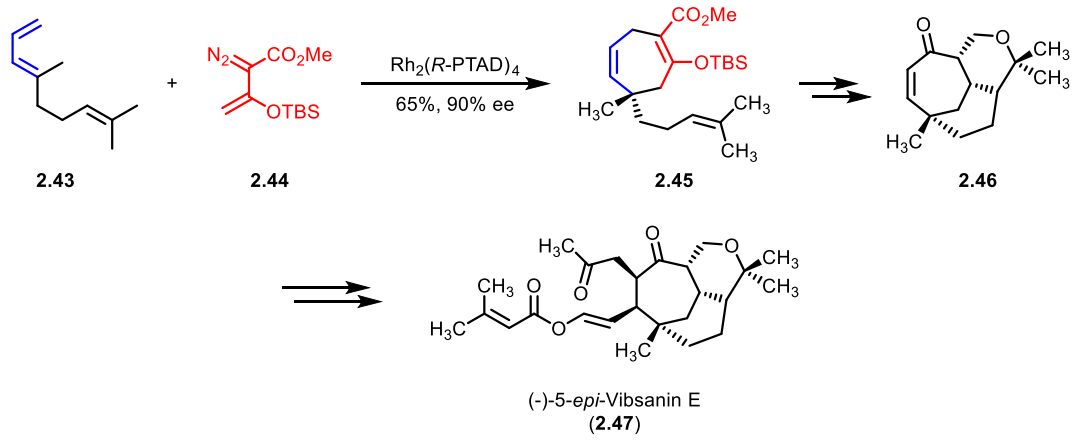


Another important example comes from the recent synthesis of (–)-5-*epi*-Vibsanin E (**2.47**).[28] In this synthesis, the asymmetric [4+3] cycloaddition was used to construct the core of the natural product (Scheme 2.8). When diene **2.43** was allowed to react with diazo **2.44**, using $Rh_2$(*R*-PTAD)$_4$ as a catalyst, the cycloheptadiene **2.45** was produced in 65% yield and 90% ee. This was transformed into intermediate **2.46** in 9 steps, which was then used to prepare **2.47**.

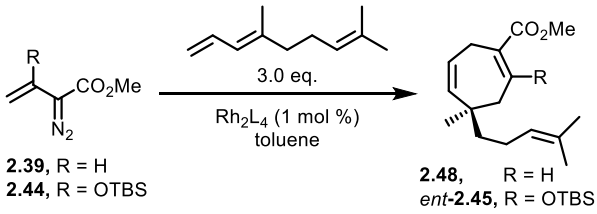
**Scheme 2.8** The [4+3] as a key step in the synthesis of (–)-5-*epi*-Vibsanin E




This study revealed an important trend with respect to catalyst and diazo combinations required for high enantioselectivity in the [4+3] cycloaddition (Table 2.1). Both the unsubtituted vinyl diazo **2.39** as well as the siloxyvinyl diazo **2.44** were evaluated in this reaction. It was found that with **2.39**, the enantioselectivity in the reaction was generally poor regardless of the catalyst used (entries 1 and 2). Interestingly, the siloxyvinyl diazo **2.44** was especially selective with $Rh_2$(*S*-PTAD)$_4$ as the catalyst, generally forming *ent*-**2.45** in greater than 90% ee. This is in stark contrast to the reaction with $Rh_2$(*S*-DOSP)$_4$, in which case *ent*-**2.45** is formed in only 45% ee. The excellent compatibility of **2.44** with $Rh_2$(*S*-PTAD)$_4$ for cycloaddition was

demonstrated with a range of other acyclic dienes and has been used previously for asymmetric synthesis of tropanes by the [4+3] cycloaddition method as well.[19]

**Table 2.1** Effect of vinyl group substitution and catalyst on enantioselectivity




**2.39**, R = H
**2.44**, R = OTBS

**2.48**, R = H
*ent*-**2.45**, R = OTBS

| entry | $Rh_2L_4$ | R | temp (°C) | yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | $Rh_2$(*S*-DOSP)$_4$ | H | rt | 62 | 50 |
| 2 | $Rh_2$(*S*-PTAD)$_4$ | H | rt | 67 | 40 |
| 3 | $Rh_2$(*S*-DOSP)$_4$ | OTBS | -78 to rt | 55 | 45 |
| 4 | $Rh_2$(*S*-PTAD)$_4$ | OTBS | -20 to -15 | 55 | 91 |
| 5 | $Rh_2$(*S*-PTAD)$_4$ | OTBS | -10 | 67 | 90 |
| 6 | $Rh_2$(*S*-PTAD)$_4$ | OTBS | 0 to 5 | 70 | 87 |

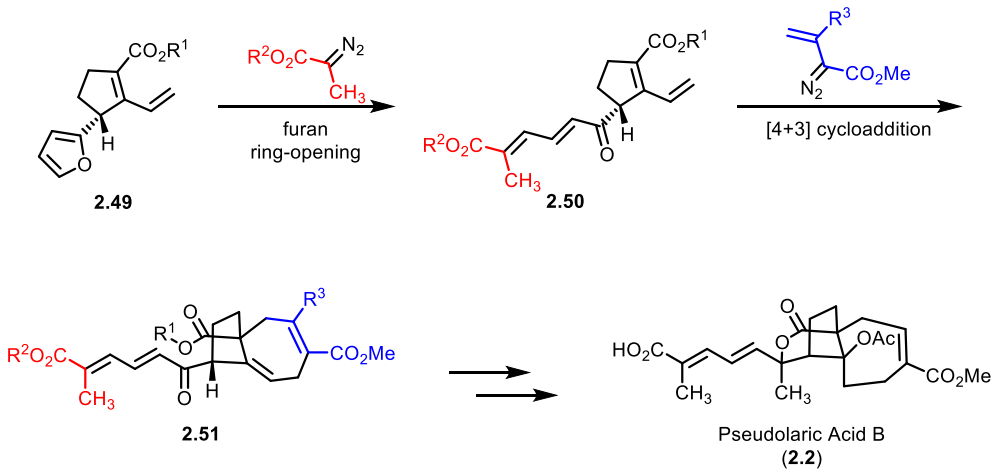
The weakness of using siloxyvinyl diazo **2.44** in the context of a total synthesis of **2.47** is that it requires a three-step removal of the OTBS group. Still, this is a minor inconvenience considering that, with the unsubstituted diazo **2.39**, the reaction is not yet possible with high levels of asymmetric induction. One could imagine a scenario, however, in which the included OTBS group afforded by the use of **2.44** is desirable for a total synthesis. Overall, this system has the advantage of a great deal of flexibility.

### 2.1.1.4 A Retrosynthetic Route to Pseudolaric Acid B

When I began my work in the Davies group, a fellow group member, Yajing Lian, had proposed a route for the synthesis of Pseudolaric Acid B (**2.2**). The synthesis would rely on both a furan ring-opening reaction as well as a [4+3] cycloaddition reaction to install the majority of the natural product's functionality (Scheme 2.9). First, a chiral furan precursor **2.49** would be subjected to the furan ring-opening reaction to give the

unraveled product **2.50**. It would be expected that the electron-rich furan of **2.49** would react preferentially over the electron-deficient diene. Second, this diene would participate in a [4+3] cycloaddition reaction to give an advanced intermediate **2.51**. It was then proposed that this intermediate could be converted to the natural product with only a few additional synthetic manipulations.

**Scheme 2.9** Synthetic Plan for Pseudolaric Acid B – Proposed by Dr. Yajing Lian

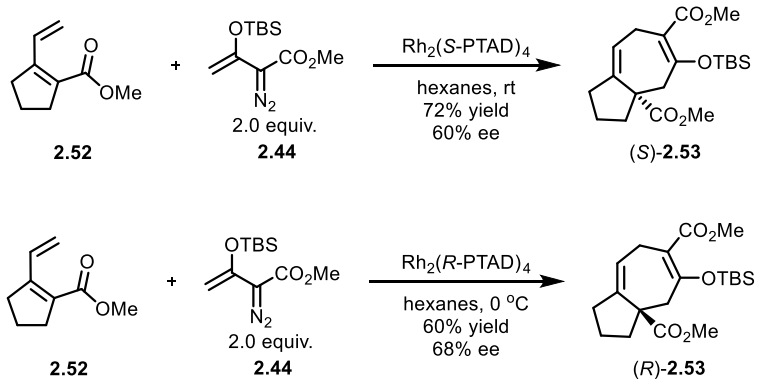



Before the synthesis could be pursued, a few preliminary studies were required. First, though 2-methylfuran has been unraveled and isomerized to give a diene with alkene stereochemistry identical to **2.50** (see **2.23**, eq. 2.1), this reaction was completed with the furan substrate as solvent. Better conditions would need to be found, since the use of a complex substrate such as **2.49** as solvent would be impractical. Second, cyclopropanation reactions of electrophilic rhodium-carbenes are typically carried out with electron-rich alkenes. The practicality of the [4+3] approach proposed in Scheme **2.9** using an electron-deficient diene would need to be explored.

Dr. Yajing Lian explored the cycloaddition approach with a model substrate, **2.52** (Scheme 2.10). Using the siloxyvinyl diazo **2.44** together with $Rh_2(PTAD)_4$, the

cycloaddition reaction took place in good yield. At room temperature, the product was formed in 60% ee, and at 0 °C it was formed in 68% ee. This model study gave credence to a [4+3] cycloaddition strategy for the synthesis of Pseudolaric Acid B.

**Scheme 2.10** [4+3] Cycloaddition model study – Conducted by Dr. Yajing Lian



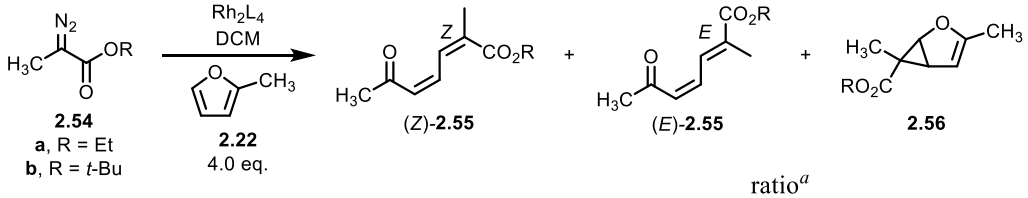

## 2.1.2 Results and Discussion

### 2.1.2.1 Furan Ring-Opening Model Study

When my work on this project began, it remained to be seen if an alkyl-substituted furan could undergo the ring-opening reaction to form the diene selectively with the appropriate stereochemistry, and whether it could be done without a large excess of the furan. To this end, a brief study of the furan system was undertaken (Table 2.2). Using 4.0 equiv. of 2-methylfuran (**2.22**), the reaction with diazopropionate **2.54** was examined with a variety of catalysts, and with two different esters. Considering the proposed mechanism for the ring-opening (Scheme 2.5), it was envisioned that an electron-deficient catalyst would enhance the zwitterionic pathway leading to the desired ring-opening product. The reaction was therefore run using $Rh_2(TFA)_4$ as the catalyst. With this catalyst, essentially only **2.55** was formed, as a 1:1 mixture of double bond isomers (entry 1). Changing to a *t*-Bu ester improved the ratio slightly towards the desired *E*-**2.55**

(entry 2), but the reaction was still relatively unselective. When using a more electron-rich catalyst, $Rh_2(OAc)_4$ (entry 3), **2.55** was formed as only the *E* isomer, but now the cyclopropane product **2.56** was the major product. It was known that this product could be isomerized to the desired product with iodine,[11] meaning the use of $Rh_2(OAc)_4$ could be a reasonable solution, if other catalysts failed to give *E*-**2.55** selectively. Again, the *t*-Bu ester favorably changed the ratio, but only moderately (entry 4). It seemed that a catalyst with an electronic nature between $Rh_2(TFA)_4$ and $Rh_2(OAc)_4$ was necessary. Thus, two mixed catalysts were used (entries 5 and 6), but neither gave cleanly the *E* product. Finally, the chiral catalyst $Rh_2$(*S*-DOSP)$_4$ was used (entry 7), and in this case the desired product was formed as the major product. Unfortunately, the cyclopropane was still a major byproduct.

**Table 2.2** Model study for furan ring-opening reaction




**2.54**
**a**, R = Et
**b**, R = *t*-Bu

**2.22**
4.0 eq.

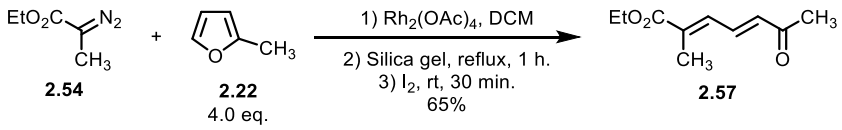
(*Z*)-**2.55** + (*E*)-**2.55** + **2.56**

| | | | ratio[a] | | |
|---|---|---|---|---|---|
| entry | catalyst | R | (*Z*)-**2.55** | (*E*)-**2.55** | **2.56** |
| 1 | $Rh_2(TFA)_4$ | Et | 1.1 | 1.0 | trace |
| 2 | $Rh_2(TFA)_4$ | *t*-Bu | 0.6 | 1.0 | - |
| 3 | $Rh_2(OAc)_4$ | Et | - | 1.0 | 2.2 |
| 4 | $Rh_2(OAc)_4$ | *t*-Bu | - | 1.0 | 1.9 |
| 5 | $Rh_2(TFA)_3OAc$ | *t*-Bu | 0.6 | 1.0 | 0.4 |
| 6 | $Rh_2(OAc)_3TFA$ | *t*-Bu | - | 1.0 | 1.4 |
| 7 | $Rh_2$(*S*-DOSP)$_4$ | *t*-Bu | - | 1.0 | 0.7 |

[a]Ratio determined by $^1$H NMR analysis of the crude reaction mixture.

It was then discovered that **2.56** rearranged upon treatment with silica gel to give *E*-**2.55**. Thus, a reaction was conducted (Eq. 2.2) in which **2.54** was added dropwise to a solution of 2-methylfuran (**2.22**) and $Rh_2(OAc)_4$, followed by heating at reflux with silica

gel, and stirring at room temperature with iodine. This gave **2.57** in 65% yield. Comfortable that the desired product **2.57** could be prepared without large excess of the furan, pursuit of the total synthesis began.

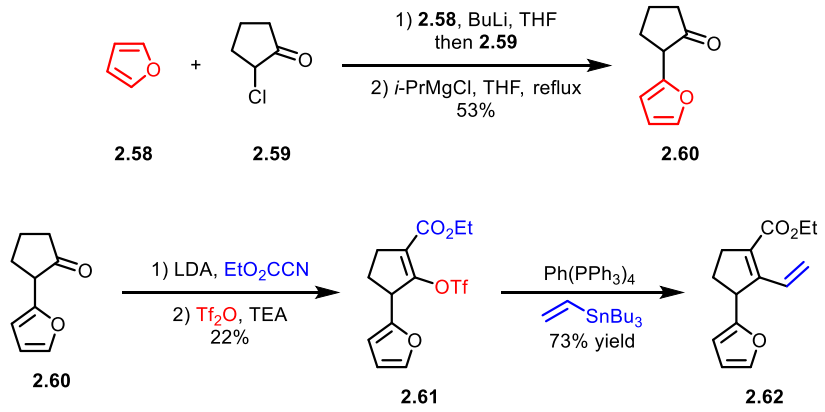



(Eq. 2.2)

### 2.1.2.2 First Generation Approach

In Dr. Yajing Lian's retrosynthetic approach (Scheme 2.9), it was envisioned that the furan substrate **2.49** would be prepared asymmetrically for the two subsequent carbene reactions. For the initial exploration of the total synthesis, however, the racemic substrate **2.62** was prepared to investigate the ring-opening and [4+3] cycloaddition reactions. The necessary ketone **2.60** for the synthesis of this substrate was prepared using a literature reaction for the related 2-furanylcyclohexanone (Scheme 2.11).[29] Thus 2-chlorocyclopentanone (**2.59**) was treated with 2-lithiofuran to form the carbonyl addition product. A subsequent rearrangement promoted by *i*-PrMgCl gave the ketone **2.60**.

**Scheme 2.11** Preparation of the racemic diene **2.62**

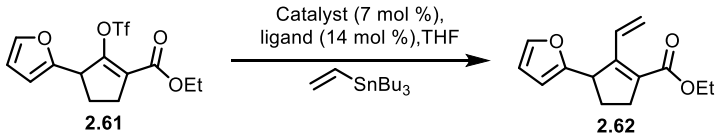



With a scalable preparation of **2.60**, attention was turned to preparation of the diene **2.62**. Treatment of the lithium enolate of **2.60** with ethylcyanoformate[30] installed the

ester, which was subsequently converted to the vinyl triflate **2.61** with triflic anhydride and triethylamine. Finally, a Stille coupling with tributyl(vinyl)stannane gave **2.62** in 73% yield.

Some additional notes regarding these reactions: First, the low yield (22%) in preparing **2.61** from the ketone **2.60** is attributed to poor regioselectivity in the LDA deprotonation of **2.60**. If the enolate is trapped with TMSCl instead of ethylcyanoformate, a mixture of silyl enol ethers can be observed by $^1$H NMR. Second, the Stille coupling required some optimization (Table 2.3). Good yields were obtained by modifying the catalyst, temperature, reaction time, and equivalents of the organostannane.

**Table 2.3** Optimization of Stille coupling




**2.61** **2.62**

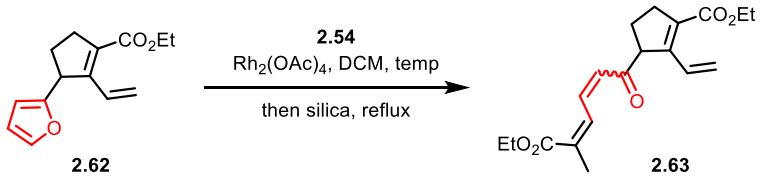
| Entry | catalyst | ligand | organostannane (equiv.) | temp (°C) | time (h) | yield (%) |
|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $PPh_3$ | 1.2 | 55 | 24 | 41 |
| 2[a] | $Pd(OAc)_2$ | $PPh_3$ | 1.2 | 55 | 7 | 42 |
| 3 | $Pd(OAc)_2$ | $PPh_3$ | 1.2 | 65 | 8 | 51 |
| 4[b] | $Pd(OAc)_2$ | $PPh_3$ | 1.2 | 65-55 | 22 | 66 |
| 5[b] | $Pd(PPh_3)_4$ | - | 1.5 | 70 | 14 | 73 |

[a]An additional 7 % $Pd(OAc)_2$, and 14 % $PPh_3$ were added after 1 hour to counteract formation of insoluble Pd black. [b]RM was degassed prior to addition of organostannane.

With diene **2.62** in hand, the ring-opening of the furan was investigated (Table 2.4). Thus, **2.62** was treated with ethy 2-diazopropanoate (**2.54**), and the crude mixture was heated at reflux in the presence of silica gel to cause rearrangement of the (presumed) furanyl cyclopropane intermediate. Under these conditions, the disubstituted alkene

partially rearranged to the *E* isomer, and a mixture of isomers of **2.63** was isolated. Using 2.5 equivalents of the diazo, and conducting the reaction at reflux resulted in a 52% isolated yield of **2.63**.

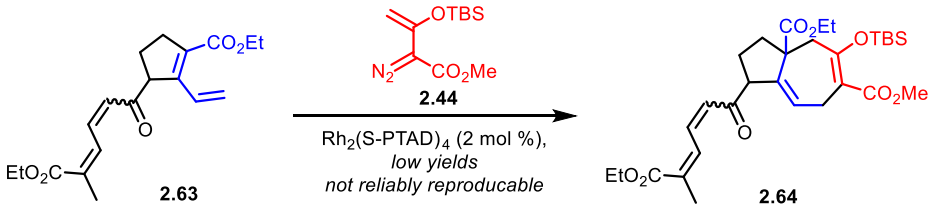
**Table 2.4** Some optimization of the ring-opening reaction




| entry | diazo (equiv.) | add. time (h) | temp (°C) | yield (%)[a] |
|---|---|---|---|---|
| 1 | 4.0 | 1.5 | rt | 39 |
| 2 | 5.0 | 2 | rt | 41 |
| 3 | 2.5 | 2 | reflux (40) | 52 |

[a]Isolated yield of a mixture of isomers.

Rather than subjecting the mixture to iodine induced isomerization, this material was used directly to test the cycloaddition reaction. When **2.63** was subjected to conditions for the cycloaddition, using diazo **2.44** and $Rh_2$(*S*-PTAD)$_4$ as catalyst, though the product **2.64** was formed, yields were low, and the reaction was not reliably reproducible.



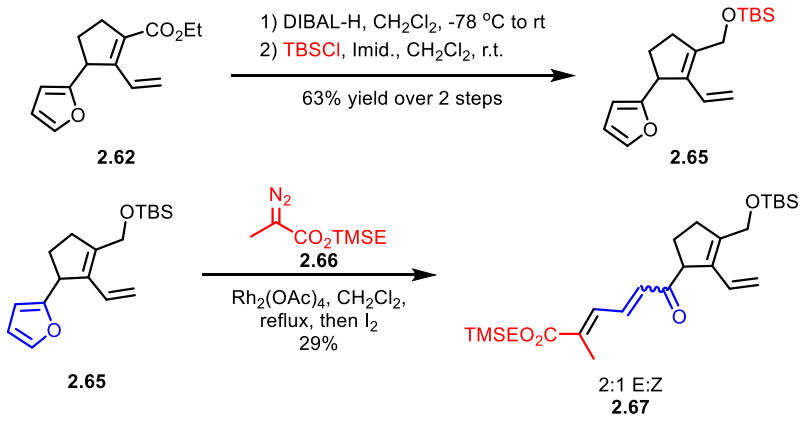

(Eq. 2.3)

This suggested that the alkene in **2.63** was less reactive than in the model system (**2.52**, Scheme 2.10), which is not surprising. The extra substituent of **2.63** (a bulky side-chain) would be expected to increase the steric congestion around the alkene of interest. Combined with the electron-deficient nature of the alkene, and the electron-rich nature of the diazo compound, this system does not seem to be well suited for a favorable reaction.

Therefore, two changes were made to the substrates to enhance the chances of a favorable cycloaddition reaction: 1) The withdrawing group on the diene for the [4+3] was reduced to a primary alcohol to make the diene more reactive; and 2) rather than the siloxyvinyl diazo **2.44**, the more reactive unsubstituted vinyl diazo **2.39** was used.

Scheme 2.12 shows the preparation of the substrates for this approach. The ester **2.62** was smoothly converted to the protected primary alcohol **2.65** in 63% yield over 2 steps. This new substrate was then used in the furan ring-opening reaction. Rather than ethyl 2-diazopropanote (**2.54**), the related 2-(trimethylsilyl)ethyl 2-diazopropanoate (**2.66**) was used. This would enable easy deprotection of this ester in the final stages of the synthesis by treatment with fluoride without affecting the other esters in the natural product. With $Rh_2(OAc)_4$ and **2.66** in DCM at reflux, followed by stirring with iodine, the unraveled product **2.67** was isolated in 29% yield as a 2:1 mixture of isomers. It seemed the isomerization reaction with iodine was slow with this substrate, and the *Z*:*E* ratio was variable. (note: **2.66** is missing HRMS data – no identifiable fragmentation observed).

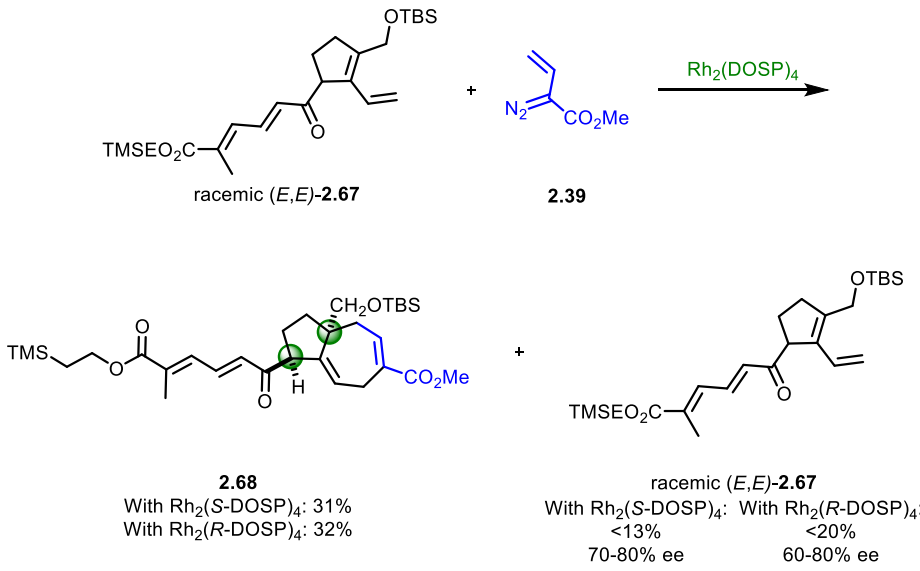
**Scheme 2.12** Preparation of a new substrate for the [4+3] cycloaddition




Instead of treating the crude mixture with iodine, the other product that is formed in the reaction (presumably the furanylcyclopropane) could be isolated and treated with

iodine. In this manner, a small amount of (*E*,*E*)-**2.67** could be isolated cleanly for characterization and for testing in the cycloaddition reaction with **2.39**. When (*E*,*E*)-**2.67** was allowed to react with **2.39** in the presence of $Rh_2(DOSP)_4$, the cycloadduct **2.68** was indeed formed in 31-32% yield. Interestingly, this product was formed as a single diastereomer. When the starting material **2.67** was isolated from the reaction mixture, a preliminary chiral HPLC analysis indicated that it may have been enantioenriched (the product was not clean, possibly because the tetrasubstituted double bond of **2.67** isomerized during isolation). Together with the observation that a single diastereomer of **2.68** was formed, these results suggested that a kinetic resolution had taken place. This was encouraging, since the use of an enantioenriched sample of **2.67** might not be necessary.

**Scheme 2.13** Testing the cycloaddition reaction of (*E*,*E*)-**2.67**




Unfortunately, however, NOE analysis of **2.68** indicated that the product was formed in the *anti* configuration (Figure 2.2). This is the opposite configuration of the two chiral centers necessary for a synthesis of Pseudolaric Acid B. Though there would likely be

complications arising from isomerization of the nearby alkene, an epimerization of the α-keto chiral center of **2.68** might be possible.

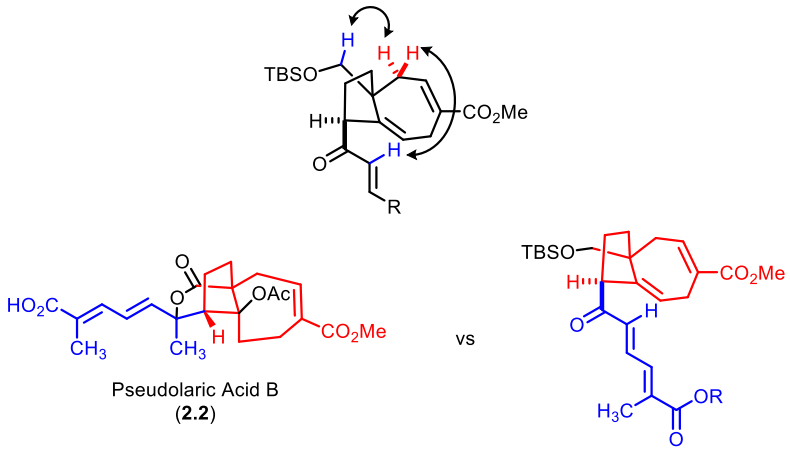


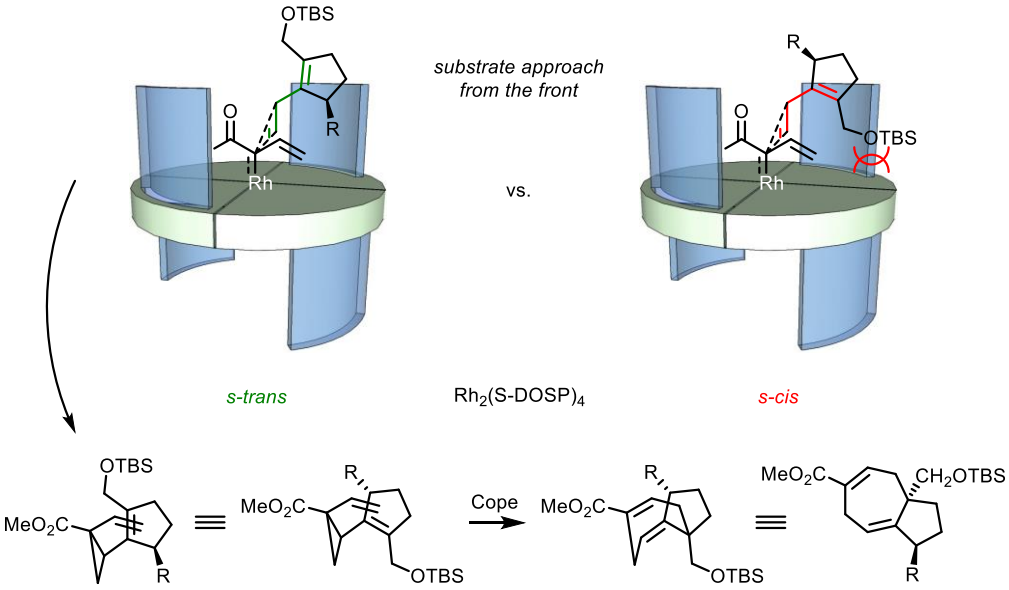

**Figure 2.2** NOE correlations for cycloaddition product **2.68**

### 2.1.2.3 Hypothesis for Diastereoselectivity and Model Study

Curious as to the origin of the diastereoselectivity, two possible transition states for the cycloaddition reaction were investigated (Scheme 2.14). Using the model for $Rh_2$(*S*-DOSP)$_4$ as a guide,[31] it was considered that the substrate could approach the carbene in either an *s-cis* or an *s-trans* orientation. In the *s-cis* orientation, the $sp^2$ hybridization of the diene carbon would force the OTBS group into the same space as the catalyst "wall" (represented by the central disk in the model). In this case, the chiral center of the substrate is pointing up and away from the catalyst and ligands. In the *s-trans* orientation, however, the chiral center is pointing down as drawn. With one enantiomer of this substrate the R group would point away from the rhodium catalyst/carbene, while with the other enantiomer, the R group would point towards the catalyst/carbene. Thus, the enantiomer as drawn in the *s-trans* orientation would be expected to be much more reactive than its opposite. If this transition state as drawn is carried through the

cyclopropane and the Cope rearrangement, it can be see that the relative orientation between the two chiral centers in the product is *anti*.

**Scheme 2.14** Two possible transition states in the diastereoselective [4+3] cycloaddition reaction

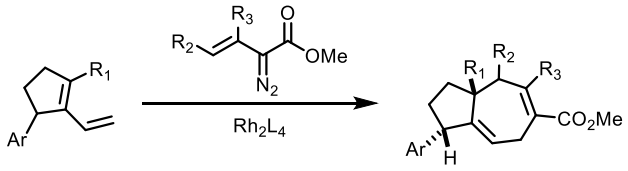



In considering this hypothetical model, it was noted that the current R group was a somewhat flexible diene chain. If this group were rigid and inflexible instead, it might be possible to force the substrate to react through the *s-cis* confirmation. In this case, the opposite enantiomer should be more reactive, and the reaction might lead to the formation of the correct diastereomer. It was envisioned that a bulky aryl group (such as a protected furan) might serve in this capacity. Thus, a brief study was conducted using phenyl groups as the "R" group (Table 2.5).

Five unique substrates were prepared (**2.69a-e**), with varying substitution patterns: a phenyl group (**2.69a**,**b**) and 4-*tert*-butylphenyl group (**2.69c-e**) as the rigid aryl groups, and ethyl ester (**a**,**c**), $CH_2OTBS$ (**b**,**d**), and H (**e**) as the groups attached to the diene (note: characterization data for **2.69c** is missing an IR spectrum). These substrates were

examined primarily with the unsubstituted vinyl diazo **2.39** (entries 1-4). In each of these cases, the cycloadducts **2.70a-d** were isolated in low yields, and the starting materials were not completely consumed. Very low levels of enantioinduction were measured for **2.70b** and **c**, and the starting materials were generally enriched slightly, but ee's were very low. With siloxyvinyl diazo **2.44** (entry 5), only a trace of the desired product was observed. Additionally, NOE experiments performed on products **2.70b** and **d** suggested that the products were formed as the *anti*-isomer, as in the previous system. These results demonstrate that using a bulky, rigid aryl group does not in fact switch the diastereoselectivity. Rather, it simply seems to add steric congestion to the already crowded reaction site.

**Table 2.5** Study on the [4+3] cycloaddition




**2.69a-e** **2.70a-g**

| entry | Ar | $R_1$ | $R_2$ | $R_3$ | SM/ product | $L_4$ | yield (%) | ee (%) | yield: recov. SM (% ee) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Ph | $CO_2Et$ | H | H | **a**/**a** | *S*-DOSP | 22 | - | 43 |
| 2 | Ph | $CH_2OTBS$ | H | H | **b**/**b** | *S*-DOSP | 35 | ~30 | 42 (16)[a] |
| 3 | *p*-*t*Bu-Ph | $CO_2Et$ | H | H | **c**/**c** | *S*-DOSP | 12 | 33 | 47 (14) |
| 4 | *p*-*t*Bu-Ph | $CH_2OTBS$ | H | H | **d**/**d** | *S*-DOSP | 16 | - | 42 (6)[a] |
| 5 | *p*-*t*Bu-Ph | $CH_2OTBS$ | H | OTBS | **d**/**e** | *S*-PTAD | trace | - | 23 |
| 6 | *p*-*t*Bu-Ph | $CH_2OTBS$ | Ph | H | **d**/**-** | *S*-DOSP | SM completely consumed | | |
| 7 | *p*-*t*Bu-Ph | H | H | H | **e**/**-** | *S*-DOSP | SM completely consumed | | |

[a]ee determined by desilylation of the recovered starting material followed by HPLC analysis.

It was interesting to find, then, that with methyl styryldiazoacetate (entry 6), the starting material was completely consumed, and the product seemed to be the [4+3] cycloadduct as a mixture of diastereomers. It is not clear why this diazo reacts cleanly with complete consumption of the starting material. One possible explanation is that the

styryl diazo is simply more robust than the unsubstituted vinyl **2.39**, which is known to react readily with itself to form trimers.[32] Additionally, the styryldiazoacetates are known to undergo highly enantioselective cyclopropanation reactions with $Rh_2$(*S*-DOSP)$_4$.[33] In the current system, good facial selectivity imparted by the catalyst regardless of the enantiomer of the substrate would result in a mixture of diastereomers.

One final experiment involved using the unsubstituted vinyl diazo and substrate **2.69e**, in which the bulky ester/silyl ether group is replaced with a small H atom (entry 7). In this case, the starting material was consumed completely, even with diazo **2.39**. The product appeared to be the [4+3] cycloadduct, formed as a 2:1 mixture of diastereomers. This result would be consistent with the proposed model for this reaction, since removing the bulky group attached to the diene would allow the substrate to approach in an *s-cis* fashion. If this is the case, clearly the effect of the R group (aryl group, in this case) is less pronounced, since both enantiomers reacted readily.

The results thus far suggested that the current approach was likely to be very challenging, since the site of reaction for the [4+3] cycloaddition was so sterically congested, and the preferred diastereomer was opposite to the natural product. With the difficulties associated with preparing **2.67** and using it in the [4+3] cycloaddition, it was decided a new approach would be pursued.

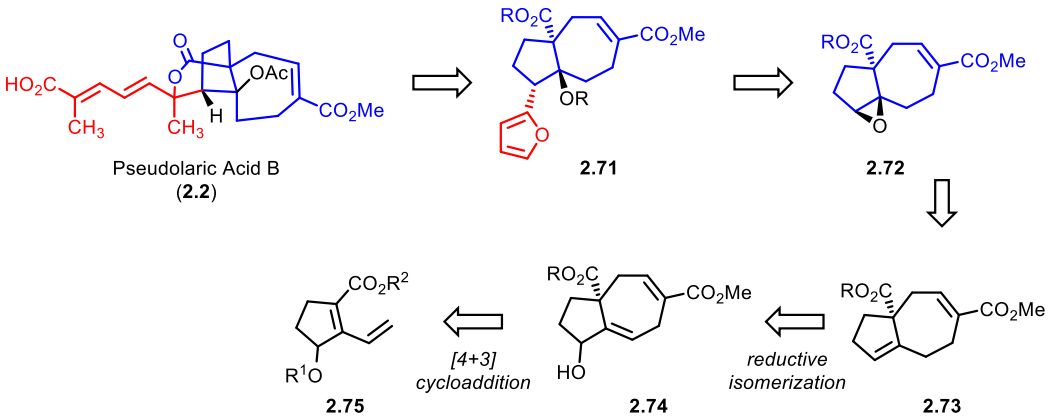
### 2.1.2.4 Second Generation Approach

A new synthetic approach was designed for Pseudolaric Acid B that would take into account the diastereoselectivity inherent to the [4+3] cycloaddition (Scheme 2.15). In this revised approach, it was envisioned that the furan ring-opening could occur late in the synthesis, with **2.71** as the substrate, followed by methyl addition and lactonization to

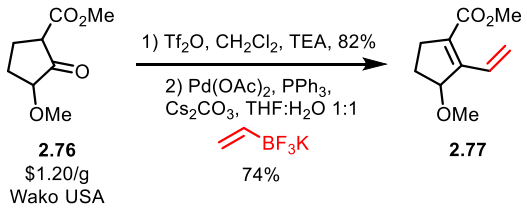
give the natural product. This intermediate could come from an epoxide **2.72** by addition of a furan nucleophile. The epoxide, in turn, would be prepared by epoxidation of alkene **2.73**, directed away from the ester on the bottom face of the molecule. It was expected that **2.73** could be prepared by reductive isomerization of **2.74**, which would be directly available by the [4+3] cycloaddition.

In this approach, the diastereoselectivity of the cycloaddition reaction would be irrelevant, since that chiral center would be destroyed during the reductive isomerization. Additionally, the chiral center created during the cycloaddition reaction would ultimately set the stereochemistry of 2 out of the 3 remaining stereocenters in the molecule.

**Scheme 2.15** Redesigned synthetic approach for Pseudolaric Acid B



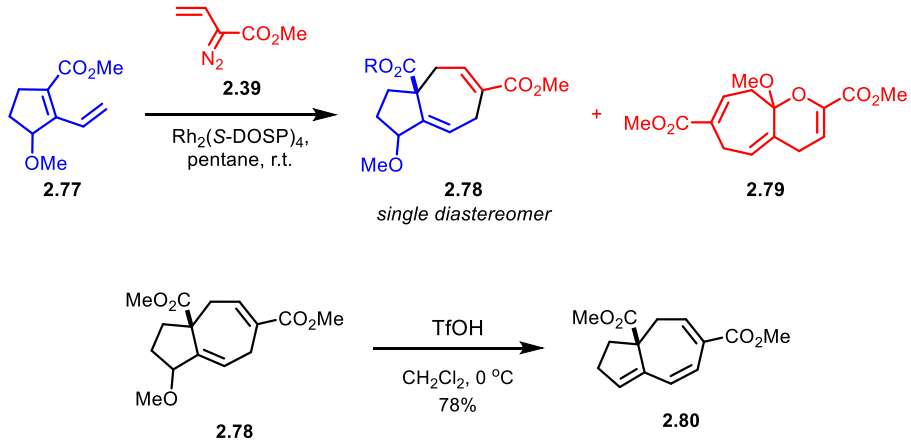

It was expected that the opening of epoxide **2.72** with a furan nucleophile would be somewhat challenging, since this compound is fairly sterically congested. However, it was also expected that the substrate could be easily accessed *via* only a few straightforward steps. Before investing in the preparation of **2.74**, however, a model system for the cycloaddition reaction was investigated to explore the general feasibility of the oxy substrate **2.75** (Eq. 2.4). Compound **2.76** was commercially available from Wako USA, and was used to quickly prepare a model substrate, **2.77**, in two steps.




(Eq. 2.4)

When this substrate was examined in the [4+3] cycloaddition reaction with diazo **2.39** (Scheme 2.16), the cycloadduct **2.78** was indeed formed, but was isolated together with compound **2.79**, also formed in the reaction.[32] However, when this mixture was treated with triflic acid in DCM, **2.78** was smoothly converted to triene **2.80**, which could be cleanly isolated in 78% yield.

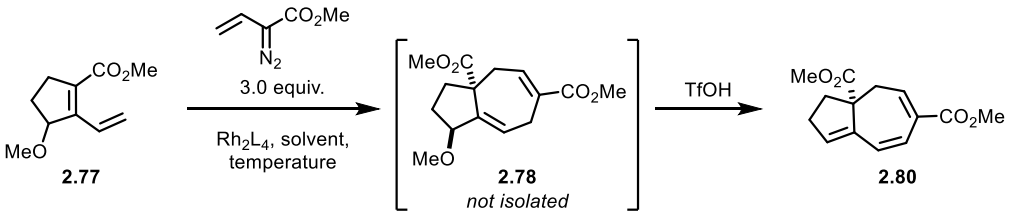
**Scheme 2.16** Initial exploration of the [4+3] cycloaddition with **2.77**




With a two-step procedure for isolation of **2.80**, the reaction of **2.77** with **2.39** was investigated under a variety of conditions (Table 2.6). In general, isolated yields and levels of enantioselectivity were low for **2.80**. The product could be isolated in up to 73% ee with $Rh_2$(*R*-BTPCP)$_4$ at 0 °C, but in a low 11% yield. Clearly, the use of a chiral catalyst with **2.39** was not likely to be a solution for an asymmetric cycloaddition reaction. It is noteworthy, however, that in this system, as before, the cycloadducts were formed as a single diastereomer. This diastereomer was assigned to be *anti*, based on the

results in the previous systems. Therefore, if the starting material (**2.77**) could be accessed in an enantiopure form, presumably the product **2.80** could be prepared enantioselectively as well.

**Table 2.6** [4+3] Cycloaddition model system[a]




| entry | R | $L_4$ | solvent | temp. (°C) | yield (%)[b] | ee (%) |
|---|---|---|---|---|---|---|
| 1 | H | *S*-DOSP | pentane | 23 | 20 | 66 |
| 2 | H | *S*-DOSP | pentane | 23 | 32[c] | 59 |
| 3 | H | *R*-BTPCP | $CH_2Cl_2$ | 23 | 31 | 58 |
| 4 | H | *R*-BTPCP | $CH_2Cl_2$ | -40 | N.R. | - |
| 5 | H | *R*-BTPCP | $CH_2Cl_2$ | 0 | 11 | 73 |
| 6 | H | *S*-PTAD | pentane | 23 | 7 | -31 |
| 7 | H | *S*-PTTL | $PhCF_3$ | 23 | 8 | -42 |

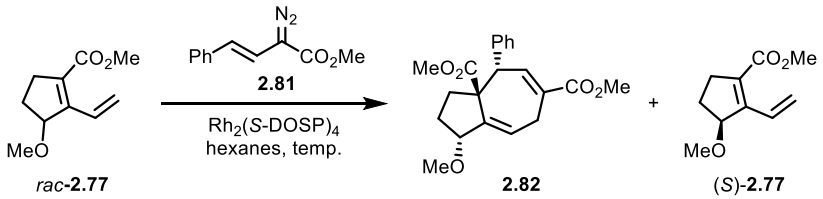
[a]Reactions were conducted by 3 hour addition of the diazo (0.25M in solvent) to a solution of the diene (0.5M in solvent) and 1 mol% catalyst. [b]Isolated yields of **2.80**. [c]Reaction conducted with 3 mol% catalyst.

Since the [4+3] cycloaddition seemed to be reliably diastereoselective, an intriguing possibility had revealed itself. If the initial cyclopropanation of *rac*-**2.77** could be conducted with good facial selectivity on the carbene, a kinetic resolution might be possible. Since reactions with unsubstituted vinyl diazo **2.39** typically occur with only poor-moderate levels of enantioselectivity, the styryl diazoacetate **2.81** was considered, which is known to undergo selective cyclopropanations with $Rh_2$(DOSP)$_4$.[33]

When styryl diazo **2.81** was used for a kinetic resolution (Table 2.7), it was found that, with 1.0 equivalent of the diazo, at 0 °C, with $Rh_2$(*S*-DOSP)$_4$ as catalyst, the starting material **2.77** could be isolated in 30% yield as a single enantiomer. These experiments show that a kinetic resolution is indeed possible in these systems. The absolute

configuration of **2.77** is tentatively assigned based on the model for $Rh_2$(*S*-DOSP)$_4$ catalyzed cyclopropantion reactions[31] and the model for diastereoselectivity proposed in this system (Scheme 2.14).

**Table 2.7** Kinetic resolution of **2.77**[a]

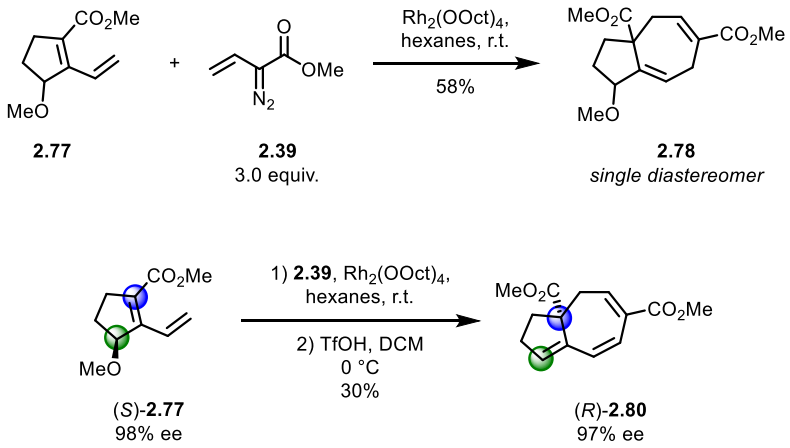



| entry | equiv. **2.81** | temp ($^o$C) | yield **2.77** (%) | ee **2.77** (%) |
|---|---|---|---|---|
| 1 | 0.5 | 0 | 25 | 41 |
| 2 | 0.8 | 0 | 44 | 78 |
| 3 | 1.0 | r.t. | 31 | 80 |
| 4 | 1.0 | 0 | 30 | 99 |

[a]The absolute stereochemistry of **2.77** from this reaction was tentatively assigned based on the model for $Rh_2$(*S*-DOSP)$_4$ cyclopropanations and the diastereoselectivity model proposed in Scheme 2.14 of this thesis. **2.82** was not characterized.

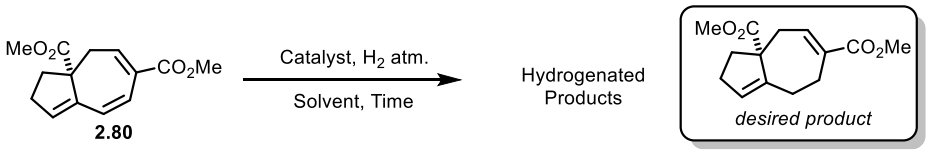
With an effective kinetic resolution, a test reaction was conducted with an achiral catalyst and the unsubstituted vinyl diazo (Scheme 2.17). With $Rh_2(OOct)_4$, the cycloadduct **2.78** was isolated in 58% yield as a single diastereomer. When this was extended to the enriched material **2.77**, the enriched product **2.80** was isolated in 30% yield over two steps with complete transfer of chiral information from one chiral center to another (green to blue, Scheme 2.17).

**Scheme 2.17** Preparation of enantioenriched **2.80**




With an effective and simple preparation of enantioenriched **2.80**, a brief attempt was given to selective hydrogenation of **2.80** to give a diene like **2.73** (Scheme 2.15). Unfortunately, however, using a variety of conditions, **2.80** could not be cleanly converted to the desired diene (Table 2.8). Either over-hydrogenation was observed, or incomplete conversion. With Wilkinson's catalyst (entries 18-22), one major product was observed, but it could not be isolated cleanly, and the structure of the compound was not known.

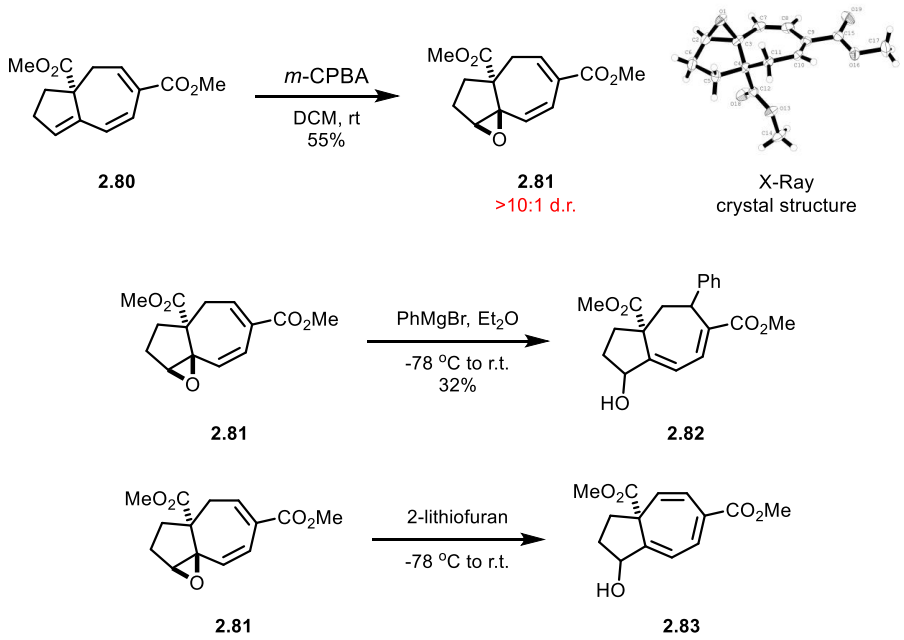
**Table 2.8** Attempted selective hydrogenation of triene **2.80**




| entry | catalyst | solvent | atm. $H_2$ | time | result |
|---|---|---|---|---|---|
| 1 | Pd/C | MeOH | 2.0 | 18 h. | Complete Hydrogenation |
| 2 | Pd/C | MeOH | 1.0 | 1.5 h. | Complete Hydrogenation |
| 3 | Pt/C | MeOH | 1.0 | 1.5 h. | Over-hydrogenation |
| 4 | Pd/C | EtOAc | 1.0 | 40 min. | Over-hydrogenation |
| 5 | Pt/C | EtOAc | 1.0 | 40 min. | Incomplete Conversion |
| 6 | Pd/C | THF | 1.0 | 2 h. | Over-hydrogenation |
| 7 | Pt/C | THF | 1.0 | 2 h. | Over-hydrogenation |
| 8 | $Pd/BaSO_4$ | THF | 1.0 | 2 h. | Over-hydrogenation |
| 9 | $Pd/SrCO_3$ (red.) | THF | 1.0 | 2 h. | Over-hydrogenation |
| 10 | Pt/C | TBME | 1.0 | 30 min. | Mixture of products |
| 11 | $PtO_2$ | TBME | 1.0 | 30 min. | Incomplete conversion |
| 12 | Ru/C | Hexanes | 1.0 | 18 h. | N.R. |
| 13 | Ru/C | MeOH | 1.0 | 18 h. | N.R. |
| 14 | $LAH/NiCp_2$ | THF | 1.0 | 18 h. | N.R. |
| 15 | $NaH/Ni(OAc)_2$ | THF | 0 | 1 h. | Isomerization? |
| 16 | $CoCl_2/NaBH_4$/MeOH | THF | 0 | 18 h. | N.R. |
| 17 | $CoCl_2$/LAH | THF | 0 | 18 h. | Mixture of products |
| 18 | $ClRh(PPh_3)_3$ | $C_6H_6$ | 1.0 | 18 h. | N.R. |
| 19 | $ClRh(PPh_3)_3$ | PhMe | 3.0 | 3 h. | N.R. |
| 20 | $ClRh(PPh_3)_3$ | 1:1 $C_6H_6$/EtOH | 3.0 | 24 h. | Minor Conversion |
| 21 | $ClRh(PPh_3)_3$ | EtOH | 3.0 | 24 h. | One major product |
| 22 | $ClRh(PPh_3)_3$ | EtOH | 3.0 | 36 h. | Same conversion |

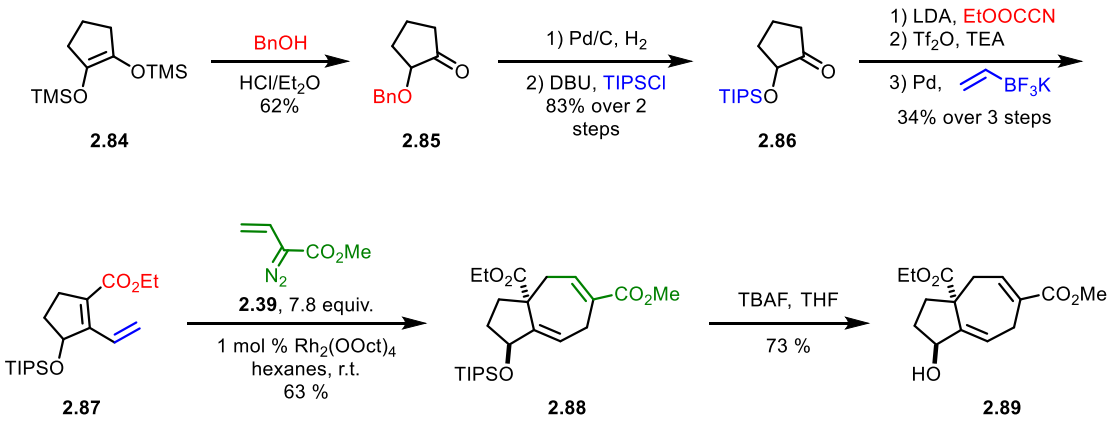
Therefore, **2.80** was allowed to react with *m*-CPBA to form epoxide **2.81**. This epoxide was then explored in several reactions (Scheme 2.18). Attempting to open the epoxide with phenylmagnesium bromide resulted in addition of the Grignard reagent to the β-position of the unsaturated ester to give **2.82**. Reaction with 2-lithio furan (prepared from furan and BuLi) resulted in simple deprotonation to give **2.83**. In both cases, the epoxide was opened. Though these reactions failed to give the desired product, the preparation of **2.81** as the desired diastereomer (confirmed by X-Ray crystallography) was encouraging for the exploration of the originally proposed system (Scheme 2.15).

**Scheme 2.18** Epoxidation of **2.80** and reactions of the epoxide




Having developed an effective kinetic resolution and applied it to the synthesis of an enanioenriched [4+3] product in the model system, the real system was investigated (Scheme 2.19). Beginning with **2.84**, 2-triisopropylsilyloxy cyclopentanone (**2.86**) was accessed in 3 convenient steps. This was then converted to the necessary diene **2.87** by the usual 3-step procedure, involving ethoxycarbonylation, triflation, and cross coupling, in this case with a vinyl trifluoroborate. This diene was then allowed to react with diazo **2.39**, using $Rh_2(OOct)_4$ as catalyst, to give the desired cycloadduct **2.88** in 63% yield as a single diastereomer. The diastereomer was tentatively assigned to be *anti*, in accordance with the results seen in previous systems. Then the triisopropylsilyl group was removed using TBAF to give the alcohol intermediate **2.89** in 73% yield (note: **2.89** is missing HRMS data).

**Scheme 2.19** Preparation and [4+3] cycloaddition of diene **2.84**

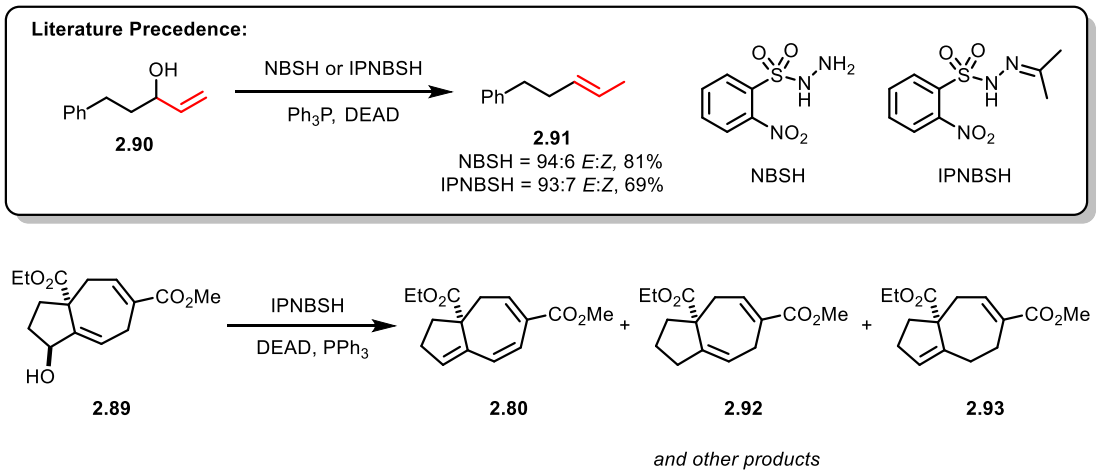



With alcohol **2.89** in hand, the reductive isomerization to prepare the epoxide precursor was examined. It was expected that the transformation could be achieved by the use of NBSH[34] or IPNBSH[35] as reagents under Mitsunobu conditions, to furnish the rearranged, reduced product. It is well precedented that these reagents selectively reduce allylic alcohols with complete migration of the alkene (Scheme 2.20).[35,36] The reaction is believed to occur by direct displacement of the alcohol with the hydrazide reagent via a modified Mitsunobu reaction, followed by decomposition to form a diimide-like intermediate, which rearranges stereospecifically with extrusion of $N_2$. An example of the regiocontrol possible in the reaction is shown with substrate **2.90**, in which direct $S_N2$ displacement occurs at the secondary site over $S_N2'$ at the unsubstituted vinyl position. This gives the internal alkene **2.91** in good yields.

With examples of good region control for the rearranged product, it was anticipated that extension of this reaction to the preparation of **2.93** from **2.89** would be simple. Unfortunately, however, under the typical conditions, using either NBSH or IPNBSH, a mixture of compounds was formed (Scheme 2.20). While separation and characterization of the mixture was not possible, is believed to have contained triene **2.80**, both dienes

**2.92** and **2.93** as well as several other products that could not be identified. Presumably **2.80** comes about *via* elimination rather than displacement under the reaction conditions. A mixture of isomers **2.92** and **2.93** indicates that the regiocontrol for the initial displacement reaction is poor.

**Scheme 2.20** Reductive transposition of allylic alcohols




It is hypothesized that clean attack at the alcohol carbon is not possible in this system since the bulky ester group is presumably located on the face of the molecule where nucleophilic attack would occur. Unfortunately, though **2.93** could likely be pursued by another route, these results suggest that opening of an epoxide (like **2.72**, Scheme 2.15) by nucleophilic displacement would probably fail for similar reasons. Therefore, this route for the total synthesis was not pursued further.

## 2.1.3 Conclusion

In conclusion, two separate approaches for the synthesis of Pseudolaric Acid B were investigated, utilizing both a furan ring-opening and a [4+3] cycloaddition reaction. For the first approach, synthesis of the necessary substrate was somewhat challenging, and yields were low. The substrate for the cycloaddition was very sterically crowded, making

for a difficult reaction. Additionally, the diastereoselectivity inherent in the substrate for the [4+3] provided the wrong diastereomer. A model system was investigated to explore the feasibility of reversing this selectivity, but no evidence for such a switch was observed.

In the second approach, a model system was investigated that led to the development of an effective kinetic resolution of a novel [4+3] substrate. When the real system for the second synthetic strategy was investigated, however, a reductive transposition of an allylic alcohol gave a mixture of compounds. This was attributed to the bulk around the alcohol site, suggesting that the strategy (nucleophilic epoxide opening at that site) was likely to fail due to the steric constraints of the system.

Without a doubt, there are many more investigations that could be completed in an attempt to prepare Pseudolaric Acid B using the carbene reactions discussed. Ultimately, the project reached a point where it made the most sense to set it down and move to other more productive projects. Nevertheless, a great deal of information was gleaned from these studies, including the subtleties of the way these substrates undergo cyclopropanation reactions, and how this influences the diastereoselectivity of the reaction.

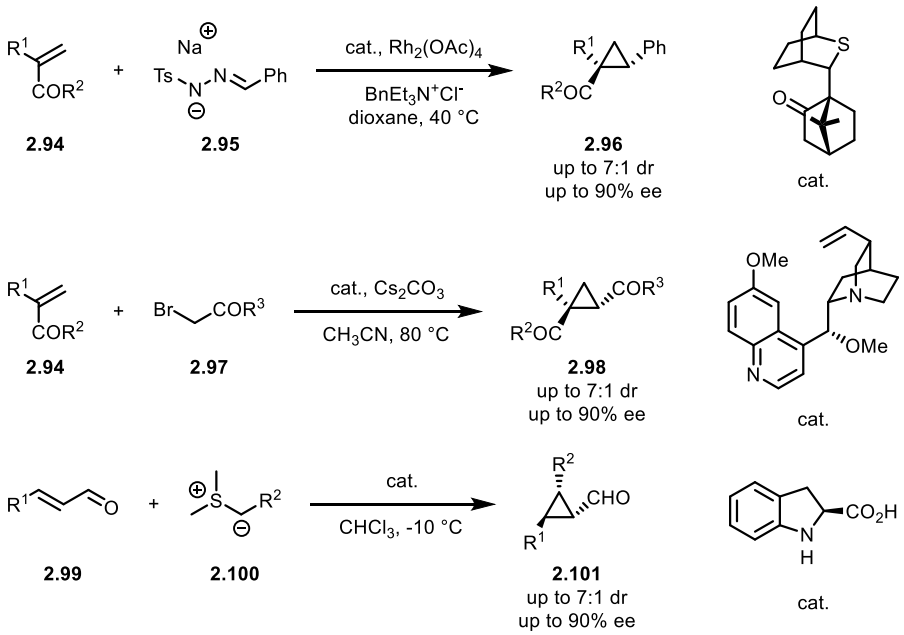
The effective kinetic resolution could become an interesting methodology study, applied to a variety of substrates with different substitutents at the chiral center. This would allow cycloadducts to be prepared with high levels of enantioselectivity using the unsubstituted vinyl diazo (which is typically relatively non-selective). About 5 different substrates were discussed in this thesis, but one could imagine other interesting substitutents as well.

## 2.2 Cyclopropanation of Electron-Deficient Alkenes

### 2.2.1 Introduction

While alkenes typically react with electrophilic species, when substituted with electron-withdrawing groups, they can become electrophilic themselves. This is clear by their propensity for 1,4-michael addition reactions. One might expect, then, that such compounds would be relatively unreactive towards electrophilic carbene intermediates. As a result, cyclopropanation of electron-deficient alkenes has tended to be accomplished by strategies other than direct carbene cyclopropanation. One such strategy is to use ylides in organocatalytic reactions (Scheme 2.21). Developed by Aggarwal,[37,38] Gaunt,[39] and MacMillan,[40] these cyclopropanations take place by initial nucleophilic addition to the alkene.

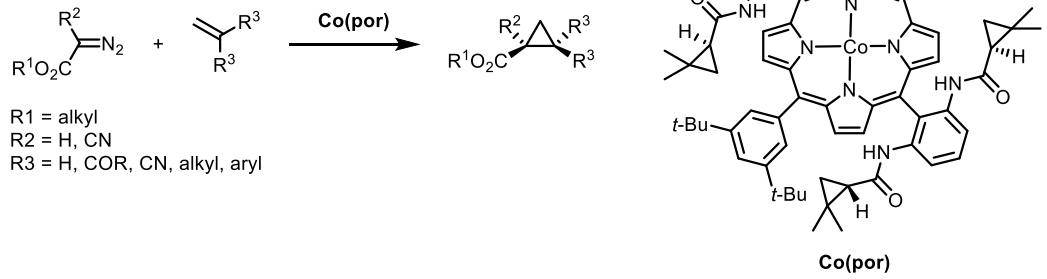
**Scheme 2.21** Cyclopropanation of electron-deficient alkenes with ylides




Some efforts have been made, however, towards cyclopropanation of electron-deficient alkenes with metal carbenes. Perhaps the most successful system has been

Zhang's cobalt porphyrin catalyst with acceptor and acceptor/acceptor diazo compounds (Scheme 2.22).[41,42] The mechanism of this cyclopropanation is believed to involve radical intermediates, rather than a direct cyclopropanation, which explains why electron-deficient alkenes are suitable substrates.[43]

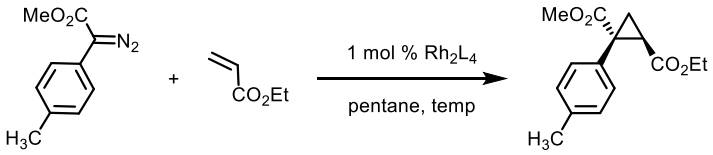
**Scheme 2.22** Cobalt porphyrin catalyzed cyclopropanation of electron-deficient olefins




With only one exception,[44] rhodium-carbenes have not been used for direct cyclopropanation of electron-deficient alkenes. This one example used ethyl diazoacetate, and the product was formed with poor dr. It was in this context that Dr. Hengbin Wang conducted his initial studies in this area.[45] He found that good yields and levels of enantioselectivity were possible with rhodium carbenes derived from donor/acceptor diazo compounds. He examined the reaction with a variety of catalysts, and found that with $Rh_2$(*S*-TCPTAD)$_4$, cyclopropane **2.104** could be isolated in 71% yield and in 84% ee (Table 2.9). Interestingly, the tetrachlorophthalimidyl-derived catalysts performed much better in this reaction than the parent phthalimidyl-derived catalysts.

Furthermore, by varying the size of the ester, the enantioselectivity of the process could be improved further (Table 2.10). Optimally, a *t*-Bu ester gave the best result with **2.105**, giving cylopropane **2.106** in 91% ee.

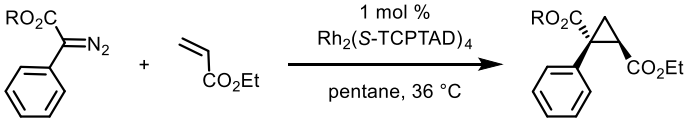
**Table 2.9** Cyclopropanation of ethyl acrylate




**2.102** **2.103** **2.104**

| entry | catalyst | equiv. **2.103** | temp (°C) | dr | yield(%) | ee (%) |
|---|---|---|---|---|---|---|
| 1 | $Rh_2$(S-DOSP)$_4$ | 5.0 | 36 | >97:3 | 59 | 77 |
| 2 | $Rh_2$(S-PTAD)$_4$ | 5.0 | 36 | >97:3 | 70 | 35 |
| 3 | $Rh_2$(S-PTTL)$_4$ | 5.0 | 36 | >97:3 | 68 | 27 |
| 4 | $Rh_2$(S-NTTL)$_4$ | 5.0 | 36 | >97:3 | 69 | 24 |
| 5 | $Rh_2$(S-BPTV)$_4$ | 5.0 | 36 | >97:3 | 65 | 5 |
| 6 | $Rh_2$(S-TCPTTL)$_4$ | 5.0 | 36 | >97:3 | 71 | 74 |
| 7 | $Rh_2$(S-TCPTV)$_4$ | 5.0 | 36 | >97:3 | 62 | 65 |
| **8** | **$Rh_2$(S-TCPTAD)$_4$** | 5.0 | **36** | **>97:3** | **71** | **84** |
| 9 | $Rh_2$(S-TCPTAD)$_4$ | 2.0 | 36 | >97:3 | 65 | 79 |
| 10 | $Rh_2$(S-TCPTAD)$_4$ | 1.0 | 36 | >97:3 | 60 | 73 |
| 11 | $Rh_2$(S-TCPTAD)$_4$ | 5.0 | 23 | >97:3 | 22 | 82 |
| 12[a] | $Rh_2$(S-TCPTAD)$_4$ | 5.0 | 40 | 92:8 | 81 | 71 |

**Table 2.10** Effect of ester size on enantioselectivity

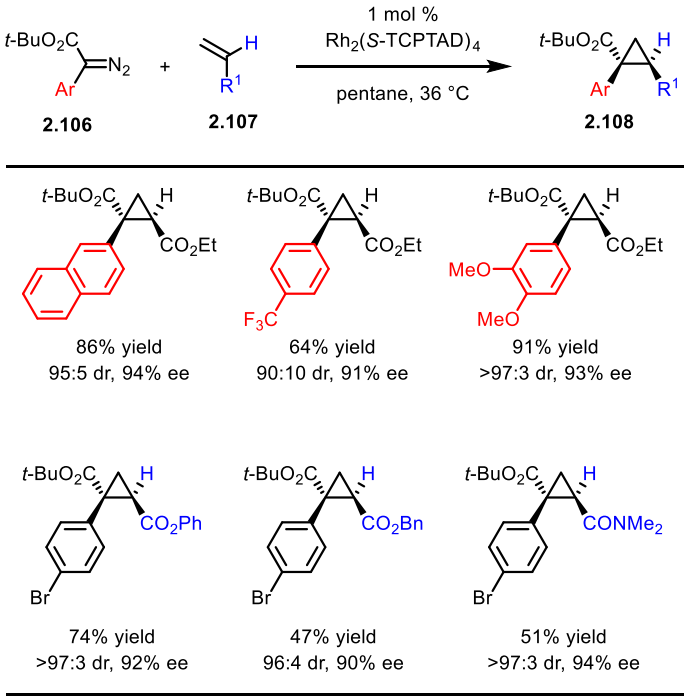



**2.105** **2.103** **2.106**

| entry | R | dr | yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | Me | 97:3 | 83 | 86 |
| 2 | Et | >97:3 | 78 | 85 |
| 3 | *n*-Bu | >97:3 | 84 | 81 |
| 4 | *t*-Bu | >97:3 | 78 | 91 |

Dr. Wang subsequently showed that the reaction could be extended to a variety of acrylate derivatives. Some of these examples are shown in Scheme 2.23. Electron-rich and electron-deficient aryl groups work well. Additionally, phenyl acrylate, benzyl acrylate, and *N*,*N*-dimethylacrylamide were all excellent substrates in the reaction, giving good yields and levels of enantioselectivity generally greater than 90% ee. Numerous other substrates were examined beyond what is shown in Scheme 2.23.

**Scheme 2.23** Some examples cyclopropanation of electron-deficient alkenes

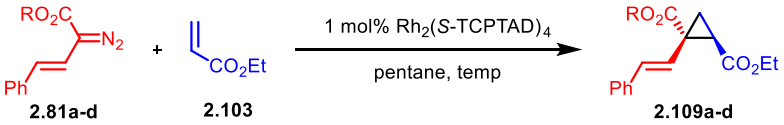



## 2.2.2 Results and Discussion

With an impressive scope for the cyclopropanation of electron-deficient alkenes with aryldiazo acetates, it was of interest to explore vinyldiazo acetates in the reaction. The investigation of vinyldiazoacetates in this reaction was my contribution to this study. Thus, styryldiazoacetates **2.81a-d** were prepared and used in the reaction (Table 2.11) with ethyl acrylate (**2.103**). As with the aryldiazo acetates, the reaction proceeded in

higher yield if conducted at higher temperature. Additionally, the larger esters gave slightly higher levels of enantioselectivity. Though, in general, with **2.81a-d**, the enantioselectivities were higher than the corresponding aryldiazoacetates **2.105**.

**Table 2.11** Effect of ester size on reaction of styryldiazo acetate with ethyl acrylate



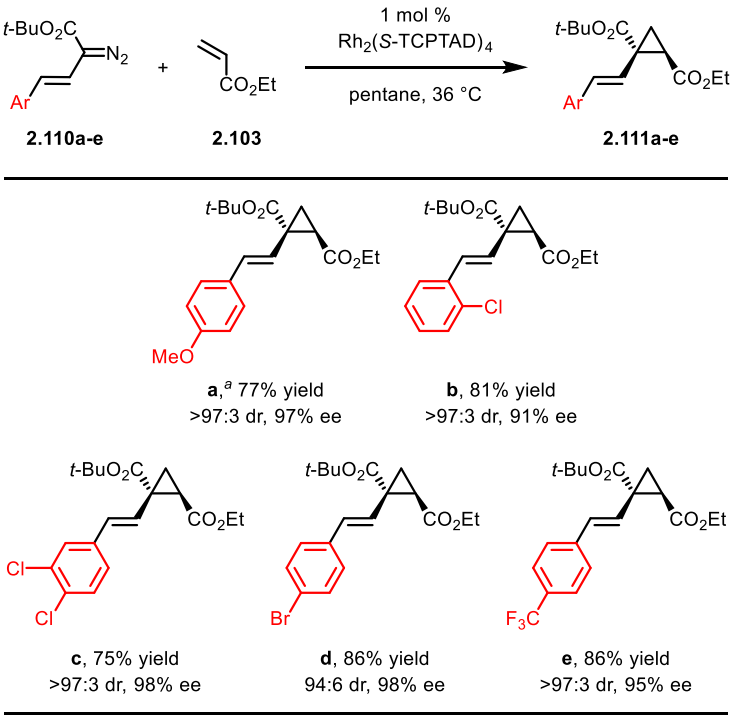

**2.81a-d** **2.103** **2.109a-d**

| entry | R | temp (°C) | yield (%)[a] | d.r.[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **a**, Me | 23 | 53 | >20:1 | 96 |
| 2 | **a**, Me | 36 | 77 | >20:1 | 95 |
| 3 | **b**, Et | 36 | 85 | >20:1 | 97 |
| 4 | **c**, *i*-Pr | 36 | 87 | >20:1 | 98 |
| 5 | **d**, *t*-Bu | 36 | 89 | >20:1 | 97 |

[a]Isolated yield. [b]From $^1$H NMR of the crude reaction mixture. [c]Determined by chiral HPLC.

The reaction was extended to a small series of styryldiazoacetates (Scheme 2.24). Each diazo **2.110a-e** efficiently underwent the reaction, giving yields of 75-86%. The enantioselectivities were greater than 90% for all substrates. The 2-chlorostyryldiazoacetate **2.110b** gave the cyclopropane in 91% ee, while the others were produced with 95-98% ee. The reaction worked well with electron-donating and electron-withdrawing substitutents (OMe, **a**; and $CF_3$, **e**). Additionally, with these substrates, it was demonstrated that the reaction did not require as much as 1 mol % catalyst. With **2.110a**, only 0.2 mol % of the catalyst Rh2(*S*-TCPTAD)4 was used, and the cyclopropane **2.111a** was still produced in good yield and with 97% ee. Though a detailed study was not conducted regarding the effects of catalyst loading on the reaction, this result demonstrates the potential efficiency of the reaction.

**Scheme 2.24** Reactions of various styryldiazo acetates with ethyl acrylate



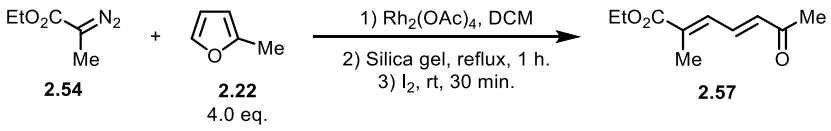

[a]Reaction conducted with 0.2 mol % $Rh_2$(*S*-TCPTAD)$_4$.

## 2.2.3 Conclusion

Together with Dr. Hengbin Wang's results, the results presented above in section 2.2.2 make up the complete experimental study of cyclopropanation of acrylate derivatives. As of the time of the study, this represents the first general, asymmetric, rhodium-catalyzed cyclopropanation of acrylates with donor-acceptor carbenes. The reaction is general, and with bulky *t*-Bu esters, high levels of enantioselectivity can be achieved. Some collaborators investigated this reaction computationally as well, the results of which suggested that a unique mechanism may be taking place, though it was concluded that further study would be required.

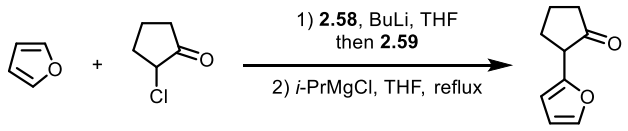
## 2.3 Experimental Section

## 2.3.1 Furan Ring-Opening




**(2*E*,4*E*)-ethyl 2-methyl-6-oxohepta-2,4-dienoate (2.57):** A solution of $Rh_2(OAc)_4$ (4.4 mg, 0.01 mmol, 2 mol %) in DCM (6 mL) was degassed by bubbling with argon for 10 minutes. A solution of ethyl 2-diazopropanoate (**2.54**) (64 mg, 0.5 mmol, 1.0 eq.) in DCM (6 mL) was similarly degassed for 10 minutes. 2-methyl furan (0.18 mL, 2.0 mmol, 4.0 eq.) was added to the solution of catalyst in one portion, followed by the solution of diazo drop-wise over 3 hours. After addition, silica gel (approx. 300 mg) was added and the reaction mixture was stirred at reflux for about 1 hour until the least polar spot had vanished by TLC. Iodine (15 mg) was added and the reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, diethyl ether (10 mL) was added, and the mixture was filtered to remove silica gel. The filtrate was washed with saturate aqueous $Na_2S_2O_3$ (8 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified via flash column chromatography (85:15 pentane:ether) to give a yellow oil (91 mg, 65 % yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, 1H, *J* = 11.8, 15.8 Hz), 7.22 (d, 1H, *J* = 11.8 Hz), 6.40 (d, 1H, *J* = 15.8 Hz), 4.24 (q, 2H, *J* = 7.2 Hz), 2.32 (s, 3H), 2.07 (s, 3H), 1.32 (t, 3H, *J* = 7.2 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 188.2, 167.5, 136.8, 136.3, 135, 61.3, 28.3, 14.4, 13.6; IR (neat): 2983, 1706, 1667, 1218, 1101, 977 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{15}O_3$ 183.1016, found 183.1013;

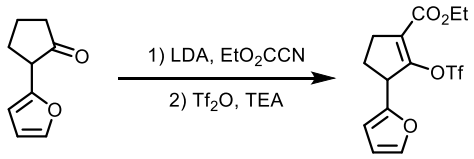
## 2.3.2 First generation synthetic approach




**2.58** **2.59** **2.60**

**2-(furan-2-yl)cyclopentanone (2.60)**: To a -30 °C solution of furan (16.1 g, 236 mmol, 1.4 eq.) in THF (150 mL) was added a solution of *n*-BuLi (94.4 mL, 2.5 M in hexane, 236 mmol, 1.4 eq.) drop-wise. The reaction mixture was stirred for 10 minutes at the same temperature before it was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was then cooled to 0 °C and 2-chlorocyclopentanone (20.0 g, 169 mmol, 1.0 eq.) in THF (20 mL) was added drop-wise, allowing the red color to dissipate between drops. The reaction mixture was stirred for 3 hours, slowly warming to room temperature. The reaction was quenched with aqueous $NH_4Cl$ (75 mL) and enough water was added to dissolve the formed precipitate. The aqueous layer was extracted with $Et_2O$ (3 x 30 mL) and the combined organic layers dried ($MgSO_4$), filtered and concentrated. The crude concentrate was dissolved in THF (100 mL), cooled to 0 °C, and isopropylmagnesium chloride (93.0 mL, 2.0 M in THF, 186 mmol, 1.1 eq.) was added drop-wise. The reaction mixture was stirred for 1 hour at 0 °C, and then heated to reflux for 4 hours. The mixture was cooled to room temperature and allowed to stir overnight. Work-up as before gave the crude product as a dark oil. This was partially purified by column chromatography (7:1 hexanes:ethyl acetate) to give a dark red oil. Careful distillation at 0.76 mmHg and 90-93 $^{o}$C gave the product as a pale yellow oil (13.4 g, 53 % yield). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, 1H, *J* = 1.9 Hz), 6.31 (dd, 1H, *J* = 3.1, 1.9 Hz), 6.17 (d, 1H, *J* = 3.1 Hz), 3.41 (t, 1H, *J* = 8.0 Hz), 2.43-2.09 (m, 5H), 1.92 (m,

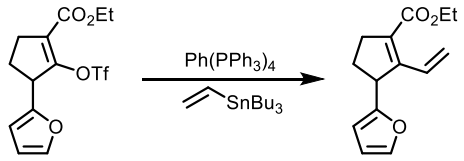
1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 215.5, 151.5, 142.0, 110.3, 106.7, 48.6, 37.9, 29.4, 21.0; IR (neat): 2968, 2880, 1743, 732 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_9H_{11}O_2$ 151.0754, found 151.0751;




**2.60** **2.61**

**ethyl 3-(furan-2-yl)-2-(((trifluoromethyl)sulfonyl)oxy)cyclopent-1-enecarboxylate (2.61):** Diisopropylamine (2.4 g, 24 mmol, 1.2 eq.) was dissolved in 48 mL of dry THF and cooled to -40 °C. *n*-BuLi (9.6 mL, 2.5 M in hexane, 24 mmol, 1.2 eq.) was added drop-wise. The reaction mixture was stirred at this temperature for 20 minutes before it was cooled to -78 °C. A solution of **2.60** (3.0 g, 20 mmol, 1.0 eq.) in dry THF (20 mL) was then added drop-wise and the orange/red reaction mixture was stirred for 10 minutes. Ethyl cyanoformate (2.4 g, 24 mmol, 1.2 eq.) was added quickly in one portion at -78 °C. The reaction mixture was stirred for 30 minutes and then poured into a cold mixture of $Et_2O$ and water (100 mL, 1:1, v/v). The layers were separated and the aqueous phase was saturated with $NaCl_{(s)}$ and extracted with cold $Et_2O$ (2 x 30 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated. The crude concentrate was purified by flash column chromatography (9:1 hexane:EtOAc) to give the intermediary β-keto ester (2.6 g, 59 % yield) as a complex mixture of diasteromers/tautomers. 2.5 g of this mixture (11 mmol, 1.0 eq.) was dissolved in dry DCM (45 mL) and cooled to -78 °C. Triethylamine (1.8 g, 18 mmol, 1.6 eq.) was added drop-wise to the reaction mixture. The reaction mixture was stirred for 20 minutes at the same temperature and triflic

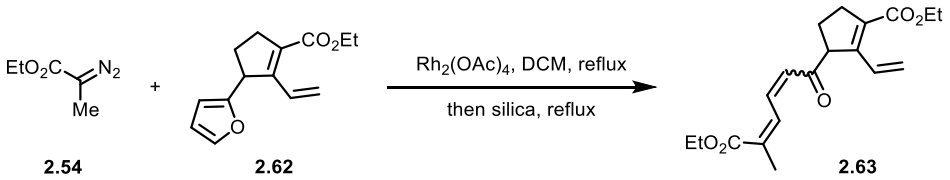
anhydride (4.0 g, 14 mmol, 1.3 eq.) was added drop-wise. The reaction mixture was stirred another 30 minutes and then poured into water. The layers were separated and the aqueous phase was extracted with DCM (3x). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The crude was purified by flash column chromatography (19:1 pentane:ether) to give **2.61** as a light yellow oil (1.5 g, 37 % yield, 22% overall). $R_f$ = 0.24 (19:1 pentane:ether); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, 1H, *J* = 1.8 Hz), 6.33 (dd, 1H, *J* = 3.2, 1.8 Hz), 6.19 (d, 1H, *J* = 3.2 Hz), 4.30 (m, 3H), 2.84 (m, 1H), 2.77 (m, 1H), 2.41 (m, 1H), 2.18 (m, 1H), 1.34 (t, 3H, *J* = 7.2 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 162.3, 152.0, 151.7, 142.7, 125.2, 118.5 (q, *J* = 318 Hz), 110.5, 107.5, 61.5, 44.5, 28.1, 26.6, 14.1; IR (neat): 2985, 1719, 1205 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{14}F_3O_6S$ 355.0458, found 355.0455;




**2.61** **2.62**

**ethyl 3-(furan-2-yl)-2-vinylcyclopent-1-enecarboxylate (2.62)**: The triflate **2.61** (1.5 g, 4.2 mmol, 1.0 eq.) was dissolved in THF (15 mL) and degassed with argon for 10 minutes. $Pd(PPh_3)_4$ (340 mg, 0.30 mmol, 0.07 eq.) was added followed by vinyltributyl tin (730 mg, 6.3 mmol, 1.5 eq.). The reaction mixture was heated to 70 °C overnight (approx. 14 hours). The reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography (39:1 pentane:ether) to give a clear oil (720 mg, 73 % yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, 1H, *J* = 17.8, 11.2 Hz), 7.31 (d, 1H, *J* = 1.8 Hz), 6.27 (dd, 1H, *J* = 3.0, 1.8 Hz), 5.98 (d, 1H, *J* = 3.0 Hz), 5.39 (d,

1H, *J* = 17.8 Hz), 5.36 (d, 1H, *J* = 11.2 Hz), 4.34 (d, 1H, *J* = 9.2 Hz), 4.26 (q, 2H, *J* = 7.2 Hz), 2.84 (m, 1H), 2.71 (m, 1H), 2.22 (m, 1H), 2.04 (m, 1H), 1.34 (t, 3H, *J* = 7.2 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 165.9, 156.9, 150.6, 142.3, 141.3, 132.1, 121.5, 110.4, 105.3, 60.5, 45.4, 33.0, 29.9, 14.5; IR (neat): 2977, 1702, 1223, 1106, 730 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}O_3$ 233.1172, found 233.1171;

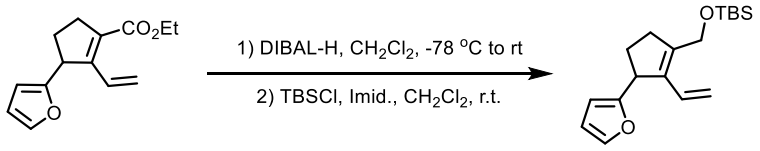



**2.54** **2.62** **2.63**

**ethyl 3-((2*Z*,4*E*)-6-ethoxy-5-methyl-6-oxohexa-2,4-dienoyl)-2-vinylcyclopent-1-enecarboxylate (2.63):** An oven-dried round-bottomed flask was fitted with a magnetic stirrer and a reflux condenser. $Rh_2(OAc)_4$ (4.0 mg, 0.005 mmol, 1 mol %) and furan **2.62** (116 mg, 0.50 mmol, 1.0 eq.) were added. The flask was evacuated under high vacuum and back-filled with argon. DCM (2 mL) was added and the solution was degassed with argon for 5 minutes. 2-diazopropanoate (160 mg, 1.3 mmol, 2.5 eq.) was dissolved in DCM (4 mL) and degassed with argon for 5 minutes. The diazo solution was added drop-wise to the reaction mixture, at reflux, over 2 hours. Silica gel (ca. 1.0 g) was added, and the reaction mixture was heated to reflux for 2.5 hours, until the least polar compound had vanished by TLC. Diethyl ether (3 mL) was added and the mixture filtered to remove silica. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (9:1 hexane:ethyl acetate) to give **2.63** as a yellow oil (86 mg, 52 % yield), as a 3:1 mixture of *cis:trans* double bond isomers (at the disubstituted double bond).

If the crude reaction mixture was not treated with silica gel at reflux, the *cis* isomer could be isolated: $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, 1H, *J* = 11.7 Hz), 7.51 (dd, 1H, *J* = 17.8, 11.0 Hz), 6.86 (app t, 1H, *J* = 11.7 Hz), 6.23 (d, 1H, *J* = 11.7 Hz), 5.40 (d, 1H, *J* = 11.0 Hz), 5.36 (d, 1H, *J* = 17.8 Hz), 4.26 (m, 4H), 4.04 (d, 1H, *J* = 9.4 Hz), 2.85 (m, 2H), 2.25 (m, 1H), 2.02 (s, 3H), 1.99 (m, 1H), 1.34 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 201.3, 168.1, 165.4, 148.9, 138.0, 136.9, 133.9, 132.6, 131.1, 126.5, 122.1, 61.3, 60.8, 60.7, 33.9, 26.1, 14.5, 13.0; IR (film): 2980, 1704, 1617, 1582, 1228 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{25}O_5$ 333.1697, found 333.1693;

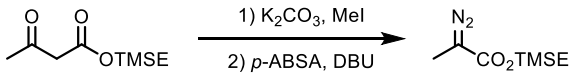
If the crude mixture was not treated with silica gel at reflux, the least polar compound could be isolated by chromatography (presumed to be the cyclopropane). If this intermediate was then subjected to silica gel in DCM at reflux, the *trans* product could be cleanly isolated and characterized: $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, 1H, *J* = 15.1, 11.9 Hz), 7.50 (dd, 1H, *J* = 17.7, 11.0 Hz), 7.21 (dd, 1H, *J* = 11.9 Hz), 6.45 (d, 1H, *J* = 15.1 Hz), 5.38 (d, 1H, *J* = 11.0 Hz), 5.30 (d, 1H, *J* = 17.7 Hz), 4.24 (m, 4H), 4.12 (d, 1H, *J* = 10.4 Hz), 2.86 (m, 2H), 2.27 (m, 1H), 2.07 (s, 3H), 1.95 (m, 1H), 1.32 (m, 6H); IR (neat): 2980, 1705, 1584, 1224, 1104 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{25}O_5$ 333.1697, found 333.1694;




**2.62** **2.65**

***tert*-butyl((3-(furan-2-yl)-2-vinylcyclopent-1-en-1-yl)methoxy)dimethylsilane (2.65):** To a -78 °C solution of the ester **2.62** (529 mg, 1.6 mmol, 1.0 equiv.) in DCM (15 mL)

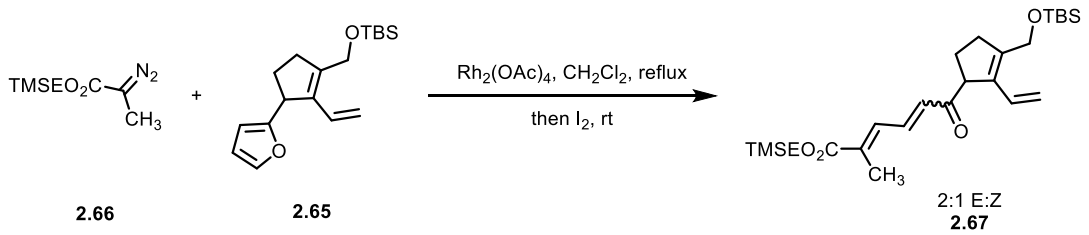
was added a toluene solution of DIBAL-H (3.6 mL, 1.0 M, 2.2 equiv.) dropwise. The mixture was stirred at this temperature for 15 minutes, allowed to warm slowly to 0 $^{o}$C and then stirred overnight. The reaction mixture was quenched with water and an aqueous solution of Rochelle's salt was added, followed by DCM (15 mL). The aqueous layer was extracted with DCM (3 x 15 mL). The organic layers were dried ($Na_2SO_4$), and concentrated. The clear crude oil was used immediately in the next reaction: the oil was dissolved in 15 mL DCM and cooled to 0 $^{o}$C. TBSCl (290 mg, 1.9 mmol, 1.2 equiv.) and imidazole (163 mg, 2.4 mmol, 1.5 equiv.) were added and the mixture stirred overnight. The solid was filtered and rinsed with DCM. The filtrate was concentrated and purified on a short silica gel column (5 cm) eluting with pentane/diethyl ether (59:1). This gave the product as a colorless oil (307 mg, 63% yield over 2 steps). $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.30 (d, 1H, *J* = 1.6 Hz); 6.61 (dd, 1H, *J* = 16.6, 11.5 Hz); 6.26 (dd, 1H, *J* = 2.9, 1.6 Hz); 5.93 (d, 1H, *J* = 2.9 Hz); 5.04 (d, 1H, *J* = 16.6 Hz); 5.03 (d, 1H, *J* = 11.5 Hz); 4.47 (d, 1H, *J* = 12.9 Hz); 4.39 (d, 1H, *J* = 12.9 Hz); 4.17 (d, 1H, *J* = 9.0 Hz); 2.63 (m, 1H); 2.54 (m, 1H); 2.22 (m, 1H); 1.98 (m, 1H); 0.92 (s, 9H); 0.10 (s, 3H); 0.09 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.5, 143.7, 140.9, 135.2, 129.5, 115.3, 110.2, 104.7, 59.9, 45.1, 33.5, 30.1, 26.1, 18.6, -5.0; IR (neat): 2928, 2856, 1073, 834 cm$^{-1}$; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{28}O_2NaSi$ 327.1751, found 327.1752;




**2.66**

**2-(trimethylsilyl)ethyl 2-diazopropanoate (2.66):** 2-(trimethylsilyl)ethyl acetoacetate[46] (5.2 g, 26 mmol, 1.0 equiv.) and iodomethane (4.4 g, 31 mmol, 1.2 equiv.) were

dissolved in 150 mL acetone and potassium carbonate (3.6 g, 26 mmol, 1.0 equiv.) was added. The mixture was heated to reflux for 15 hours. The solid was removed by filtration and the filtrate concentrated by rotary evaporation. The resulting residue was treated with diethyl ether (50 mL) and the solids removed by filtration, washing with diethyl ether (50 mL). The filtrate was again concentrated in vacuo to give a clear, pale yellow oil that was predominately the mono 2-methylated acetoacetate by $^{1}$H NMR (5.0 g, 89 % yield). This was used immediately in the next reaction: The acetoacetate from the previous step (5.0 g, 23 mmol, 1.0 equiv.), along with *p*-ABSA (8.4 g, 35 mmol, 1.5 equiv.) was dissolved in acetonitrile (50 mL), and cooled to 0 °C. DBU (7.0 g, 46 mmol, 2.0 equiv) was added dropwise and the reaction mixture was stirred overnight, warming to room temperature. The mixture was quenched with aqueous saturated sodium bicarbonate (50 mL), and extracted with diethyl ether (2 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and purified by column chromatography (19:1 pentane:ether) to give the diazo as a yellow/orange oil (2.4 g, 52 % yield). $^{1}$H NMR (600 MHz, $CDCl_3$): δ 4.25-4.20 (m, 2H), 1.92 (s, 3H), 0.99-0.94 (m, 2H), 0.00 (s, 9H). $^{13}$C (150 MHz, $CDCl_3$) δ 168.2, 63.2, 17.7, 8.5, -1.4 (resonance resulting from the diazo carbon was not detected); IR (neat): 2954, 2077, 1687, 1124 $cm^{-1}$; HRMS – Mass spectra of this compound did not show any identifiable peaks or fragments by a variety of ionization methods.



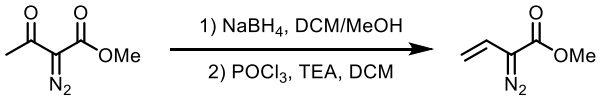

**2.66** **2.65** **2.67**

**(2*E*,4*E*)-2-(trimethylsilyl)ethyl 6-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-vinylcyclopent-2-en-1-yl)-2-methyl-6-oxohexa-2,4-dienoate (2.67):** The diazo **2.66** (462 mg, 2.3 mmol, 2.0 equiv.), in 5 mL DCM, was added dropwise over 2 hours to a solution of furan **2.65** (351 mg, 1.15 mmol, 1.0 equiv.) and $Rh_2(OAc)_4$ (10 mg, 0.02 mmol, 0.02 equiv.) in DCM (5 mL) at reflux. The reaction mixture was allowed to cool to room temperature and a solution of iodine in DCM was added (5.5 mL, 0.0104 M, 5 mol% $I_2$), and the mixture stirred at room temperature overnight. The RM was concentrated and washed with $Na_2S_2O_3$, and the aqueous layer extracted with DCM (10 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated. The crude was purified column chromatography (19:1 pentane:ether) to give the product **2.67** as a yellow oil (2:1 mixture of *E*:*Z* double bond isomers, 161 mg, 29% yield);

If the reaction was not treated with iodine, another minor product was observed, presumed to be the product resulting from cyclopropanation of the furan with the rhodium carbenoid. If this product is isolated and itself treated with iodine in DCM overnight, the *E*/*E* diene can be cleanly formed as the exclusive product:

Characterization data for (***E*/*E*)-2.67**: $^1$H NMR (600 MHz; $CDCl_3$) δ 7.56 (dd, 1H, *J* = 15.0, 11.9 Hz), 7.18 (d, 1H, *J* = 11.9 Hz), 6.63 (dd, 1H, *J* = 17.3, 11.0 Hz), 6.45 (d, 1H, *J* = 15 Hz), 5.06 (d, 1H, *J* = 11 Hz), 5.00 (d, 1H, *J* = 17.3 Hz), 4.44 (s, 2H), 4.27 (dd, 2H, *J* = 8.6, 6.9 Hz), 3.94 (d, 1H, *J* = 9.1 Hz), 2.70 (m, 2H), 2.25 (m, 1H), 2.06 (s, 3H), 1.91 (m, 1H), 1.06 (dd, 2H, *J* = 6.9, 8.6 Hz), 0.93 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.06 (s,

9H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 201.9, 167.9, 146.1, 137.2, 136.5, 131.2, 133.8, 131.0, 129.6, 116.0, 63.6, 59.7, 59.0, 34.7, 26.3, 26.1, 18.6, 17.6, 13.6, -1.3, -5.0; IR (neat): 2952, 1708, 1683, 1224, 835 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{45}O_4Si_2$ 477.2851, found 477.2852;

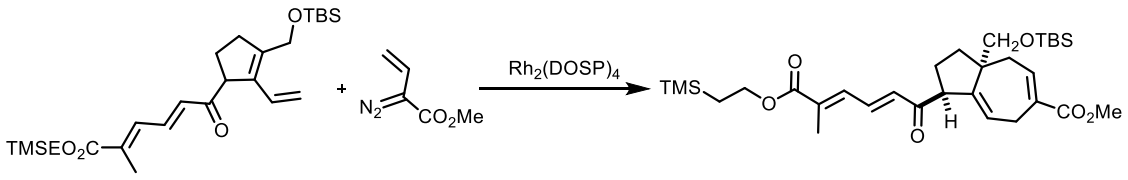



**2.39**

**methyl 2-diazo-3-butenoate (2.39):** The diazo was prepared according to a modified literature procedure.[28] To a 0 $^oC$ solution of methyl 2-diazo-3-oxobutanoate (10.0 g, 70.4 mmol, 1.0 equiv.) in DCM/MeOH (1:1, v/v, 80 mL) was added sodium borohydride (3.2 g, 84.5 mmol, 1.2 equiv.) in 3 portions over 15 minutes. The mixture was stirred for 2 hours, over which time it was allowed to warm to room temperature. The mixture was quenched by pouring into a mixture of DCM and water (75 mL each). The aqueous layer was extracted with DCM until the yellow color had been nearly completely removed (~4 x 50 mL). The organic extracts were combined and dried ($MgSO_4$), filtered, and concentrated to give a yellow oil that was predominately the alcohol diazo (6.9 g, 69 % yield). This was used without further purification.

The alcohol diazo from the previous step was dissolved in DCM (125 mL) along with triethylamine (33.3 mL, 239 mmol, 5.0 equiv.) and the mixture cooled to 0 $^oC$. Phosphorus oxychloride (8.9 mL, 95.8 mmol, 2.0 equiv.) was added dropwise to the mixture. The reaction mixture was stirred for 3 hours, and quenched by pouring into a mixture of ice and water (20 g/100 mL). The aqueous layer was extracted with DCM (50 mL). The organic layers were combined and dried ($MgSO_4$), filtered, and carefully

concentrated in vacuo to give a dark oil. The crude was purified by column chromatography (9:1 pentane:ether). The orange fractions were combined and carefully reduced to approximately ½ volume by rotary evaporation. The solution was diluted back to 2x its volume with pentane. The solution was concentrated again to a concentration of 26 % diazo by mass in pentane (as determined by relative integration in the $^1$H NMR spectrum). 13.4 g of such a solution was thus obtained (3.5 g diazo, 58 % yield). The diazo was used as such, and stored in solution at < -50 $^o$C to avoid decomposition.

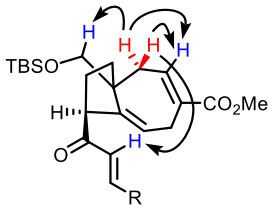



(*E*,*E*)-**2.67** **2.39** **2.68**

**methyl 3a-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-((2*E*,4*E*)-5-methyl-6-oxo-6-(2-(trimethylsilyl)ethoxy)hexa-2,4-dienoyl)-1,2,3,3a,4,7-hexahydroazulene-6-carboxylate (2.68):** Intermediate (***E***,***E***)**-2.67** (72 mg, 0.15 mmol, 1.0 equiv.) and $Rh_2$(*S*-DOSP)$_4$ (10 mg, 4 mol %) were dissolved in 4 mL pentane. A solution of diazo **2.39** (95 mg, 0.75 mmol, 5.0 equiv.) in pentane (prepared as mentioned above) was diluted to 4 mL with pentane and added dropwise to the mixture over 3 hours. The reaction mixture was concentrated and purified (14:1 hexanes:ethyl acetate eluent) to give the desired compound **2.68** as a light yellow oil (27 mg, 31% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 7.52 (dd, 1H, *J* = 15.2, 11.9 Hz), 7.23 (d, 1H, *J* = 11.9 Hz), 7.08 (d, 1H, *J* = 8.6 Hz), 6.52 (d, 1H, *J* = 15.2 Hz), 5.43 (m, 1H), 4.29 (t, 2H, *J* = 8.4 Hz), 3.73 (s, 3H), 3.68 (m, 1H), 3.53 (d, 1H, *J* = 9.5 Hz), 3.38 (d, 1H, *J* = 9.5 Hz), 3.23 (d, 1H, *J* = 22.4 Hz), 3.14 (d, 1H,

*J* = 22.4 Hz), 2.64 (dd, 1H, *J* = 16.2, 8.1 Hz), 2.36 (dq, 1H, *J* = 16.2, 2.9 Hz), 2.13 (m, 1H), 2.07 (s, 3H), 1.93 (m, 2H), 1.60 (m, 1H), 1.07 (t, 2H, *J* = 8.4 Hz), 0.89 (s, 9H), 0.07 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 200.5, 168.4, 167.9, 146.3, 140.4, 136.9, 136.5, 135.1, 132.9, 129.9, 121.7, 64.5, 63.7, 57.8, 52.1, 51.6, 36.4, 34.9, 29.0, 26.6, 26.0, 18.4, -1.28, -5.4; IR (film): 2952, 1709, 1248, 1226, 835 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{31}H_{51}O_6Si_2$ 575.3218, found 575.3214;

The diastereomer was assigned by NOE analysis:

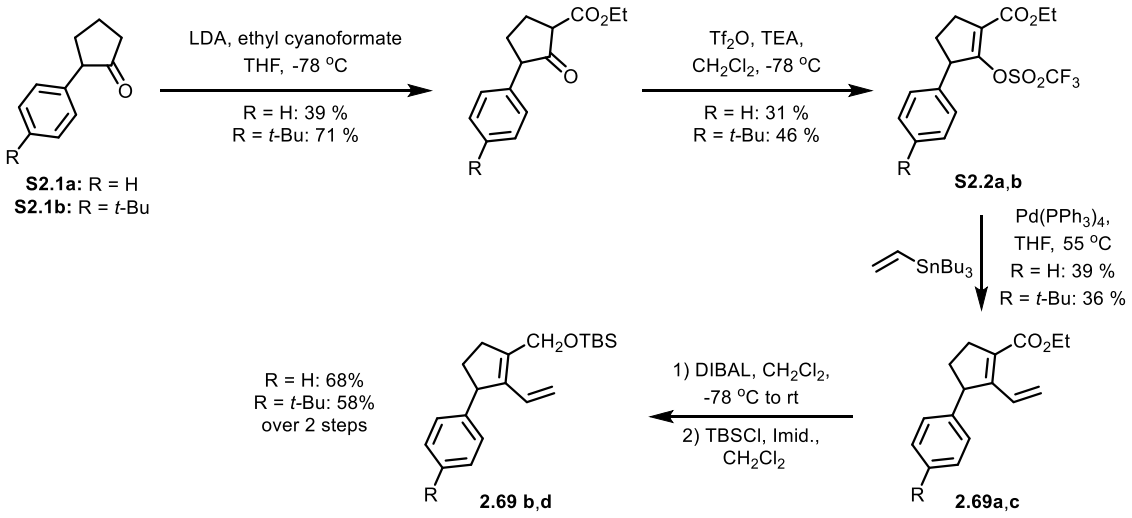



## 2.3.3 Model Study for [4+3] Cycloaddition

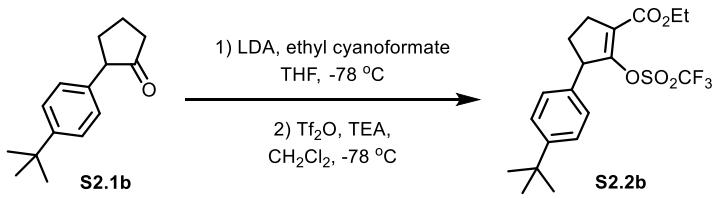
### *Preparation of Dienes:*

Dienes for the [4+3] model study were prepared according to Scheme 2.25 below. Cyclopentanones **S2.1a**,**b** were prepared according to a literature procedure.[47]

**Scheme 2.25**. Preparation of substrates for cycloaddition model study

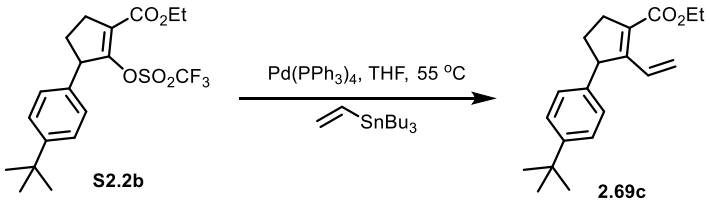


The procedures for this 5-step sequence are given below for R = *t*-Bu in the above scheme. The analogous compounds for which R = H were prepared by the same procedures.



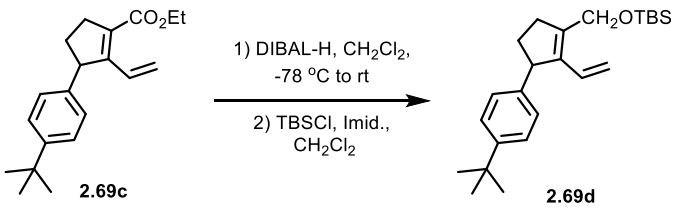

**ethyl 3-(4-(*tert*-butyl)phenyl)-2-(((trifluoromethyl)sulfonyl)oxy)cyclopent-1-enecarboxylate (S2.2b):** To a -40 °C solution of diisopropylamine (12.2 mL, 86.2 mmol, 1.2 equiv.) in THF (250 mL) was added BuLi (34.5 mL, 2.5M in hexanes, 1.2 equiv.) dropwise. The reaction mixture was stirred for one hour and cooled to -78 °C. Then 2-(p-*tert*-butylphenyl)cyclopentanone **S2.1b** (15.5 g, 71.8 mmol, 1.0 equiv.) in 50 mL THF was added dropwise over 20 minutes. The mixture was stirred for 15 minutes and ethyl cyanoformate (8.5 mL, 86.2 mmol, 1.2 equiv.) was added rapidly in one portion. The mixture was stirred at this temperature for one hour and then left in the freezer (-25 °C) overnight. The RM was poured into water and diethyl ether (250 mL each). The layers were separated and the aqueous layer extracted with ether (2 x 200 mL). The combined organic layers were dried ($Na_2SO_4$), concentrated and purified by column chromatography (9:1 hexanes:ethyl acetate) to give the β-keto ester as a pale oil (14.6 g, 71 % yield), as mixture of diastereomers and tautomers. This was immediately used in the next reaction: the oil (14.6 g, 50.7 mmol, 1.0 equiv.) was dissolved in 200 mL of DCM and cooled to -78 °C. Triethylamine (14.1 mL, 101.4 mmol, 2.0 equiv.) was added via syringe and triflic anhydride (10.2 mL, 60.8 mmol, 1.2 equiv.) was added carefully dropwise. The mixture was stirred for 1 hour and poured into saturated aqueous sodium

bicarbonate (100 mL). The aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried ($MgSO_4$), and concentrated. The crude residue was purified by column chromatography (29:1 pentane:ether) to give **S2.2b** as a pale oil (9.84 g, 46 % yield). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.37 (d, 2H, *J* = 8.2 Hz), 7.13 (d, 2H, *J* = 8.2 Hz), 4.32 (q, 2H, *J* = 7 Hz), 4.15 (td, 1H, *J* = 6.3, 3.1 Hz), 2.84 (m, 2H), 2.55 (m, 1H), 1.99 (m, 1H), 1.36 (t, 3H, *J* = 7 Hz), 1.33 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 162.7, 154.8, 150.7, 137.0, 127.4, 126.0, 124.9, 118.4 (q, *J* = 318 Hz, $CF_3$), 61.6, 50.9, 34.7, 31.5, 30.2, 28.5, 14.2; IR (neat): 2963, 1719, 1425, 1206, 832 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{24}O_5F_3S$ 421.1291, found 421.1288;



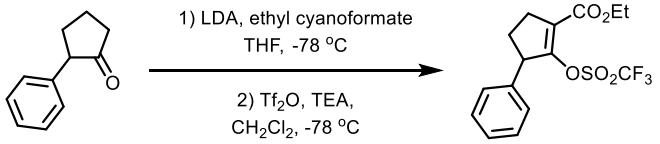

**ethyl 3-(4-(*tert*-butyl)phenyl)-2-vinylcyclopent-1-enecarboxylate (2.69c):** The vinyl triflate **S2.2b** from the previous step (9.8 g, 23.4 mmol, 1.0 equiv.) was dissolved in THF (100 mL) and $Pd(PPh_3)_4$ (1.9 g, 1.6 mmol, 7 mol %), and vinyltributylstannane (10.3 mL, 35.1 mmol, 1.5 equiv.) were added. The mixture was heated to 65 °C overnight. The RM was allowed to cool to room temperature and concentrated. The crude residue was purified by column chromatography (59:1 pentane:ether) to give the product **2.69c** as a clear oil (2.52 g, 36 % yield). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.49 (dd, 1H, *J* = 17.6, 11.0 Hz), 7.30 (d, 2H, *J* = 8.4 Hz), 7.06 (d, 2H, *J* = 8.4 Hz), 5.29 (d, 1H, *J* = 11 Hz), 5.23 (d, 1H, *J* = 17.6 Hz), 4.28 (m, 3H), 2.83 (m, 1H), 2.73 (m, 1H), 2.35 (m, 1H), 1.82 (m, 1H), 1.36 (t, 3H, *J* = 7 Hz), 1.31 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.1, 153.2, 149.2,

141.7, 132.0, 130.7, 126.9, 125.7, 122.4, 60.4, 52.1, 34.6, 33.0, 32.9, 31.6, 14.6; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{27}O_2$ 299.2006, found 299.2006;



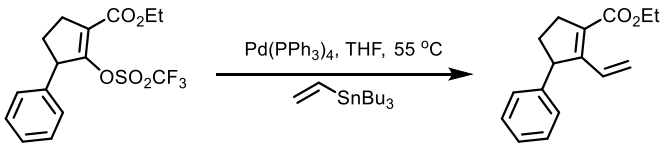

***tert*-butyl((3-(4-(*tert*-butyl)phenyl)-2-vinylcyclopent-1-en-1-yl)methoxy)dimethylsilane (2.69d):** To a -78 °C solution of the ester **2.69c** from the previous step (1.8 g, 6.0 mmol, 1.0 equiv.) in DCM (60 mL) was added a DCM solution of DIBAL-H (13.3 mL, 1.0 M, 2.2 equiv.) dropwise via syringe. The reaction mixture was stirred at this temperature for 2 hours and warmed to room temperature over 1 hour. The mixture was quenched by the dropwise addition of MeOH, and stirred until bubbling ceased. Water (25 mL) was added, followed by DCM (25 mL) and an aqueous solution of Rochelle's salt (25 mL). The reaction mixture was stirred vigorously for 20 minutes. The layers were separated and the aqueous layer washed with DCM (3 x 20 mL). The combined organic layers were dried ($Na_2SO_4$), and concentrated. The crude was purified by column chromatography (4:1 hexanes:ethyl acetate) to give a clear oil (994 mg, 65% yield). While not completely clean, this was immediately used in the next step: the oil (980 mg, 3.8 mmol, 1.0 equiv.) was dissolved in DCM (30 mL). TBSCl (687 mg, 4.6 mmol, 1.2 equiv.) and imidazole (310 mg, 4.6 mmol, 1.2 equiv.) were added and the mixture was stirred for 1 hour. The solid was filtered and the filtrate concentrated. The residue was taken up in a small amount of 19:1 pentane:ether and purified by column chromatography in the same solvent to give the product **2.69d** as a clear oil (1.29 g, 89 %

yield). $^{1}$H NMR (600 MHz; $CDCl_3$) δ 7.29 (d, 2H, *J* = 8.1 Hz), 7.08 (d, 2H, *J* = 8.1 Hz), 6.62 (dd, 1H, *J* = 17.6, 11.0 Hz), 4.97 (d, 1H, *J* = 11.0 Hz), 4.88 (d, 1H, *J* = 17.6 Hz), 4.50 (s, 2H), 4.08 (d, 1H, *J* = 9.1 Hz), 2.66 (m, 1H), 2.55 (m, 1H), 2.36 (m, 1H), 1.77 (m, 1H), 1.32 (s, 9H), 0.96 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 148.7, 143.5, 143.0, 137.6, 129.5, 126.9, 125.4, 116.1, 59.9, 51.8, 34.5, 33.7, 33.4, 31.6, 26.2, 18.6, -5; IR (neat): 2954, 2929, 2856, 833, 774 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{39}OSi$ 371.2765, found 371.2763;



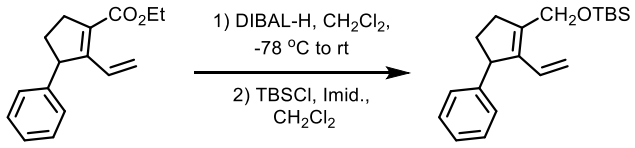

**S2.1a** **S2.2a**

**ethyl 3-phenyl-2-(((trifluoromethyl)sulfonyl)oxy)cyclopent-1-enecarboxylate (S2.2a):** This compound was prepared from **S2.1a** via a two step sequence in 39 % and 31 % yields respectively. The procedure was analogous to that for the preparation of **S2.2b**. $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.50-7.12 (m, 5H), 4.30 (q, 2H, *J* = 7.1 Hz), 4.16 (m, 1H), 2.81 (m, 2H), 2.54 (m, 1H), 1.94 (m, 1H), 1.33 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 162.6, 154.4, 140.1, 129.1, 127.8, 127.7, 125.4, 118.3 (q, *J* = 320 Hz), 61.6, 51.4, 30.4, 28.4, 14.2; IR (film): 2983, 1717, 1424, 1205 cm$^{-1}$; HRMS (ESI) *m/z*: $[M+K]^+$ calcd for $C_{15}H_{15}O_5F_3KS$ 403.0224, found 403.0227;




**S2.2a** **2.69a**

**ethyl 3-phenyl-2-vinylcyclopent-1-enecarboxylate (2.69b):** This compound was prepared from **S2.2a** in 39 % yield. The procedure was analogous to that for the preparation of **2.69b**. $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.46 (dd, 1H, *J* = 17.8, 11.0 Hz), 7.09-7.32 (m, 5H), 5.25 (d, 1H, *J* = 11 Hz), 5.17 (d, 1H, *J* = 17.8 Hz), 4.27 (m, 3H), 2.83 (m, 1H), 2.72 (ddd, 1H, *J* = 17.2, 9.0, 3.4 Hz), 2.37 (dq, 1H, *J* = 13.0, 9.0 Hz), 1.79 (ddt, 1H, *J* = 13.0, 8.2, 3.4 Hz), 1.35 (t, 3H, *J* = 7.2 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.0, 152.9, 144.8, 132.2, 130.7, 128.8, 127.2, 126.5, 122.3, 60.5, 53.0, 33.0, 32.9, 14.6; IR (film): 2959, 1702, 1225, 1105 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}O_2$ 243.138, found 243.138;

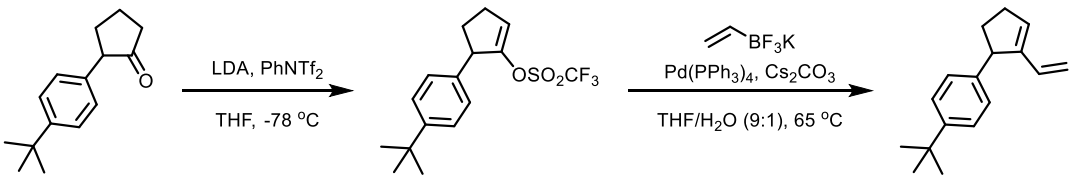



**2.69a** **2.69b**

***tert*-butyldimethyl((3-phenyl-2-vinylcyclopent-1-en-1-yl)methoxy)silane (2.69b):** This compound was prepared from **2.69a** over 2 steps in 68 % overall yield. The procedure was analogous to that for the preparation of **2.69d**. $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.27 (t, 2H, *J* = 7.4 Hz), 7.16 (m, 3H), 6.60 (dd, 1H, *J* = 17.4, 11.0 Hz), 4.96 (d, 1H, *J* = 11 Hz), 4.84 (d, 1H, *J* = 17.4 Hz), 4.49 (s, 2H), 4.10 (d, 1H, *J* = 9 Hz), 2.65 (m, 1H), 2.56 (m, 1H), 1.76 (m, 1H), 0.95 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 146.2, 143.8, 137.4, 128.6, 127.3, 126.1, 116.1, 59.8, 52.3, 33.7, 33.3,

26.2, 18.6, -5; IR (neat): 2928, 2856, 1080, 834 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{31}OSi$ 315.2139, found 315.2141;

Diene **2.69e** was also prepared from **7b**, according to the scheme shown below.



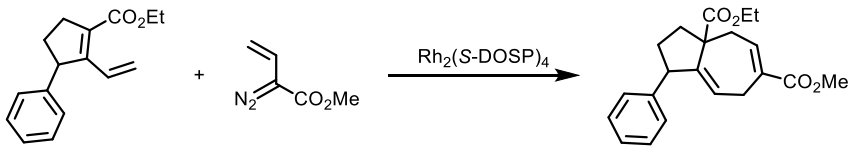

**1-(*tert*-butyl)-4-(2-vinylcyclopent-2-en-1-yl)benzene (2.69e):** To a -50 °C solution of diisopropylamine (0.51 mL, 3.6 mmol, 1.2 equiv.) was added BuLi dropwise (1.4 mL, 2.5 M in hexanes, 1.2 equiv.). The mixture was stirred for 1 hour and cooled to -78 °C. Then 2-(*p*-*tert*-butyl phenyl)cyclopentanone **S2.1b** (648 mg, 3.0 mmol, 1.0 equiv.) in 6 mL THF was added dropwise. The mixture was stirred for 10 minutes and N-phenyl-bis(trifluoromethanesulfonimide) (1.3 g, 3.6 mmol, 1.2 equiv.) in 4 mL THF was added in one portion. The mixture was stirred at room temperature overnight and quenched with saturated aqueous sodium bicarbonate and extracted with ether (2 x 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude was purified by column chromatography (19:1 pentane:ether) to give a yellow colored oil (583 mg, 56 % yield) that appeared to be primarily the vinyl triflate **S2.3** by $^1H$ NMR. This was used immediately in the next reaction: the vinyl triflate (583 mg, 2.0 mmol, 1.0 equiv.) was dissolved in THF/$H_2O$ (9:1, 20 mL total) and cesium carbonate (2.0 g, 6.0 mmol, 3.0 equiv.) and potassium vinyltrifluoroborate (536 mg, 4.0 mmol, 2.0 equiv.) were added, followed by $Pd(PPh_3)_4$ (162 mg, 0.14 mmol, 7 mol %). The reaction mixture was heated to 65 °C in an oil bath for 6 hours. The mixture was quenched with saturated aqueous

sodium bicarbonate and extracted with diethyl ether (2 x 20 mL). The organic layers were dried over magnesium sulfate and concentrated. The crude residue was purified by column chromatography (hexanes), to give the product as a clear oil (110 mg, 24 % yield). $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.29 (d, 2H, *J* = 8.2 Hz), 7.09 (d, 2H, *J* = 8.2 Hz), 6.49 (dd, 1H, *J* = 17.4, 10.8 Hz), 6.0 (s, 1H), 4.92 (d, 1H, *J* = 10.8 Hz), 4.86 (d, 1H, *J* = 17.4 Hz), 4.0 (m, 1H), 2.59-2.37 (m, 3H), 1.88-1.82 (m, 1H), 1.31 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 148.7, 145.3, 142.7, 133.0, 132.6, 126.9, 125.4, 115.5, 49.8, 35.3 (2C's), 34.5, 31.6; IR (neat): 2959, 2902, 2866, 2844, 900 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{23}$ 227.1794, found 227.1791;

## *[4+3] cycloaddition model study reactions:*

*General Procedure:*

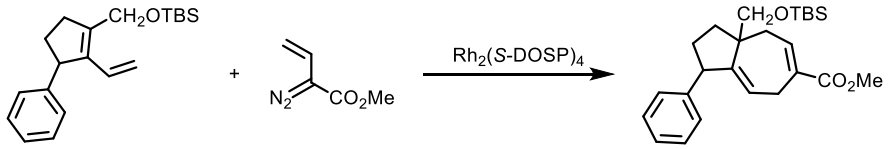
To a stirred solution of the diene (1.0 equiv.) and Rh catalyst (2 mol %) in pentane was added a solution of the diazo (2-5 equiv.) in pentane dropwise over 3 hours. The reaction mixture was stirred the indicated amount of time, concentrated *in vacuo* and purified by flash column chromatography on silica gel.




**2.69a** **2.39** **2.70a**

**3a-ethyl 6-methyl 1-phenyl-1,2,3,3a,4,7-hexahydroazulene-3a,6-dicarboxylate (2.70a):** Using the general procedure for the [4+3] cycloaddition, the reaction between diene **2.69a** (104 mg, 0.43 mmol, 1.0 equiv.) in 4 mL pentane and diazo **2.39** (162 mg,

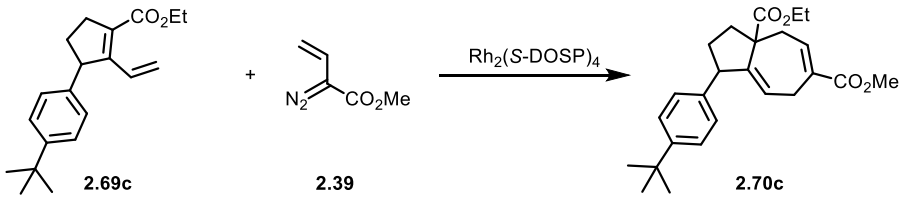
1.29 mmol, 3.0 equiv.) in 2.5 mL pentane, in the presence of $Rh_2$(*S*-DOSP)$_4$ (16 mg, 2 mol %) was stirred overnight after the diazo addition and purified by column chromatography (9:1 hexanes:ethyl acetate eluent) to give the desired compound as a colorless oil (25 mg, 22% yield). The starting material was also recovered in 43% yield. $^1$H NMR (400 MHz; $CDCl_3$) δ 7.32 (t, 2H, *J* = 7 Hz), 7.22 (m, 3H), 7.05 (m, 1H), 5.16 (m, 1H), 4.20 (m, 2H), 3.84 (m, 1H), 3.70 (s, 3H), 3.04 (s, 2H), 2.97 (dd, 1H, *J* = 17.5, 6.7 Hz), 2.58 (dq, 1H, *J* = 17.5, 3.5 Hz), 2.17 (m, 2H), 1.88 (m, 2H), 1.27 (t, 3H, *J* = 7 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 175.5, 168.5, 151.4, 143.5, 139.9, 129.0, 128.9, 128.6, 126.7, 122.0, 61.2, 55.4, 53.7, 52.1, 39.3, 36.1, 33.7, 26.9, 14.4; IR (film): 2951, 1709, 1240, 700 cm$^{-1}$; HRMS (APCI) *m/z*: [M-H]$^-$ calcd for $C_{21}H_{23}O_4$ 339.1602, found 339.1601;




**2.69b** **2.39** **2.70b**

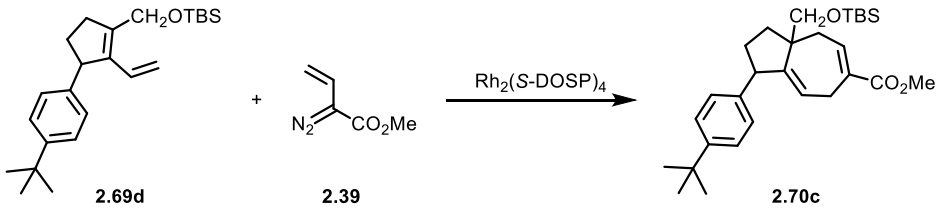
**methyl 3a-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-phenyl-1,2,3,3a,4,7-hexahydroazulene-6-carboxylate (2.70b):** Using the general procedure for the [4+3] cycloaddition, the reaction between diene **2.69b** (50 mg, 0.16 mmol, 1.0 equiv.) in 2 mL pentane and diazo **2.39** (60 mg, 0.48 mmol, 3.0 equiv.) in 2 mL pentane, in the presence of $Rh_2$(S-DOSP)$_4$ (6 mg, 2 mol %), was concentrated and purified by chromatography (39:1 pentane:ether) to give the desired compound as a colorless oil (23 mg, 35% yield). The starting material was also recovered in 42% yield. $^1$H NMR (600 MHz; $CDCl_3$) δ 7.31 (t, 2H, *J* = 7.4 Hz), 7.21 (t, 1H, *J* = 7.4 Hz), 7.18 (d, 2H, *J* = 7.4 Hz), 7.09 (d, 1H, *J* = 8.1

Hz), 4.99 (m, 1H), 3.72 (s, 3H), 3.69 (d, 1H, *J* = 9.5 Hz), 3.64 (m, 1H), 3.55 (d, 1H, *J* = 9.5 Hz), 3.18 (d, 1H, *J* = 21.9 Hz), 3.07 (dd, 1H, *J* = 21.9, 6.7 Hz), 2.66 (ddd, 1H, *J* = 17.2, 8.1, 2.4 Hz), 2.47 (dq, 1H, *J* = 17.2, 3.33 Hz), 2.09 (m, 2H), 1.79 (m, 1H), 1.57 (m, 1H), 0.92 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.7, 152.4, 144.8, 140.6, 128.8, 128.5, 126.3, 120.0, 65.8, 53.7, 52.0, 36.4, 35.4, 32.5, 28.5, 26.1, 18.5, -5.0; IR (film): 2951, 2856, 1714, 1250, 1086, 837 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{37}O_3Si$ 413.2507, found 413.2506; Product determined to have 30% ee by chiral HPLC: AD-H column, 0.5mL/min, 0.5% *i*-Pr in hexanes. Retention times: 10.3 min (major), 11.63 min (minor).




**3a-ethyl 6-methyl 1-(4-(*tert*-butyl)phenyl)-1,2,3,3a,4,7-hexahydroazulene-3a,6-dicarboxylate (2.70c):** Using the general procedure for the [4+3] cycloaddition, the reaction between diene **2.69c** (100 mg, 0.34 mmol, 1.0 equiv.) in 5 mL pentane and diazo **2.39** (126 mg, 1.0 mmol, 3.0 equiv.) in 5 mL of pentane, in the presence of $Rh_2$(*S*-DOSP)$_4$ (13 mg, 2 mol %) was concentrated and purified by chromatography (14:1 hexanes:ethyl acetate) to give the desired compound as a colorless oil (16 mg, 12% yield). The starting material was also recovered in 47% yield. $^1$H NMR (600 MHz; $CDCl_3$) δ 7.33 (d, 2H, *J* = 8.4 Hz), 7.14 (d, 2H, *J* = 8.4 Hz), 7.05 (m, 1H), 5.19 (m, 1H), 4.20 (m, 2H), 3.82 (m, 1H), 3.70 (s, 3H), 3.05 (m, 2H), 2.96 (ddd, 1H, *J* = 17.6, 7.1, 2.9 Hz), 2.58 (dq, 1H, *J* = 17.6, 3.33 Hz), 2.16 (m, 2H), 1.87 (m, 2H), 1.33 (s, 9H), 1.27 (t,

3H, *J* = 7.1 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 175.6, 168.5, 151.5, 149.4, 140.3, 140.0, 129.0, 128.4, 125.5, 121.9, 61.1, 55.4, 53.2, 52.1, 39.3, 36.1, 34.6, 33.7, 31.6, 26.8, 14.4; IR (film): 2956, 2869, 1720, 1243 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{33}O_4$ 397.2373, found 397.2373; The product was determined to have 33% ee by chiral HPLC: AD-H column, 0.5 mL/min, 1% *i*PrOH in hexanes. Retention times: 20.2 min (minor), 21.11 min (major).

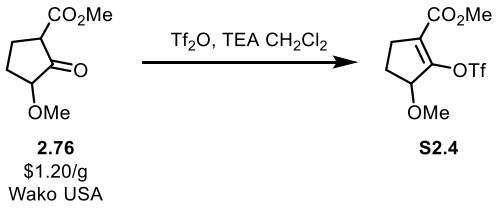



**2.69d** **2.39** **2.70c**

**methyl 1-(4-(*tert*-butyl)phenyl)-3a-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,2,3,3a,4,7-hexahydroazulene-6-carboxylate (2.70c):** Using the general procedure for the [4+3] cycloaddition, the reaction between diene **2.69d** (100 mg, 0.27 mmol, 1.0 equiv.) in 5 mL pentane and diazo **2.39** (102 mg, 0.81 mmol, 3.0 equiv.) in 5 mL of pentane, in the presence of $Rh_2$(*S*-DOSP)$_4$ (10 mg, 2 mol %) was stirred overnight and purified by chromatography (39:1 pentane:ether) to give the desired compound as a colorless oil (20 mg, 16% yield). The starting material was also recovered in 47% yield. $^1$H NMR (600 MHz; $CDCl_3$) δ 7.32 (d, 2H, *J* = 8.6 Hz), 7.09 (m, 3H), 5.01 (p, 1H, *J* = 3.3 Hz), 3.7 (s, 3H), 3.68 (d, 1H, *J* = 9.5 Hz), 3.61 (m, 1H), 3.54 (d, 1H, *J* = 9.5 Hz), 3.17 (d, 1H, *J* = 21.9 Hz), 3.07 (dd, 1H, *J* = 21.9, 6.7 Hz), 2.65 (ddd, 1H, *J* = 16.7, 8.1, 1.9 Hz), 2.46 (dq, 1H, *J* = 16.7, 3.3 Hz), 2.07 (m, 2H), 1.77 (m, 1H), 1.56 (m, 1H), 1.32 (s, 9H), 0.91 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.7, 152.4, 149.0, 141.6, 129.7, 128.4, 125.3, 119.8, 65.8, 53.2, 52.0, 50.9, 36.4, 35.4, 34.6, 32.5, 31.6, 28.5,

26.1, 18.5, -5.2; IR (film): 2952, 2857, 1714, 1249, 1093, 835 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{29}H_{45}O_3Si$ 469.3133, found 469.3130;

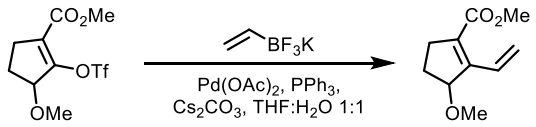
## 2.3.4 Second Generation Synthesis




**2.76**
$1.20/g
Wako USA

**S2.4**

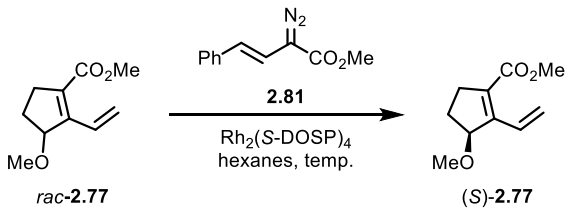
**methyl 3-methoxy-2-(((trifluoromethyl)sulfonyl)oxy)cyclopent-1-enecarboxylate (S2.4):** Methyl 3-methoxy-2-oxo-cyclopentanecarboxylate (**2.76**, purchased from Wako USA) (20.0 g, 116 mmol, 1.0 equiv.) and triethylamine (32 mL, 232 mmol, 2.0 equiv.) were dissolved in 400 mL DCM. The mixture was cooled to -78 $^oC$ and triflic anhydride (24 mL, 140 mmol, 1.2 equiv.) was added dropwise at a rate of 1.0 mL/min. The mixture was stirred for 3 hours and then poured into saturated aqueous sodium bicarbonate solution (250 mL). The aqueous layer was extracted with DCM (200 mL). The organic layers were combined, dried (MgSO4) and concentrated. The crude residue was purified by column chromatography (silica gel, 300 g, 9:1 hexanes:EtOAc eluent) to give the intermediate vinyl triflate as a yellow oil (30.5 g, 86% yield). $^1H$ NMR (400 MHz; $CDCl_3$) δ 4.52 (m, 1H), 3.78 (s, 3H), 3.35 (s, 3H), 2.74 (dddd, 1H, *J* = 16.7, 9.1, 4.7, 2.9 Hz), 2.57 (dddd, 1H, *J* = 16.7, 8.6, 4.5, 1.3 Hz), 2.26 (dddd, 1H, *J* = 13.6, 8.6, 7.8, 4.7 Hz), 1.88 (ddt, 1H, *J* = 13.6, 9.1, 4.5 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 162.6, 151.8, 126.0, 118.5 (q, *J* = 320 Hz), 82.4, 56.9, 52.1, 26.9, 26.2; IR (neat): 2956, 1728, 1202, 1130, 838 $cm^{-1}$; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_9H_{11}O_6F_3NaS$ 327.0121, found 327.0120;



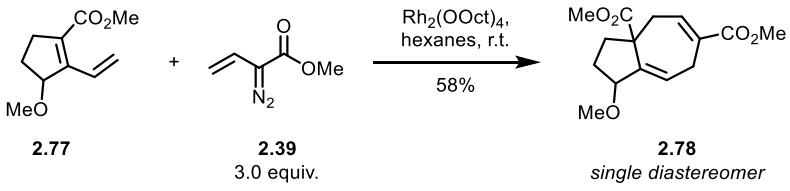

**S2.4** **2.77**

**methyl 3-methoxy-2-vinylcyclopent-1-enecarboxylate (2.77):** The vinyl triflate (10.0 g, 32.9 mmol, 1.0 equiv.) was added to a solution of potassium vinyltrifluoroborate (4.9 g, 36.2 mmol, 1.1 equiv.), $Pd(OAc)_2$ (360 mg, 1.6 mmol, 0.05 equiv.), triphenylphosphine (865 mg, 3.3 mmol, 0.10 equiv.), and cesium carbonate (32.2 g, 98.7 mmol, 3.0 equiv.) in 10:1 THF:$H_2O$ (150 mL). The reaction mixture was heated to 55 $^oC$ for 2 hours, until the starting material had vanished by TLC. The reaction mixture was poured into water, and the organic layer washed with 1M HCl (100 mL). The aqueous layers were combined and extracted with $Et_2O$. The combined organic layers were dried ($MgSO_4$), and concentrated. The crude residue was filtered through a short pad (1.5 inches) of neutral alumina (9:1 hexanes:EtOAc eluent) and concentrated. The resulting oil was distilled using the Kugelrohr apparatus (0.5 mmHg, 90-100 $^oC$) to give the product as a pale yellow oil (5.13 g, 86% yield). $^1H$ NMR (600 MHz; $CDCl_3$) δ 7.39 (dd, 1H, *J* = 17.6, 11.1 Hz), 5.70 (d, 1H, *J* = 17.6 Hz), 5.47 (d, 1H, *J* = 11.1 Hz), 4.80 (dt, 1H, *J* = 6.9, 2.3 Hz), 3.76 (s, 3H), 3.31 (s, 3H), 2.82 (m, 1H), 2.60 (ddd, 1H, *J* = 17.7, 9.0, 3.5 Hz), 2.05 (ddt, 1H, *J* = 13.8, 9.0, 6.9 Hz), 1.97-1.91 (m, 1H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 166.1, 149.2, 132.7, 130.2, 121.5, 85.4, 55.4, 51.6, 32.0, 27.1; IR (neat): 2949, 2819, 1709, 1231, 1084 $cm^{-1}$; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{14}O_3Na$ 205.0835, found 205.0834;

***Procedure for kinetic resolution of 2.77:***

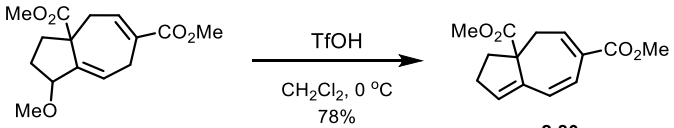



The racemic diene **2.77** (91 mg, 0.5 mmol, 1.0 equiv.) and $Rh_2$(*S*-DOSP)$_4$ (18 mg, 0.01 mmol, 0.02 equiv) were dissolved in hexanes (3 mL) and cooled to 0 $^oC$. Then methyl styryldiazoacetate **2.81** (101 mg, 0.5 mmol, 1.0 equiv.) was dissolved in hexanes (3 mL) and added dropwise to the cold reaction mixture over 3 hours. The RM was stirred 10 minutes and concentrated in vacuo. The crude green residue was purified by column chromatography (19:1 hexanes:EtOAc) to recover the SM (27 mg, 30% yield, 99% ee). The ee after kinetic resolution was determined by chiral HPLC: OJ column, 0.5 mL/min, 0.5 % *i*PrOH in hexanes. After kinetic resolution with S-DOSP, HPLC resolution times: 16.9 min (minor), 19.9 min (major). The absolute configuration was assigned tentatively based on the model for $Rh_2$(*S*-DOSP)$_4$ catalyzed cyclopropanation reactions and the proposed model for diastereoselectivity (Scheme 2.14). *If this project is to be continued, the absolute configuration will need to be unambiguously determined.*




**dimethyl 1-methoxy-1,2,3,3a,4,7-hexahydroazulene-3a,6-dicarboxylate (2.78):** Diene **2.77** (910 mg, 5.0 mmol, 1.0 equiv.) and $Rh_2(OOct)_4$ (78 mg, 0.1 mmol, 0.02 equiv) were dissolved in hexanes (10 mL). The diazo **2** (9.0 g of a 21% by mass solution in pentane)

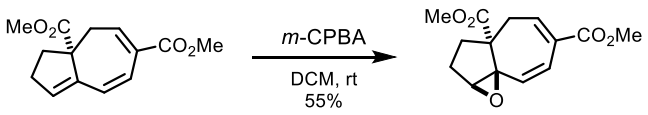
was further diluted with 24 mL of hexanes. The new orange solution was added dropwise to the reaction mixture over 3 hours. The reaction mixture was then stirred at room temperature overnight. The mixture was concentrated and purified by column chromatography (85:15 hexanes:EtOAc) to give the product as a green tinged oil (809 mg, 58% yield). The product could not be isolated pure by chromatography, and was therefore subjected to acid catalyzed elimination (see next step).




**2.78** **2.80**

**dimethyl 2,3,3a,4-tetrahydroazulene-3a,6-dicarboxylate (2.80):** The bicycle **2.78** (777 mg, 2.78 mmol, 1.0 equiv.) was dissolved in DCM (15 mL) and cooled to 0 $^{o}$C. Then triflic acid (0.03 mL, 0.27 mmol, 0.10 equiv.) was added dropwise and the mixture stirred for 3 hours, warming to room temperature. Another 10 mol % triflic acid was added and the mixture stirred at r.t. overnight. The mixture was quenched by addition of saturated aqueous sodium bicarbonate solution (10 mL) and was stirred vigorously for 20 minutes. The aqueous layer was extracted with DCM (15 mL) and the organic layers combined, dried ($MgSO_4$), and concentrated. The crude residue was purified by column chromatography (9:1 hexanes:EtOAc) to give the product as a yellow oil that solidified upon standing at -25 °C (528 mg, 77% yield). $^{1}$H NMR (600 MHz; $CDCl_3$) δ 7.15 (dd, 1H, *J* = 9.0, 4.0 Hz), 6.50 (d, 1H, *J* = 12.1 Hz), 6.36 (d, 1H, *J* = 12.1 Hz), 6.05 (t, 1H, *J* = 2.9 Hz), 3.76 (s, 3H), 3.62 (s, 3H), 3.09 (dd, 1H, *J* = 15.2, 9.0 Hz), 2.35 - 2.56 (m, 3H), 2.29 (dd, 1H, *J* = 15.2, 4.0 Hz), 1.98 (dt, 1H, *J* = 13.0, 9.0 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 175.5, 167.8, 144.3, 140.7, 137.2, 130.4, 127.3, 120.9, 60.1, 52.5, 52.3, 40.4,

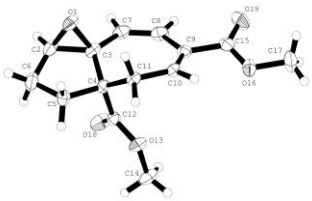
37.6, 30.8; IR (film): 2951, 2844, 1716, 1257 $cm^{-1}$; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{16}O_4Na$ 271.0941, found 271.0931; The ee of **2.80** when enantiomerically pure **2.77** was used in the cycloaddition reaction was determined by HPLC: OB-H column, 1.0 mL/min, 0.5% *i*PrOH in hexanes. HPLC retention times: 14.03 (major), 20.27 (minor).

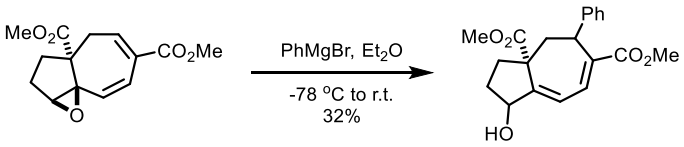



**2.80** **2.81**
>10:1 d.r.

**dimethyl 2,3,3a,4-tetrahydro-1aH-azuleno[1,8a-b]oxirene-3a,6-dicarboxylate (2.81):** The triene **2.80** (91 mg, 0.37 mmol, 1.0 equiv.) was dissolved in DCM (4 mL). 4-chloroperbenzoic acid (64 mg, 0.37 mmol, 1.0 equiv.) was added in one portion and the mixture stirred for 2 hours at room temperature. The reaction mixture was washed with 0.5 M aqueous NaOH, and the aqueous layer extracted with DCM (5 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated. The crude was purified by column chromatography (5:1 hexanes:EtOAc) to give the product as a fluffy white solid (54 mg, 55% yield). $^1H$ NMR (400 MHz; $CDCl_3$) δ 7.30 (dd, 1H, *J* = 8.5, 2.8 Hz), 6.78 (d, 1H, *J* = 12.2 Hz), 5.76 (d, 1H, *J* = 12.2 Hz), 3.79 (s, 1H), 3.76 (s, 3H), 3.63 (s, 3H), 3.04 (dd, 1H, *J* = 17.7, 8.5 Hz), 2.57 (dd, 1H, *J* = 17.7, 2.8 Hz), 2.10 (dd, 1H, *J* = 13.8, 7.8 Hz), 2.05 - 1.98 (m, 1H), 1.77 (dd, 1H, *J* = 13.1, 7.7 Hz), 1.54 (ddd, 1H, *J* = 13.1, 10.7, 7.8 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 174.3, 167.8, 143.1, 129.1, 128.5, 127.3, 68.1, 67.1, 53.8, 52.5, 52.4, 33.4, 32.8, 28.0; IR (film): 2951, 1713, 1261, 1243 $cm^{-1}$; HRMS (ESI) *m/z*: [M+H]+ calcd for $C_{14}H_{17}O_5$ 265.1071, found 265.1075;

The relative stereochemistry was confirmed by X-Ray crystallographic analysis:



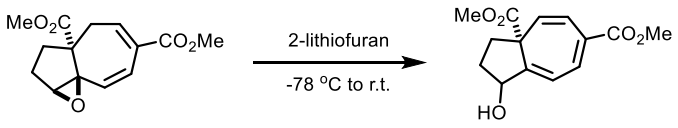



**2.81** **2.82**

**dimethyl 1-hydroxy-5-phenyl-1,2,3,3a,4,5-hexahydroazulene-3a,6-dicarboxylate (2.82):** The epoxide **2.81** (25 mg, 0.09 mmol, 1.0 equiv.) was dissolved in $Et_2O$ (1 mL) and cooled to -78 $^oC$. A solution of phenylmagnesium bromide (0.03 mL, 3.0 M in $Et_2O$, 0.09 mmol, 1.0 equiv.) was added dropwise and the mixture became a cloudy white suspension. The mixture was allowed to warm to room temperature and it was stirred overnight. The mixture was quenched with aqueous ammonium chloride (2 mL), and the aqueous layer extracted with $Et_2O$ (2 mL). The ether layers were dried ($MgSO_4$), concentrated and purified by column chromatography (3:2 hexanes:EtOAc) to give the product as a white powder (10 mg, 32% yield).

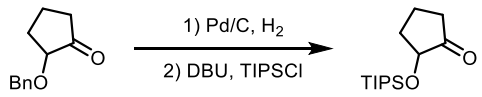
$^1H$ NMR (400 MHz; $CDCl_3$) δ 7.26 (m, 2H), 7.18 (m, 4H), 6.18 (d, 1H, *J* = 7.3 Hz), 4.75 (t, 1H, *J* = 6.6 Hz), 4.39 (dd, 1H, *J* = 13.6, 7.3 Hz), 3.74 (s, 3H), 3.48 (s, 3H), 2.52 (dd, 1H, *J* = 13.6, 7.3 Hz), 2.21 (t, 1H, *J* = 13.6 Hz), 2.12 (dt, 1H, *J* = 13.5, 6.6 Hz), 2.04 (dq, 1H, *J* = 13.4, 6.6 Hz), 1.91 (dt, 1H, *J* = 13.5, 6.6 Hz), 1.73 (bs, 1H, ), 1.67 (dq, 1H, *J* = 13.4, 6.6 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.9, 168.6, 158.1, 144.6, 137.1, 133.8,

128.7, 127.5, 126.5, 118.4, 76.4, 54.6, 52.7, 51.9, 48.2, 45.9, 37.2, 33.2; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{22}O_5Na$ 365.136, found 365.136;



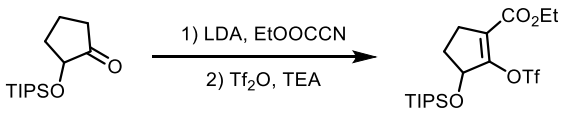

**2.81** **2.83**

**dimethyl 1-hydroxy-1,2,3,3a-tetrahydroazulene-3a,6-dicarboxylate (2.83):** The epoxide **2.81** (60 mg, 0.23 mmol, 1.0 equiv.) was dissolved in 2 mL THF and cooled to -78 °C. A solution of 2-lithiofuran (0.6 mL, 0.38 M, 1.0 equiv., prepared by addition of BuLi to a THF solution of furan in THF) was added to the mixture and the mixture was allowed to warm to room temperature and stirred 2 days. $Et_2O$ and $H_2O$ were added (3 mL each) and the aqueous layer extracted with DCM (3 mL). The organic layers were combined and dried ($MgSO_4$), concentrated, and purified by column chromatography (1:1 hexanes:EtOAc) to give the product as a clear oil (10 mg, 16% yield). $^1H$ NMR (600 MHz; $CDCl_3$) δ 7.72 (d, 1H, *J* = 6.7 Hz), 6.93 (d, 1H, J = 9.9 Hz), 6.64 (dd, 1H, *J* = 6.7, 2.2 Hz), 5.35 (d, 1H, *J* = 9.9 Hz), 4.96 (q, 1H, *J* = 6.8 Hz), 3.82 (s, 3H), 3.46 (s, 3H), 2.33 (m, 2H), 2.12 (m, 1H), 1.81 (d, 1H, *J* = 7.4 Hz), 1.51 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 173.2, 167.8, 151.2, 135.8, 130.3, 126.3, 126.0, 118.8, 76.2, 53.9, 52.5, 52.4, 35.5, 35.2; IR (film): 3446, 2952, 1712, 1253, 726 $cm^{-1}$; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}O_5$ 265.1071, found 265.1072;



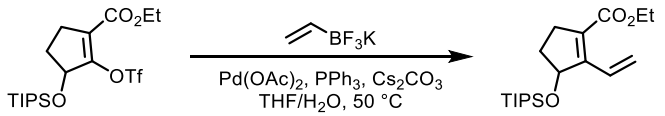

**2.85** **2.86**

**2-((triisopropylsilyl)oxy)cyclopentanone (2.86):** A 500 mL round-bottomed flask equipped with a magnetic stir bar was charged with 5% palladium on carbon (5.03 g, 5 mol% Pd). THF (275 mL) was added, followed by 2-(benzyloxy)cyclopentanone[48] (9.03 g, 47.5 mmol). The mixture was stirred vigorously overnight under an atmosphere of hydrogen (via hydrogen balloon). The catalyst was removed by filtration through celite, washing with EtOAc. The filtrate was concentrated by rotary evaporation to give 2-hydroxycyclopentanone as a clear oil. The clear oil so obtained was dissolved in 120 mL toluene, followed by chlorotriisopropylsilane (11.0 g, 57.0 mmol, 1.2 equiv.) and DBU (8.5 mL, 57.0 mmol, 1.2 equiv.). The reaction mixture was stirred for 3 hours at room temperature and then poured into water (120 mL). The aqueous layer was extracted with EtOAc (75 mL). The organics were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (19:1 pentane:$Et_2O$) to give the product as a colorless oil (10.1g, 83 % yield over two steps). $^1H$ NMR (400 MHz; $CDCl_3$) δ 4.12 (m, 1H), 2.32-2.12 (m, 3H), 2.01 (m, 1H), 1.86-1.68 (m, 2H), 1.08 (m, 21H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 216.4, 76.3, 35, 32.8, 18.1, 18.0, 16.9, 12.4; IR (neat): 2943, 2866, 1756, 1123, 881 $cm^{-1}$; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{14}H_{28}O_2SiNa$ 279.1751, found 279.1751;



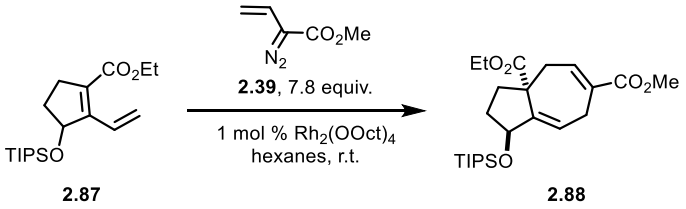

**2.86** **S2.5**

**ethyl 2-(((trifluoromethyl)sulfonyl)oxy)-3-((triisopropylsilyl)oxy)cyclopent-1-enecarboxylate (S2.5):** A solution of LiHMDS (42 mL, 1.0 M in THF, 1.2 equiv.) was diluted with THF (70 mL) and cooled to -78 °C. Ketone **2.86** (9.0 g, 35.2 mmol, 1.0 equiv.) in THF (70 mL) was added slowly dropwise. The mixture was stirred for 1 hour and freshly distilled ethyl cyanoformate was added quickly in one portion. The mixture was stirred for 2 hours and poured into water (150 mL). This solution was extracted with $Et_2O$ (2 x 150 mL). The organics were concentrated and purified by chromatography (19:1 pentane:$Et_2O$) to give the β-keto ester as a mixture of diastereomers/tautomers (6.1 g, 53 % yield). This oil (6.0 g, 16.7 mmol was dissolved in $CH_2Cl_2$ (120 mL) along with triethylamine (4.7 mL, 33.4 mmol, 2.0 equiv.) and the mixture cooled to -78 °C. Triflic anhydride (3.4 mL, 20.1 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was stirred for 3 hours and was poured into saturated aqueous $NaHCO_3$ (120 mL). The aqueous layer was extracted with DCM and the organic layers were combined, dried ($MgSO_4$) and concentrated. The crude was purified by flash column chromatography (19:1 pentane:$Et_2O$) to give the product as a colorless oil (6.7 g, 87% yield from β-Keto ester); $^1$H NMR (400 MHz; $CDCl_3$) δ 5.08 (m, 1H), 4.28 (qd, 2H, *J* = 7.2, 3.2 Hz), 2.77 (dddd, 1H, *J* = 16.2, 8.9, 4.6, 2.4 Hz), 2.58 (ddd, 1H, *J* = 16.2, 8.4, 4.7 Hz), 2.31 (m, 1H), 1.88 (ddt, 1H, *J* = 13.3, 8.9, 4.7 Hz), 1.33 (t, 3H, *J* = 7.2 Hz), 1.08 (m, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 162.7, 153.4, 125.0, 118.6 (q, *J*= 319 Hz), 75.7, 61.7, 31.2, 27, 18.1, 14.2, 12.7; IR (film): 2946, 2868, 1724, 1206 cm$^{-1}$; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{18}H_{31}O_6F_3SSiNa$ 483.1455, found 483.1462;

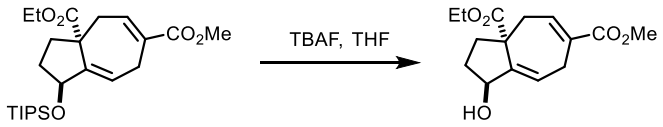



**S2.5** **2.87**

**ethyl 3-((triisopropylsilyl)oxy)-2-vinylcyclopent-1-enecarboxylate (2.87):** The vinyl triflate prepared as shown above (6.7 g, 14.5 mmol, 1.0 equiv.), potassium vinyltrifluoroborate (2.1 g, 16.0 mmol, 1.1 equiv.), $Pd(OAc)_2$, (196 mg, 0.87 mmol, 0.06 equiv.), $PPh_3$ (456 mg, 1.74 mmol, 0.12 equiv.), and $Cs_2CO_3$ (14.2 g, 43.5 mmol, 3.0 equiv.) were dissolved in THF/$H_2O$ (10:1, 75 mL). The mixture was heated to 50 °C with vigorous stirring for 3 hours followed by stirring at room temperature overnight. The reaction was washed with 1M HCl (100 mL), and $Et_2O$ added (75 mL). The organics were washed with brine, dried ($MgSO_4$), and concentrated. The crude was purified by column chromatography (0.5% to 2% Acetone in hexanes). The cleanest fraction from the column was used for analysis. The product partially co-eluted with the starting material to give a yellow oil that was 82 % pure by NMR (4.4 g of mixture = 3.6 g of product, 73 % yield). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.36 (dd, 1H, *J* = 17.9, 11.5 Hz), 5.73 (d, 1H, *J* = 17.0 Hz), 5.44 (d, 1H, *J* = 11.5 Hz), 5.29 (d, 1H, *J* = 3.7 Hz), 4.22 (q, 2H, *J* = 7.3 Hz), 2.83 (dt, 1H, *J* = 16.5, 6.9 Hz), 2.54 (ddd, 1H, *J* = 16.5, 8.5, 4.1 Hz), 2.11 (ddt, 1H, *J* = 13.3, 8.5, 6.9 Hz), 1.85 (m, 1H), 1.31 (t, 3H, *J* = 7.3 Hz), 1.08 (m, 21H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 166.1, 151.7, 131.4, 130.4, 121.2, 78.1, 60.4, 33.0, 31.6, 18.4, 14.5, 13.0; IR (neat): 2943, 2866, 1711, 1229 cm$^{-1}$; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{19}H_{34}O_3NaSi$ 361.2169, found 361.2174;




**ethyl 6-methyl 1-triisopropylsilyloxy-1,2,3,3a,4,7-hexahydroazulene-3a,6-dicarboxylate (2.88):** Diene **2.87** (82% by mass, 2.3 g, 5.5 mmol, 1.0 equiv.) and $Rh_2(OOct)_4$ (171 mg, 0.22 mmol, 0.04 equiv.) were dissolved in 15 mL hexanes and stirred for 10 minutes. Methyl 2-diazo-3-butenoate (17.3 g of a 32 % by mass solution in pentane, 43 mmol, 7.8 equiv.) was further diluted with 80 mL of hexanes. One half of this new solution was added dropwise to the reaction mixture over 2.5 hours. Meanwhile, the remainder of the diazo solution was kept at 0 °C. Once the first addition was complete, the second half of the diazo solution was added dropwise over 2.5 hours. The mixture was then stirred overnight at room temperature and concentrated under reduced pressure. The crude residue was purified by column chromatography (8 % EtOAc in hexanes) to give the product as a pale yellow oil (1.5 g, 63 % yield). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.10 (m, 1H), 5.81 (m, 1H), 4.71 (m, 1H), 4.10 (m, 2H), 3.71 (s, 3H), 3.28 (d, 1H, *J* = 21.4 Hz), 3.19 (m, 1H), 2.86 (ddd, 1H, *J* = 15.9, 8.0, 1.9 Hz), 2.49 (dq, 1H, *J* = 15.9, 3.1 Hz), 2.00 (m, 2H), 1.80 (m, 1H), 1.57 (m, 1H), 1.20 (t, 3H, *J* = 7.1 Hz), 1.16-1.06 (m, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 175.5, 168.5, 147.5, 140.4, 129.8, 119.2, 76.5, 61.0, 52.6, 52.1, 37.1, 35.3, 33.0, 28.0, 18.3, 14.3, 12.6; IR (neat): 2943, 2866, 1714, 1242 cm$^{-1}$; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{24}H_{40}O_5NaSi$ 459.2537, found 459.2539;




**2.88** **2.89**

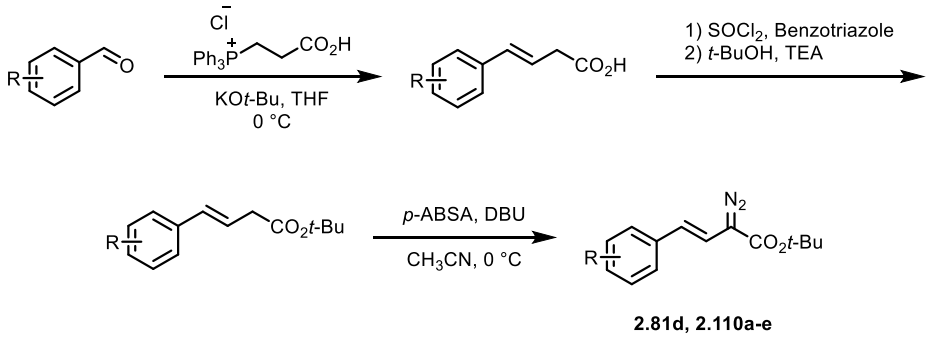
**ethyl 6-methyl 1-hydroxy-1,2,3,3a,4,7-hexahydroazulene-3a,6-dicarboxylate (2.89):** The silyl ether **2.88** (1.3 g, 3.0 mmol, 1.0 equiv.) was dissolved in THF (15 mL) and a solution of TBAF (6.0 mL, 1.0 M in THF, 2.0 equiv.) was added dropwise. The mixture was stirred for 3 hours and quenched with aqueous ammonium chloride (25 mL). The aqueous layer was extracted with $Et_2O$ (2 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude was purified by column chromatography (1:1 hexanes:EtOAc) to give the product **2.89** as a white solid (595 mg, 71 % yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 7.07 (m, 1H), 5.90 (ddd, 1H, *J* = 6.3, 4.5, 1.6 Hz), 4.64 (bs, 1H), 4.12 (m, 2H), 3.71 (s, 3H), 3.28-3.17 (m, 2H), 2.95 (ddd, 1H, *J* = 16.5, 7.8, 1.8 Hz), 2.47 (dq, 1H, *J* = 16.5, 3.1 Hz), 2.04 (m, 2H), 1.91 (m, 1H), 1.71 (bs, 1H, ), 1.63 (m, 1H), 1.21 (t, 3H, *J* = 7.1 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 175.0, 168.4, 149.2, 139.9, 129.4, 121.9, 76.4, 61.2, 54.3, 52.2, 37.1, 36.3, 33.1, 28, 14.4; IR (film): 3426, 2954, 1709, 1243 $cm^{-1}$;

## 2.3.5 Cyclopropanation of Electron-Deficient Alkenes

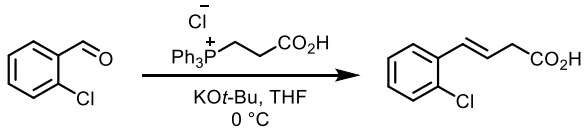
### 2.3.5.1 Synthesis of styryldiazoacetates

Diazo compound **2.81a** was prepared according to a literature procedure.[49] The *tert*-butyl styryldiazoacetates were prepared as shown in scheme 2.26 below. The procedure for the preparation of **2.110b** is given below. The remaining styryldiazoacetates were prepared analogously by the same procedure.

**Scheme 2.26** Synthesis of styryldiazo acetates

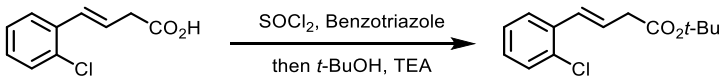



***Representative procedure for styryldiazoacetates:***

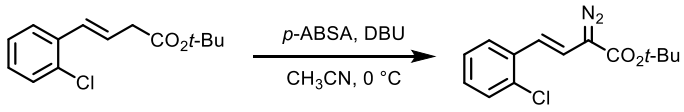



**(*E*)-4-(2-chlorophenyl)but-3-enoic acid**: To an oven-dried flask was added (2-carboxyethyl)triphenylphosphonium chloride (26.7 g, 72 mmol, 1.2 equiv). THF (200 mL) was added, under argon, followed by 2-chlorobenzaldehyde (6.7 mL, 60 mmol, 1.0 equiv). The mixture was cooled to 0 °C and stirred vigorously. Then potassium *tert*-butoxide (16.8 g, 150 mmol, 2.5 equiv) was added in one portion. The reaction mixture was stirred for 30 minutes at 0 °C before it was warmed to room temperature, and stirred overnight. The reaction mixture was diluted with $Et_2O$ (200 mL) and extracted with saturated aqueous sodium bicarbonate (3 x 150 mL). The combined aqueous extracts were washed with $Et_2O$ (3 x 100 mL) and then acidified to pH = 1.0 with concentrated HCl. $Et_2O$ (250 mL) was added and the aqueous layer removed. The ethereal layer was washed with brine, dried ($MgSO_4$) and concentrated to give the crude acid. This was purified by chromatography (10% to 15% $Et_2O$ in pentane, with 2% acetic acid). The

product so isolated was further purified by recrystallization from hexanes to give colorless needles that were pure enough for the next step: (5.5 g, ~47% yield).



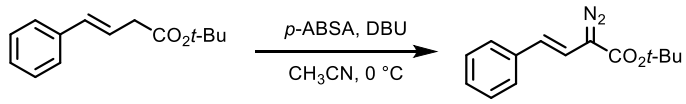

**(*E*)-*tert*-butyl 4-(2-chlorophenyl)but-3-enoate:** To a solution of the styrylacetic acid (4.0 g, 20.3 mmol, 1.0 equiv) in DCM (50 mL) was added dropwise a solution of benzotriazole (13.0 g, 16.2 mmol, 1.25 equiv) and thionyl chloride (1.9 mL, 16.2 mmol, 1.25 equiv) in DCM (17 mL) over 5 minutes. The mixture was stirred an additional 10 minutes and the precipitate filtered. The filtrate was stirred with $MgSO_4$-$7H_2O$ (5.0 g) for 10 minutes and filtered again. The filtrate was carefully poured into a solution of *tert*-butanol (50 mL) and triethylamine (5.6 mL, 40.6 mmol, 2.0 equiv). The solution was stirred under argon overnight. The reaction mixture was then washed with water (2 x 50 mL), dried ($MgSO_4$) and concentrated. The crude was purified by chromatography (3% $Et_2O$ in pentane) to give the *tert*-butyl ester as an oil, pure enough for the next step (1.6 g, 31% yield).




**2.110b**

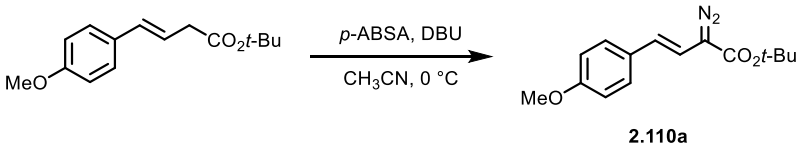
**(*E*)-*tert*-butyl 4-(2-chlorophenyl)-2-diazobut-3-enoate (2.110b):** The ester (1.6 g, 6.3 mmol, 1.0 equiv) and *p*-ABSA (2.3 g, 9.5 mmol, 1.5 equiv) were dissolved in acetonitrile (16 mL) and cooled to 0 °C. DBU (1.9 mL, 12.6 mmol, 2.0 equiv) was added dropwise. The mixture was stirred 3 hours and quenched with saturated aqueous $NH_4Cl$ (15 mL).

$Et_2O$ (20 mL) was added, and the aqueous layer removed. The organic layer was washed with brine, dried ($MgSO_4$) and the solvents removed by rotary evaporation. The solid crude residue was dissolved in pentane (150 mL) and the solids removed by filtration. The filtrate was concentrated by rotary evaporation below room temperature. The product was collected as a red crystalline solid (1.1 g, 61% yield).



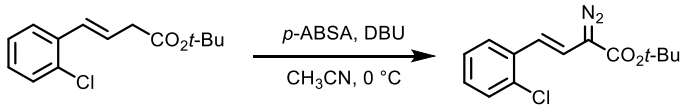

**2.81d**

**(*E*)-*tert*-butyl 2-diazo-4-phenylbut-3-enoate (2.81d):** Following the procedure above with the *tert*-butyl ester (781 mg, 3.6 mmol, 1.0 equiv), *p*-ABSA (1.3 g, 5.4 mmol, 1.5 equiv) and DBU (1.1 mL, 7.2 mmol, 2.0 equiv), the diazo was purified by column chromatography (5% $Et_2O$ in pentane). The red fractions were combined and concentrated below room temperature to give the product as a light red solid (520 mg, 59% yield). $^1$H-NMR (400 MHz; $CDCl_3$) $\delta$ 7.38-7.30 (m, 4H), 7.24-7.18 (m, 1H), 6.49 (d, 1H, $J$ = 16.3 Hz), 6.19 (d, 1H, $J$ = 16.3 Hz), 1.56 (s, 9H); $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$ 164.5, 137.1, 128.8, 127.0, 125.9, 122.6, 112.1, 82.4, 28.5, the resonance resulting from the diazo carbon was not detected; IR (neat): 2978, 2930, 2092, 1111 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{17}O_2N_2$ 245.1285, found 245.1286.



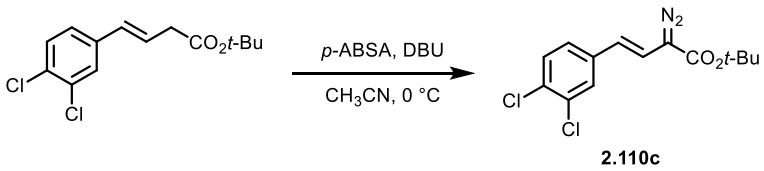

**2.110a**

**(*E*)-*tert*-butyl 2-diazo-4-(4-methoxyphenyl)but-3-enoate (2.110a):** Following the example procedure above with the *tert*-butyl ester (833 mg, 3.4 mmol, 1.0 equiv), *p*-ABSA (1.2 g, 5.0 mmol, 1.5 equiv), and DBU (1.0 mL, 6.8 mmol, 2.0 equiv) the diazo was purified by column chromatography (5% $Et_2O$ in pentane) to give the diazo as a red oil (692 mg, 74% yield). $^1$H-NMR (400 MHz; $CDCl_3$) $\delta$ 7.28 (d, 2H, $J$ = 8.6 Hz), 6.86 (d, 2H, $J$ = 8.6 Hz), 6.28 (d, 1H, $J$ = 16.3 Hz), 6.11 (d, 1H, $J$ = 16.3 Hz), 3.81 (s, 3H), 1.53 (s, 9H); $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$ 164.8, 158.9, 130.0, 127.1, 122.4, 114.2, 109.4, 82.2, 55.4, 28.5; the resonance resulting from the diazo carbon was not detected; IR (film): 2977, 2070, 1693, 1245 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{19}O_3N_2$ 275.1390, found 275.1391.



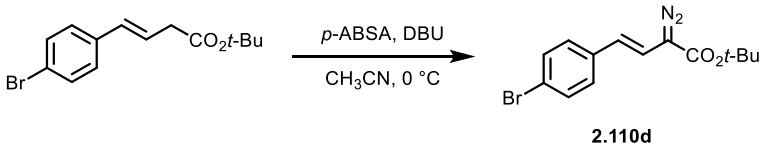

**2.110b**

**(*E*)-*tert*-butyl 4-(2-chlorophenyl)-2-diazobut-3-enoate (2.110b):** Used as the example procedure above. $^1$H-NMR (400 MHz; $CDCl_3$) $\delta$ 7.54 (dd, 1H, $J$ = 7.9, 1.6 Hz), 7.34 (d, 1H, $J$ = 7.9 Hz), 7.22 (t, 1H, $J$ = 7.9 Hz), 7.16-7.10 (m, 1H), 6.55 (d, 1H, $J$ = 16.3 Hz), 6.50 (d, 1H, $J$ = 16.3 Hz), 1.55 (s, 9H); $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$ 164.2, 135.1, 132.4, 129.9, 128.0, 126.3, 127.1, 118.3, 115.2, 82.6, 28.5; the resonance resulting from the diazo carbon was not detected; IR (neat): 2977, 2081, 1691, 1112 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{16}O_2N_2Cl$ 279.0895, found 279.0897.




**2.110c**

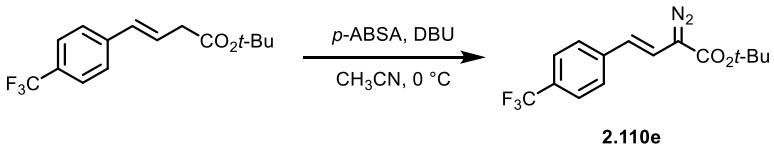
**(*E*)-*tert*-butyl 2-diazo-4-(3,4-dichlorophenyl)but-3-enoate (2.110c):** Following the example procedure above with the *tert*-butyl ester (765 mg, 2.7 mmol, 1.0 equiv), *p*-ABSA (960 mg, 4.0 mmol, 1.5 equiv) and DBU (0.81 mL, 5.4 mmol, 2.0 equiv) the diazo was purified by column chromatography (5% $Et_2O$ in pentane). The red fractions were combined and concentrated below room temperature to give the product as a light red powder (447 mg, 53 % yield). $^1$H-NMR (400 MHz; $CDCl_3$) $\delta$ 7.38 (s, 1H), 7.33 (d, 1H, $J$ = 8.4 Hz), 7.13 (d, 1H, $J$ = 8.4 Hz), 6.46 (d, 1H, $J$ = 16.7 Hz), 6.05 (d, 1H, $J$ = 16.7 Hz), 1.53 (s, 9H); $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$ 164.0, 137.3, 132.9, 130.6, 130.4, 127.5, 124.9, 119.9, 114.6, 82.8, 28.5; the resonance resulting from the diazo carbon was not detected; IR (neat): 2980, 2075, 1704, 1112 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{15}O_2N_2Cl_2$ 313.0505, found 313.0509.




**2.110d**

**(*E*)-*tert*-butyl 4-(4-bromophenyl)-2-diazobut-3-enoate (2.110d):** Following the example procedure above with the *tert*-butyl ester (625 mg, 2.1 mmol, 1.0 equiv), *p*-ABSA (757 mg, 3.2 mmol, 1.5 equiv) and DBU (0.63 mL, 4.2 mmol, 2.0 equiv) the diazo was purified by column chromatography (5% $Et_2O$ in pentane). The red fractions were combined and concentrated below room temperature to give the product as a light orange powder (275 mg, 41 % yield). $^1$H-NMR (400 MHz; $CDCl_3$) $\delta$ 7.43 (d, 2H, $J$ = 7.9 Hz),

7.21 (d, 2H, $J$ = 7.9 Hz), 6.47 (d, 1H, $J$ = 16.4 Hz), 6.11 (d, 1H, $J$ = 16.4 Hz), 1.54 (s, 9H); $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$ 164.4, 136.2, 132.0, 127.4, 121.4, 120.7, 113.2, 82.7, 28.5; the resonance resulting from the diazo carbon was not detected; IR (neat): 2978, 2078, 1697, 1247 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{14}H_{15}O_2N_2BrNa$ 345.0209, found 345.0212.




**2.110e**

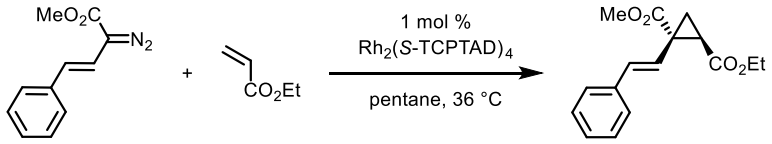
**(*E*)-*tert*-butyl 2-diazo-4-(4-(trifluoromethyl)phenyl)but-3-enoate (2.110e):** Following the example procedure above with the *tert*-butyl ester (1.2 g, 4.1 mmol, 1.0 equiv), *p*-ABSA (1.5 g, 6.1 mmol, 1.5 equiv) and DBU (1.2 mL, 8.2 mmol, 2.0 equiv) the diazo was purified by column chromatography (10% $Et_2O$ in pentane) to give the product as a light orange powder (760 mg, 58% yield). $^1$H-NMR (400 MHz; $CDCl_3$) $\delta$ 7.53 (d, 2H, $J$ = 8.2 Hz), 7.40 (d, 2H, $J$ = 8.2 Hz), 6.58 (d, 1H, $J$ = 16.3 Hz), 6.17 (d, 1H, $J$ = 16.3 Hz), 1.52 (s, 9H); $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$ 164.1, 140.6, 128.7 (q, $^2J_{CF}$ = 31.9 Hz), 126.0, 125.8 (q, $^3J_{CF}$ = 3.8 Hz), 120.9, 115.4, 82.9, 28.5; the resonances resulting from the diazo and $CF_3$ carbons were not detected; IR (neat): 2998, 2076, 1692, 1107 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{16}O_2N_2F_3$ 313.1158, found 313.1160;

### 2.3.5.2 General Procedure for Cyclopropanation

To a solution of alkene (5 equiv.) and $Rh_2$(*S*-TCPTAD)$_4$ (0.01 equiv.) in pentane (5 mL) at reflux was added a solution of diazo compound (1 equiv.) in pentane (5 mL) over 2 hours. The resulting mixture was stirred at reflux for another 1 hour before cooling

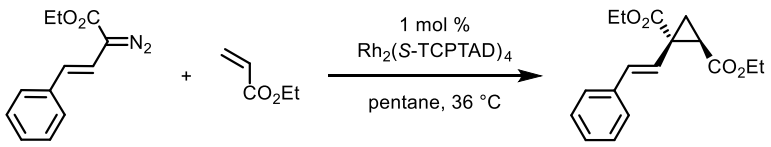
down to room temperature. The solvent was removed by rotary evaporation and the crude mixture was purified by flash chromatography.

### 2.3.5.3 Experimental Data for Cyclopropanes



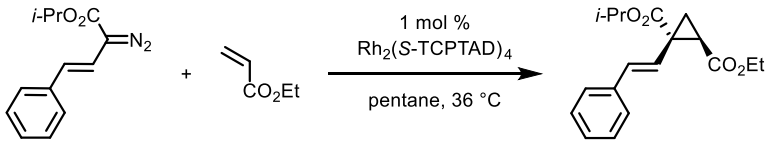

**2.81a** **2.103** **2.109a**

**(1*S*,2*R*)-2-ethyl 1-methyl 1-((*E*)-styryl)cyclopropane-1,2-dicarboxylate (2.109a):** From methyl (*E*)-4-phenyl-2-diazo-3-butenoate (101 mg, 0.5 mmol) and ethyl acrylate, via the standard procedure with $Rh_2$(*S*-TCPTAD)$_4$. Green tinged oil: 105 mg, 77 % yield. $^1$H NMR (600 MHz; $CDCl_3$) δ 7.38 (d, 2H, *J* = 7.6 Hz), 7.31 (t, 2H, *J* = 7.6 Hz), 7.24 (t, 1H, *J* = 7.6 Hz), 6.57 (d, 1H, *J* = 16.0 Hz), 6.40 (d, 1H, *J* = 16.0 Hz), 4.08 (q, 2H, *J* = 7.1 Hz), 3.75 (s, 3H), 2.57 (dd, 1H, *J* = 8.5, 6.8 Hz), 1.6 (dd, 1H, *J* = 6.8, 4.7 Hz), 1.82 (dd, 1H, *J* = 8.5, 4.7 Hz), 1.17 (t, 3H, *J* = 7.1 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.6, 168.6, 136.8, 134.2, 128.7, 127.9, 126.6, 121.3, 61.2, 52.9, 33.3, 31.4, 18.5, 14.4; IR (neat): 2982, 2953, 1721, 1181 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{19}O_4$ 275.1278, found 275.1278; The ee was determined by chiral HPLC: AD-H column, 1 mL/min, 1 % *i*-PrOH in hexanes. Major: 10.5 min, Minor: 12.6 min, 95 % ee.




**2.81b** **2.103** **2.109b**

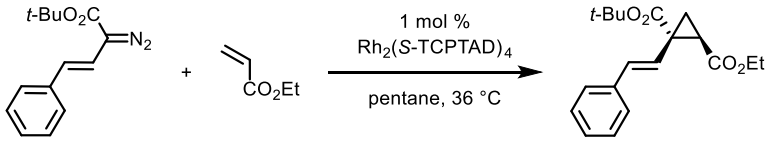
**(1*S*,2*R*)-diethyl 1-((*E*)-styryl)cyclopropane-1,2-dicarboxylate (2.109b):** From ethyl (*E*)-4-phenyl-2-diazo-3-butenoate (108 mg, 0.5 mmol, 1.0 equiv.) and ethyl acrylate, via the standard procedure with $Rh_2$(*S*-TCPTAD)$_4$. Green tinged oil: 123 mg, 85 % yield. $^1$H NMR (600 MHz; $CDCl_3$) δ 7.38 (d, 2H, *J* = 7.6 Hz), 7.31 (t, 2H, *J* = 7.6 Hz), 7.24 (t, 1H, *J* = 7.6 Hz), 6.58 (d, 1H, *J* = 16 Hz), 6.42 (d, 1H, *J* = 16 Hz), 4.20 (m, 2H), 4.08 (m, 2H), 2.57 (dd, 1H, *J* = 8.5, 6.8 Hz), 1.96 (dd, 1H, *J* = 6.8, 4.8 Hz), 1.82 (dd, 1H, *J* = 8.5, 4.8 Hz), 1.29 (t, 3H, *J* = 7.1 Hz), 1.17 (t, 3H, *J* = 7.1 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.0, 168.7, 136.9, 133.9, 128.6, 127.8, 126.6, 121.5, 61.9, 61.1, 33.4, 31.3, 18.4, 14.4, 14.3; IR (neat): 2981, 1719, 1242, 1143 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{21}O_4$ 289.1434, found 289.1434; The ee was determined by chiral HPLC: AD-H column, 1 mL/min, 1 % *i*-PrOH in hexanes. Major: 9.4 min, Minor: 11.5 min, 97 % ee.




**2.81c** **2.103** **2.109c**

**(1*S*,2*R*)-2-ethyl 1-isopropyl 1-((*E*)-styryl)cyclopropane-1,2-dicarboxylate (2.109c):** From ispropyl (*E*)-4-phenyl-2-diazo-3-butenoate (115 mg, 0.5 mmol, 1.0 equiv.) and ethyl acrylate, via the standard procedure with $Rh_2$(*S*-TCPTAD)$_4$. Green tinged oil: 131 mg, 87 % yield. $^1$H NMR (600 MHz; $CDCl_3$) δ 7.37 (d, 2H, *J* = 7.4 Hz), 7.31 (t, 2H, *J* = 7.4 Hz), 7.23 (t, 1H, *J* = 7.4 Hz), 6.57 (d, 1H, *J* = 16 Hz), 6.41 (d, 1H, *J* = 16 Hz), 5.04

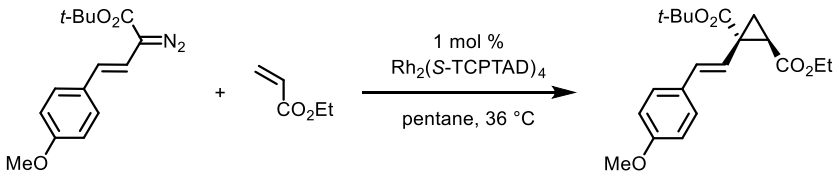
(spt, 1H, *J* = 6.3 Hz), 4.08 (m, 2H), 2.55 (dd, 1H, *J* = 8.5, 6.7 Hz), 1.94 (dd, 1H, *J* = 6.7, 4.7 Hz), 1.80 (dd, 1H, *J* = 8.5, 4.7 Hz), 1.28 (d, 3H, *J* = 6.3 Hz), 1.26 (d, 3H, *J* = 6.3 Hz), 1.17 (t, 3H, *J* = 7.1 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.4, 168.7, 136.9, 133.7, 128.6, 127.7, 126.5, 121.6, 69.3, 61.0, 33.5, 31.2, 21.8, 21.8, 18.3, 14.3; IR (neat): 2981, 1716, 1246, 1103 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{23}O_4$ 303.1591, found 303.1591; The ee was determined by chiral HPLC: AD-H column, 1 mL/min, 1 % *i*-PrOH in hexanes. Major: 8.1 min, Minor: 9.2 min, 98 % ee.




**2.81d** **2.103** **2.109d**

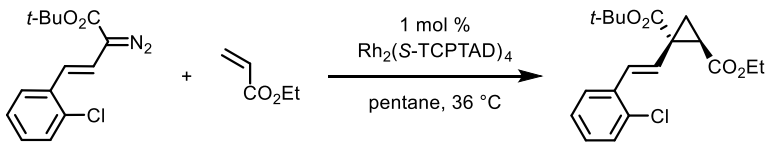
**(1*S*,2*R*)-1-*tert*-butyl 2-ethyl 1-((*E*)-styryl)cyclopropane-1,2-dicarboxylate (2.109d):** Prepared using the standard conditions with ethyl acrylate (0.27 mL, 2.5 mmol, 5.0 equiv), $Rh_2$(*S*-TCPTAD)$_4$ (11 mg, 1 mol %), in pentane (3 mL) and diazo **2.81d** (122 mg, 0.5 mmol, 1.0 equiv) in pentane (3 mL). The product was purified by column chromatography (8% $Et_2O$ in pentane) to give the product as a green tinged oil (131 mg, 89% yield) in 97% ee. $[\alpha]_D^{20}$: -70.6 (c. 2.0, $CHCl_3$); $^1$H-NMR (600 MHz; $CDCl_3$) *δ* 7.36 (d, 2H, *J* = 7.5 Hz), 7.29 (t, 2H, *J* = 7.5 Hz), 7.21 (t, 1H, *J* = 7.5 Hz), 6.53 (d, 1H, *J* = 16.1 Hz), 6.38 (d, 1H, *J* = 16.1 Hz), 4.09-4.01 (m, 2H), 2.50-2.47 (m, 1H), 1.90-1.87 (m, 1H), 1.74 (dd, 1H, *J* = 8.5, 4.6 Hz), 1.47 (s, 9H), 1.15 (t, 3H, *J* = 7.1 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) *δ* 171.0, 169.0, 137.1, 133.5, 128.6, 127.7, 126.6, 122.1, 82.0, 61.1, 34.2, 31.0, 28.2, 18.2, 14.4; IR (film): 2979, 1716, 1251, 1142 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{19}H_{24}O_4Na$ 339.1567, found 339.1568; The ee was determined by

chiral HPLC: AD-H column, 1 mL/min, 0.7 % iPrOH in hexanes. Major: 6.5 min, Minor: 8.1 min, 97% ee.



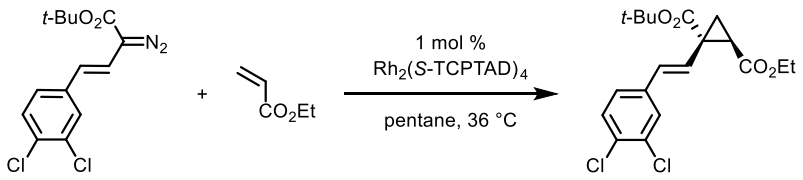

**2.110a** **2.103** **2.111a**

**(1*S*,2*R*)-1-*tert*-butyl 2-ethyl 1-((*E*)-4-methoxystyryl)cyclopropane-1,2-dicarboxylate (2.111a):** Prepared using the standard conditions with ethyl acrylate (0.27 mL, 2.5 mmol, 5.0 equiv), $Rh_2$(*S*-TCPTAD)$_4$ (1.1 mg, 0.1 mol %), in pentane (3 mL) and diazo **2.110a** (137 mg, 0.5 mmol, 1.0 equiv) in pentane (3 mL). After the diazo addition was complete another 1.1 mg (0.1 mol %) of the rhodium catalyst was added, and the mixture stirred at reflux for 1 hour before removing volatiles. The product was purified by column chromatography (10% $Et_2O$ in pentane) to give the product as a yellowish oil (134 mg, 77% yield) in 97% ee. $[\alpha]_D^{20}$: -62.2 (c. 1.8, $CHCl_3$); $^1$H-NMR (600 MHz; $CDCl_3$) $\delta$ 7.29 (d, 2H, *J* = 8.6 Hz), 6.82 (d, 2H, *J* = 8.6 Hz), 6.46 (d, 1H, *J* = 16.0 Hz), 6.23 (d, 1H, *J* = 16.0 Hz), 4.10-4.02 (m, 2H), 3.79 (s, 3H), 2.46 (dd, 1H, *J* = 8.5, 6.7 Hz), 1.87 (dd, 1H, *J* = 6.7, 4.7 Hz), 1.71 (dd, 1H, *J* = 8.5, 4.7 Hz), 1.46 (s, 9H), 1.14 (t, 3H, *J* = 7.1 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$ 171.1, 169.0, 159.3, 123.9, 129.9, 127.7, 119.7, 114.0, 81.9, 61.0, 55.4, 34.3, 30.9, 28.1, 18.1, 14.4; IR (neat): 2979, 1715, 1511, 1246 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{27}O_5$ 347.1853, found 347.1856; The ee was determined by chiral HPLC: AD-H column, 0.8 mL/min, 1 % *i*-PrOH in hexanes. Major: 13.2 min, Minor: 14.0 min, 97 % ee.



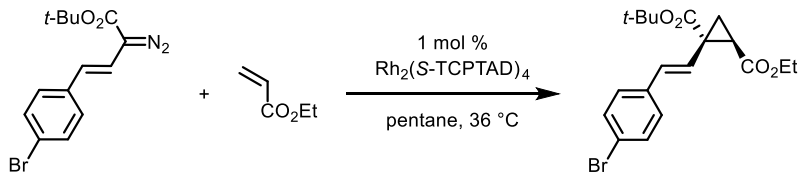

**2.110b** **2.103** **2.111b**

**(1*S*,2*R*)-1-*tert*-butyl 2-ethyl 1-((*E*)-2-chlorostyryl)cyclopropane-1,2-dicarboxylate (2.111b):** Prepared using the standard conditions with ethyl acrylate (0.27 mL, 2.5 mmol, 5.0 equiv), $Rh_2$(*S*-TCPTAD)$_4$ (11 mg, 1 mol %), in pentane (3 mL) and diazo **2.110b** (139 mg, 0.5 mmol, 1.0 equiv) in pentane (3 mL). The product was purified by column chromatography (6% $Et_2O$ in pentane) to give the product as a yellowish oil (141 mg, 81% yield) in 91% ee. $[\alpha]_D^{20}$: -66.2 (c. 1.5, $CHCl_3$); $^1$H-NMR (600 MHz; $CDCl_3$) $\delta$ 7.49 (dd, 1H, *J* = 7.6, 1.7 Hz), 7.33 (dd, 1H, *J* = 7.6, 1.4 Hz), 7.2 (td, 1H, *J* = 7.6, 1.4 Hz), 7.16 (td, 1H, *J* = 7.6, 1.7 Hz), 6.69 (d, 1H, *J* = 16.0 Hz), 6.36 (d, 1H, *J* = 16.0 Hz), 4.13-4.06 (m, 2H), 2.52 (d, 1H, *J* = 8.6, 6.7 Hz), 1.90 (dd, 1H, *J* = 6.7, 4.8 Hz), 1.78 (dd, 1H, *J* = 8.6, 4.8 Hz), 1.49 (s, 9H), 1.19 (t, 3H, *J* = 7.1 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$ 170.7, 169.1, 135.4, 133.2, 129.9, 129.8, 128.8, 127.0, 125.4, 82.2, 61.2, 34.4, 30.9, 28.2, 18.9, 14.5; IR (neat): 2979, 1716, 1250, 1143 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{24}O_4Cl$ 351.1358, found 351.1362; The ee was determined by chiral HPLC: AD-H column, 1 mL/min, 0.7 % *i*-PrOH in hexanes. Major: 5.7 min, Minor: 6.3 min, 91 % ee.



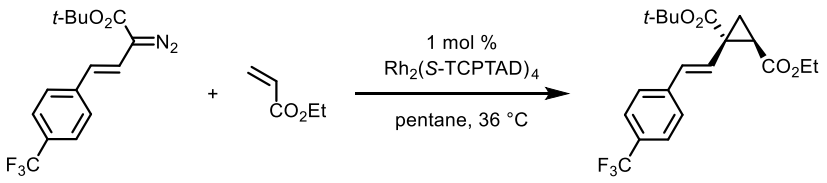

**2.110c** **2.103** **2.111c**

**(1*S*,2*R*)-1-*tert*-butyl 2-ethyl 1-((*E*)-3,4-dichlorostyryl)cyclopropane-1,2-dicarboxylate (2.111c):** Prepared using the standard conditions with ethyl acrylate (0.27 mL, 2.5 mmol, 5.0 equiv), $Rh_2$(*S*-TCPTAD)$_4$ (11 mg, 1 mol %), in pentane (3 mL) and diazo **2.110c** (157 mg, 0.5 mmol, 1.0 equiv) in pentane (3 mL). The product was purified by column chromatography (6% $Et_2O$ in pentane) to give the product as a yellowish oil (149 mg, 77% yield) in 98% ee. $[\alpha]_D^{20}$: -60.8 (c. 1.5, $CHCl_3$); $^1$H-NMR (600 MHz; $CDCl_3$) $\delta$ 7.42 (d, 1H, *J* = 1.9 Hz), 7.34 (d, 1H, *J* = 8.6 Hz), 7.17 (dd, 1H, *J* = 8.6, 1.9 Hz), 6.45 (d, 1H, *J* = 16.2 Hz), 6.38 (d, 1H, *J* = 16.2 Hz), 4.12-4.03 (m, 2H), 2.49 (dd, 1H, *J* = 8.5, 6.7 Hz), 1.84 (dd, 1H, *J* = 6.7, 4.7 Hz), 1.76 (dd, 1H, *J* = 8.5, 4.7 Hz), 1.46 (s, 9H), 1.17 (t, 3H, *J* = 7.1 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$ 170.5, 168.9, 137.2, 132.8, 131.3, 131.2, 130.6, 128.2, 125.7, 124.4, 82.3, 61.2, 34.1, 31.0, 28.1, 18.5, 14.5; IR (neat): 2979, 1716, 1184, 1131 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{23}O_4Cl_2$ 385.0968, found 385.0974; The ee was determined by chiral HPLC: SS Whelk column, 1 mL/min, 1 % *i*-PrOH in hexanes. Major: 15.2 min, Minor: 11.5 min, 98 % ee.




**2.110d** **2.103** **2.111d**

**(1*S*,2*R*)-1-*tert*-butyl 2-ethyl 1-((*E*)-4-bromostyryl)cyclopropane-1,2-dicarboxylate (2.111d):** Prepared using the standard conditions with ethyl acrylate (0.22 mL, 2.0 mmol, 5.0 equiv), $Rh_2$(*S*-TCPTAD)$_4$ (8 mg, 1 mol %), in pentane (3 mL) and diazo **2.110d** (129 mg, 0.4 mmol, 1.0 equiv) in pentane (3 mL). The product was purified by column chromatography (5% $Et_2O$ in pentane) to give the product as a yellowish oil (136 mg, 86% yield) in 98% ee. $[\alpha]_D^{20}$: -49.3 (c. 1.8, $CHCl_3$); $^1$H-NMR (600 MHz; $CDCl_3$) $\delta$ 7.42 (d, 2H, $J$ = 8.4 Hz), 7.23 (d, 2H, $J$ = 8.4 Hz), 6.49 (d, 1H, $J$ = 15.7 Hz), 6.38 (d, 1H, $J$ = 15.7 Hz), 4.11-4.02 (m, 2H), 2.50 (dd, 1H, $J$ = 8.4, 6.7 Hz), 1.87 (dd, 1H, $J$ = 6.7, 4.8 Hz), 1.76 (dd, 1H, $J$ = 8.6, 4.8 Hz), 1.47 (s, 9H), 1.16 (t, 3H, $J$ = 7.1 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$ 170.7, 169.0, 136.1, 132.3, 131.8, 128.1, 123.0, 121.5, 82.1, 61.2, 34.2, 31.0, 28.2, 18.4, 14.5; IR (neat): 2978, 1716, 1250, 1411 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{23}O_4BrNa$ 417.0672, found 417.0674; The ee was determined by chiral HPLC: SS-Whelk column, 1 mL/min, 1 % *i*PrOH in hexanes. Major: 16.8 min, Minor: 12.7 min, 98 % ee.




**(1*S*,2*R*)-1-*tert*-butyl 2-ethyl 1-((*E*)-4-(trifluoromethyl)styryl)cyclopropane-1,2-dicarboxylate (2.111e):** Prepared using the standard conditions with ethyl acrylate (0.27 mL, 2.5 mmol, 5.0 equiv), $Rh_2$(*S*-TCPTAD)$_4$ (11 mg, 1 mol %), in pentane (3 mL) and diazo **2.110e** (156 mg, 0.5 mmol, 1.0 equiv) in pentane (3 mL). The product was purified by column chromatography (5% $Et_2O$ in pentane) to give the product as a pale yellow oil (164 mg, 85% yield) in 95% ee. $[\alpha]_D^{20}$: -59.4 (c. 1.62, $CHCl_3$); $^1$H-NMR (600 MHz; $CDCl_3$) $\delta$ 7.51 (d, 2H, $J$ = 8.2 Hz), 7.42 (d, 2H, $J$ = 8.2 Hz), 6.57 (d, 1H, $J$ = 16.1 Hz), 6.47 (d, 1H, $J$ = 16.1 Hz), 4.12-4.03 (m, 2H), 2.50 (dd, 1H, $J$ = 8.5, 6.7 Hz), 1.86 (dd, 1H, $J$ = 6.7, 4.7 Hz), 1.76 (dd, 1H, $J$ = 8.5, 4.7 Hz), 1.45 (s, 9H), 1.14 (t, 3H, $J$ = 7.1 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$ 170.6, 168.9, 140.6, 132.1, 129.4 ($^2J_{CF}$ = 32.3 Hz), 126.7, 125.6 ($^3J_{CF}$ = 3.8 Hz), 125.1, 124.4 ($^1J_{CF}$ = 272 Hz), 82.3, 61.2, 34.1, 31.1, 28.1, 18.5, 14.4; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{24}O_4F_3$ 385.1621, found 385.1626; The ee was determined by chiral HPLC: SS-Whelk column, 1 mL/min, 1 % *i*-PrOH in hexanes. Major: 10.9 min, Minor: 8.3 min, 95 % ee.

## 2.3.6 X-Ray Crystal Structure Data for 2.81

**Table 1. Crystal data and structure refinement for 2.81.**

| | |
|---|---|
| Identification code | **2.81** |
| Empirical formula | C14 H16 O5 |
| Formula weight | 264.27 |
| Temperature | 173(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Monoclinic |

| | | |
|---|---|---|
| Space group | C 2/c | |
| Unit cell dimensions | a = 19.0413(13) Å | $\alpha$= 90°. |
| | b = 12.4083(7) Å | $\beta$= 130.682(3)°. |
| | c = 14.3134(16) Å | $\gamma$ = 90°. |
| Volume | 2564.6(4) $Å^3$ | |
| Z | 8 | |
| Density (calculated) | 1.369 $Mg/m^3$ | |
| Absorption coefficient | 0.104 $mm^{-1}$ | |
| F(000) | 1120 | |
| Crystal size | 0.679 x 0.496 x 0.408 $mm^3$ | |
| Theta range for data collection | 2.16 to 29.57°. | |
| Index ranges | -26<=h<=17, -17<=k<=17, -11<=l<=19 | |
| Reflections collected | 11212 | |
| Independent reflections | 3585 [R(int) = 0.0334] | |
| Completeness to theta = 29.57° | 99.6 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.9404 and 0.6414 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3585 / 0 / 188 | |
| Goodness-of-fit on $F^2$ | 1.018 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0473, wR2 = 0.1267 | |
| R indices (all data) | R1 = 0.0586, wR2 = 0.1368 | |
| Largest diff. peak and hole | 0.417 and -0.173 $e.Å^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for **2.81**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 4096(1) | 1822(2) | -2195(2) | 51(1) |
| C(2) | 5086(1) | 318(1) | -1214(1) | 26(1) |
| C(3) | 6030(1) | -74(1) | -137(1) | 22(1) |
| C(4) | 6569(1) | 590(1) | 839(1) | 20(1) |
| C(5) | 7508(1) | 392(1) | 2050(1) | 20(1) |
| C(6) | 8141(1) | -350(1) | 2037(1) | 20(1) |
| C(7) | 8279(1) | 12(1) | 1151(1) | 22(1) |
| C(8) | 8345(1) | 1486(1) | 177(1) | 35(1) |
| C(9) | 9118(1) | -437(1) | 3339(1) | 29(1) |
| C(10) | 9467(1) | -1585(1) | 3432(1) | 36(1) |
| C(11) | 8596(1) | -2231(1) | 2570(1) | 32(1) |
| C(12) | 7804(1) | -1514(1) | 1735(1) | 23(1) |
| C(13) | 6939(1) | -1826(1) | 516(1) | 28(1) |
| C(14) | 6203(1) | -1196(1) | -266(1) | 27(1) |
| O(1) | 5007(1) | 1392(1) | -1230(1) | 40(1) |
| O(2) | 4450(1) | -251(1) | -1998(1) | 40(1) |
| O(3) | 8187(1) | 1077(1) | 972(1) | 28(1) |
| O(4) | 8497(1) | -574(1) | 710(1) | 41(1) |
| O(5) | 7950(1) | -2028(1) | 2770(1) | 30(1) |

Table 3. Bond lengths [Å] and angles [°] for **2.81**.

| | |
|---|---|
| O(1)-C(1) | 1.442(3) |
| O(1)-C(2) | 1.3390(17) |
| O(2)-C(2) | 1.2054(19) |
| O(3)-C(7) | 1.3354(14) |
| O(3)-C(8) | 1.445(2) |
| O(4)-C(7) | 1.201(2) |
| O(5)-C(11) | 1.455(3) |
| O(5)-C(12) | 1.4633(18) |
| C(2)-C(3) | 1.495(2) |
| C(3)-C(4) | 1.3467(17) |
| C(3)-C(14) | 1.4692(18) |
| C(4)-C(5) | 1.4902(19) |
| C(5)-C(6) | 1.527(2) |
| C(6)-C(7) | 1.522(2) |
| C(6)-C(9) | 1.557(2) |
| C(6)-C(12) | 1.5229(17) |
| C(9)-C(10) | 1.540(2) |
| C(10)-C(11) | 1.499(2) |
| C(11)-C(12) | 1.465(2) |
| C(12)-C(13) | 1.471(2) |
| C(13)-C(14) | 1.336(2) |
| C(1)-H(1A) | 0.9800 |
| C(1)-H(1B) | 0.9800 |
| C(1)-H(1C) | 0.9800 |
| C(4)-H(4) | 0.9500 |
| C(5)-H(5A) | 0.9900 |
| C(5)-H(5B) | 0.9900 |
| C(8)-H(8A) | 0.9800 |
| C(8)-H(8B) | 0.9800 |
| C(8)-H(8C) | 0.9800 |
| C(9)-H(9A) | 0.9900 |
| C(9)-H(9B) | 0.9900 |
| C(10)-H(10A) | 0.9900 |
| C(10)-H(10B) | 0.9900 |

| | |
|---|---|
| C(11)-H(11) | 0.9300 |
| C(13)-H(13) | 0.9500 |
| C(14)-H(14) | 0.9500 |

| | |
|---|---|
| C(1)-O(1)-C(2) | 115.84(13) |
| C(7)-O(3)-C(8) | 115.41(13) |
| C(11)-O(5)-C(12) | 60.26(10) |
| O(1)-C(2)-O(2) | 122.25(15) |
| O(1)-C(2)-C(3) | 112.80(12) |
| O(2)-C(2)-C(3) | 124.94(13) |
| C(2)-C(3)-C(4) | 117.50(12) |
| C(2)-C(3)-C(14) | 113.32(11) |
| C(4)-C(3)-C(14) | 128.93(13) |
| C(3)-C(4)-C(5) | 129.13(12) |
| C(4)-C(5)-C(6) | 116.28(11) |
| C(5)-C(6)-C(7) | 113.48(10) |
| C(5)-C(6)-C(9) | 111.37(11) |
| C(5)-C(6)-C(12) | 112.72(14) |
| C(7)-C(6)-C(9) | 107.24(14) |
| C(7)-C(6)-C(12) | 108.22(11) |
| C(9)-C(6)-C(12) | 103.18(10) |
| O(3)-C(7)-O(4) | 123.12(15) |
| O(3)-C(7)-C(6) | 112.33(12) |
| O(4)-C(7)-C(6) | 124.43(11) |
| C(6)-C(9)-C(10) | 106.21(11) |
| C(9)-C(10)-C(11) | 103.92(15) |
| O(5)-C(11)-C(10) | 111.62(13) |
| O(5)-C(11)-C(12) | 60.16(11) |
| C(10)-C(11)-C(12) | 110.12(11) |
| O(5)-C(12)-C(6) | 111.02(10) |
| O(5)-C(12)-C(11) | 59.59(11) |
| O(5)-C(12)-C(13) | 114.36(14) |
| C(6)-C(12)-C(11) | 109.03(13) |
| C(6)-C(12)-C(13) | 121.71(10) |
| C(11)-C(12)-C(13) | 124.68(11) |
| C(12)-C(13)-C(14) | 126.28(11) |

| | |
|---|---|
| C(3)-C(14)-C(13) | 130.38(12) |
| O(1)-C(1)-H(1A) | 109.00 |
| O(1)-C(1)-H(1B) | 109.00 |
| O(1)-C(1)-H(1C) | 109.00 |
| H(1A)-C(1)-H(1B) | 110.00 |
| H(1A)-C(1)-H(1C) | 109.00 |
| H(1B)-C(1)-H(1C) | 109.00 |
| C(3)-C(4)-H(4) | 115.00 |
| C(5)-C(4)-H(4) | 115.00 |
| C(4)-C(5)-H(5A) | 108.00 |
| C(4)-C(5)-H(5B) | 108.00 |
| C(6)-C(5)-H(5A) | 108.00 |
| C(6)-C(5)-H(5B) | 108.00 |
| H(5A)-C(5)-H(5B) | 107.00 |
| O(3)-C(8)-H(8A) | 110.00 |
| O(3)-C(8)-H(8B) | 109.00 |
| O(3)-C(8)-H(8C) | 109.00 |
| H(8A)-C(8)-H(8B) | 109.00 |
| H(8A)-C(8)-H(8C) | 109.00 |
| H(8B)-C(8)-H(8C) | 109.00 |
| C(6)-C(9)-H(9A) | 110.00 |
| C(6)-C(9)-H(9B) | 111.00 |
| C(10)-C(9)-H(9A) | 110.00 |
| C(10)-C(9)-H(9B) | 111.00 |
| H(9A)-C(9)-H(9B) | 109.00 |
| C(9)-C(10)-H(10A) | 111.00 |
| C(9)-C(10)-H(10B) | 111.00 |
| C(11)-C(10)-H(10A) | 111.00 |
| C(11)-C(10)-H(10B) | 111.00 |
| H(10A)-C(10)-H(10B) | 109.00 |
| O(5)-C(11)-H(11) | 118.00 |
| C(10)-C(11)-H(11) | 117.00 |
| C(12)-C(11)-H(11) | 127.00 |
| C(12)-C(13)-H(13) | 117.00 |
| C(14)-C(13)-H(13) | 117.00 |
| C(3)-C(14)-H(14) | 115.00 |

C(13)-C(14)-H(14) 115.00

---

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **2.81**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 28(1) | 62(1) | 41(1) | 18(1) | 12(1) | 17(1) |
| C(2) | 23(1) | 35(1) | 20(1) | 1(1) | 14(1) | -3(1) |
| C(3) | 22(1) | 23(1) | 18(1) | 1(1) | 13(1) | -2(1) |
| C(4) | 24(1) | 18(1) | 20(1) | 1(1) | 15(1) | 1(1) |
| C(5) | 24(1) | 19(1) | 16(1) | -1(1) | 13(1) | 0(1) |
| C(6) | 24(1) | 18(1) | 18(1) | 2(1) | 13(1) | 1(1) |
| C(7) | 23(1) | 21(1) | 21(1) | 0(1) | 13(1) | -1(1) |
| C(8) | 52(1) | 29(1) | 38(1) | 8(1) | 36(1) | 2(1) |
| C(9) | 24(1) | 34(1) | 21(1) | 5(1) | 11(1) | 3(1) |
| C(10) | 33(1) | 40(1) | 34(1) | 15(1) | 21(1) | 15(1) |
| C(11) | 44(1) | 23(1) | 38(1) | 11(1) | 31(1) | 12(1) |
| C(12) | 33(1) | 17(1) | 26(1) | 3(1) | 22(1) | 2(1) |
| C(13) | 40(1) | 18(1) | 30(1) | -6(1) | 25(1) | -5(1) |
| C(14) | 32(1) | 24(1) | 24(1) | -8(1) | 17(1) | -8(1) |
| O(1) | 25(1) | 35(1) | 38(1) | 10(1) | 11(1) | 5(1) |
| O(2) | 26(1) | 52(1) | 27(1) | -8(1) | 11(1) | -9(1) |
| O(3) | 43(1) | 20(1) | 30(1) | 2(1) | 28(1) | -1(1) |
| O(4) | 67(1) | 26(1) | 57(1) | 2(1) | 53(1) | 5(1) |
| O(5) | 43(1) | 24(1) | 34(1) | 8(1) | 30(1) | 6(1) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for **2.81**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A) | 3871 | 1563 | -2996 | 73(7) |
| H(1B) | 4124 | 2611 | -2177 | 109 |
| H(1C) | 3672 | 1585 | -2069 | 109 |
| H(4) | 6316 | 1282 | 741 | 21(3) |
| H(5A) | 7432 | 81 | 2617 | 28(4) |
| H(5B) | 7823 | 1096 | 2396 | 30(4) |
| H(8A) | 8194 | 2255 | 26 | 62(6) |
| H(8B) | 7951 | 1095 | -608 | 53(5) |
| H(8C) | 8997 | 1383 | 574 | 53(5) |
| H(9A) | 9543 | 106 | 3434 | 39(4) |
| H(9B) | 9080 | -315 | 3988 | 36(4) |
| H(10A) | 9838 | -1600 | 3173 | 41(5) |
| H(10B) | 9849 | -1863 | 4285 | 47(5) |
| H(11) | 8655 | -2936 | 2410 | 36(4) |
| H(13) | 6900 | -2546 | 259 | 33(4) |
| H(14) | 5711 | -1526 | -1029 | 33(4) |

Table 6. Torsion angles [°] for **2.81**.

| | |
|---|---|
| C(1)-O(1)-C(2)-O(2) | 4.3(3) |
| C(1)-O(1)-C(2)-C(3) | -175.71(16) |
| C(8)-O(3)-C(7)-C(6) | 177.66(13) |
| C(8)-O(3)-C(7)-O(4) | 1.5(2) |
| C(11)-O(5)-C(12)-C(13) | 117.29(14) |
| C(11)-O(5)-C(12)-C(6) | -100.34(15) |
| C(12)-O(5)-C(11)-C(10) | 101.48(12) |
| O(2)-C(2)-C(3)-C(4) | -160.07(18) |
| O(1)-C(2)-C(3)-C(4) | 20.0(2) |
| O(2)-C(2)-C(3)-C(14) | 14.8(3) |
| O(1)-C(2)-C(3)-C(14) | -165.19(15) |
| C(2)-C(3)-C(14)-C(13) | -177.0(2) |
| C(4)-C(3)-C(14)-C(13) | -2.8(3) |
| C(14)-C(3)-C(4)-C(5) | 2.3(3) |
| C(2)-C(3)-C(4)-C(5) | 176.22(16) |
| C(3)-C(4)-C(5)-C(6) | 32.5(2) |
| C(4)-C(5)-C(6)-C(12) | -68.10(15) |
| C(4)-C(5)-C(6)-C(7) | 55.36(16) |
| C(4)-C(5)-C(6)-C(9) | 176.48(12) |
| C(9)-C(6)-C(7)-O(3) | -95.84(14) |
| C(12)-C(6)-C(7)-O(4) | -30.5(2) |
| C(5)-C(6)-C(9)-C(10) | 147.51(14) |
| C(5)-C(6)-C(7)-O(4) | -156.37(15) |
| C(5)-C(6)-C(12)-O(5) | -72.60(15) |
| C(5)-C(6)-C(12)-C(11) | -136.42(14) |
| C(5)-C(6)-C(12)-C(13) | 66.6(2) |
| C(7)-C(6)-C(12)-O(5) | 161.06(13) |
| C(7)-C(6)-C(12)-C(11) | 97.24(15) |
| C(7)-C(6)-C(9)-C(10) | -87.79(15) |
| C(5)-C(6)-C(7)-O(3) | 27.57(17) |
| C(9)-C(6)-C(12)-C(11) | -16.18(18) |
| C(9)-C(6)-C(12)-C(13) | -173.18(17) |
| C(9)-C(6)-C(7)-O(4) | 80.21(17) |
| C(12)-C(6)-C(7)-O(3) | 153.46(13) |

| | |
|---|---|
| C(12)-C(6)-C(9)-C(10) | 26.34(18) |
| C(9)-C(6)-C(12)-O(5) | 47.64(18) |
| C(7)-C(6)-C(12)-C(13) | -59.8(2) |
| C(6)-C(9)-C(10)-C(11) | -26.66(18) |
| C(9)-C(10)-C(11)-O(5) | -47.99(15) |
| C(9)-C(10)-C(11)-C(12) | 16.9(2) |
| O(5)-C(11)-C(12)-C(13) | -100.10(19) |
| O(5)-C(11)-C(12)-C(6) | 103.74(13) |
| C(10)-C(11)-C(12)-C(13) | 155.87(18) |
| C(10)-C(11)-C(12)-O(5) | -104.02(15) |
| C(10)-C(11)-C(12)-C(6) | -0.3(2) |
| O(5)-C(12)-C(13)-C(14) | 110.9(2) |
| C(6)-C(12)-C(13)-C(14) | -27.0(3) |
| C(11)-C(12)-C(13)-C(14) | 179.6(2) |
| C(12)-C(13)-C(14)-C(3) | -2.2(4) |

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for **2.81** [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| C(1)-H(1B)...O(3)#1 | 0.9800 | 2.5900 | 3.279(2) | 128.00 |
| C(4)-H(4)...O(1) | 0.9500 | 2.2400 | 2.6693(18) | 106.00 |
| C(8)-H(8B)...O(5)#2 | 0.9800 | 2.5900 | 3.085(2) | 111.00 |
| C(11)-H(11)...O(2)#3 | 0.9300 | 2.5300 | 3.3876(19) | 154.00 |
| C(13)-H(13)...O(4)#4 | 0.9500 | 2.5600 | 3.5029(16) | 170.00 |
| C(14)-H(14)...O(2) | 0.9500 | 2.4200 | 2.806(2) | 104.00 |

Symmetry transformations used to generate equivalent atoms:

#1 x-1,-y,1/2+z-1 #2 -x,y,1/2-z-1 #3 x,-y-1,1/2+z

#4+5

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# Chapter 3 – Stereoselective Synthesis of Allylsilanes

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## Contents

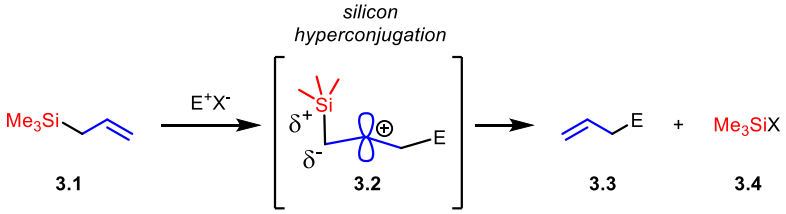
# 3.1 Introduction

## 3.1.1 Uses for Allylsilanes

### 3.1.1.1 Properties and Reactions of Allylsilanes

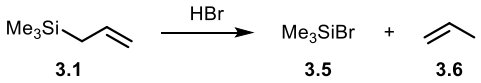
Allylsilanes represent an important class of reagents in organic synthesis. Because silicon is electropositive relative to carbon, the C–Si bond of allylsilanes enhances the nucleophilicity of the pendant alkene. Referred to as the β-silicon effect, the stabilizing nature of the silicon on carbocation intermediate **3.2** has allowed these reagents to become effective allylating reagents (see Scheme 3.1).

**Scheme 3.1** Stabilization of carbocations: the β-silicon effect and allylation of electrophiles



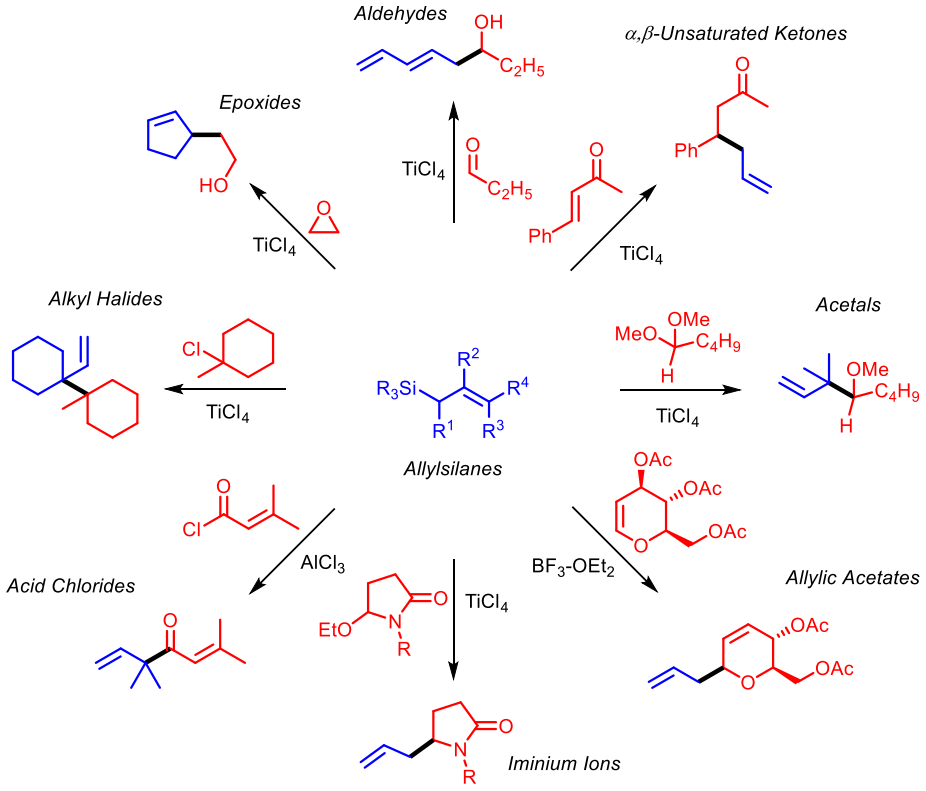

The electrophilic substitution of an allylsilane was first demonstrated in 1948 (Eq. 3.1)[1] with the allylation of HBr by allyltrimethylsilane (**3.1**). Since then, the weak nucleophilicity of allylsilanes has been widely demonstrated. It has been shown that allylsilanes are capable of transferring the allyl group to any number of electrophiles (Scheme 3.2), including alkyl halides, epoxides, aldehydes, α,β-unsaturated ketones, acetals, allylic acetates, iminium ions, and acid chlorides.[2] Additionally, this occurs routinely with migration of the allyl group (see Scheme 3.1 and Scheme 3.2), enabling predictability in reaction outcome. There is rich literature precedence for the scope of

this transformation,[3–7] but allylation of electrophiles is undoubtedly the most commonly used reaction of these reagents.




(Eq. 3.1)

**Scheme 3.2** Reactions of allylsilanes with electrophiles

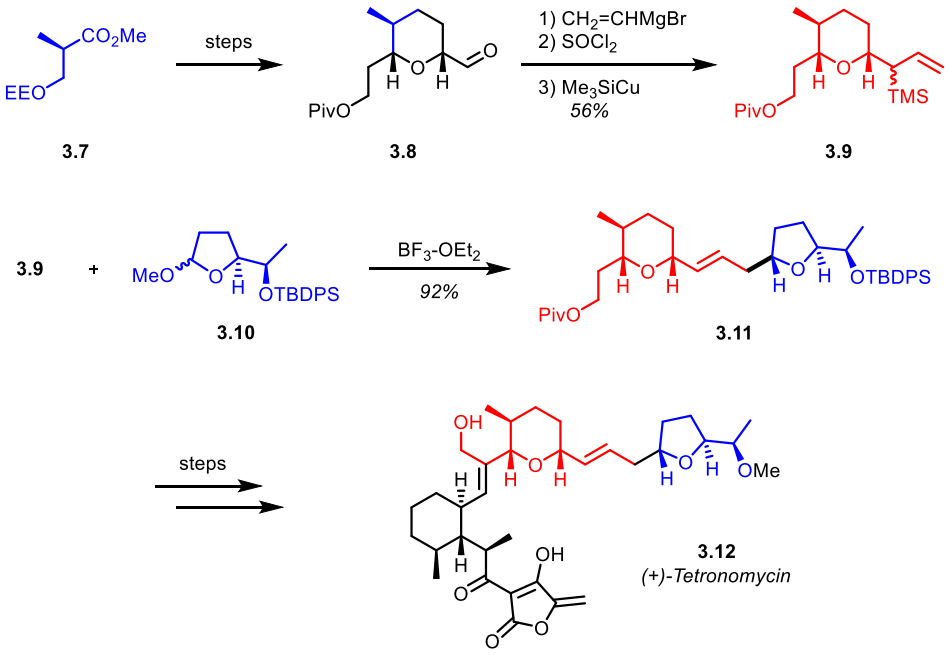



### 3.1.1.2 Allylsilanes in Total Synthesis

The versatility of allylsilanes makes them very useful as building blocks in organic synthesis and allylsilanes have found widespread use in the construction of complex organic molecules. The use of allylsilanes in total synthesis has been examined in several excellent reviews.[8,9] One example of such an application comes from Yoshii's total synthesis of (+)-Tetronomycin (**3.12**, Scheme 3.3).[10] In this synthesis, the polyether fragment of the natural product was prepared by an allylsilane coupling between

tetrahydropyranyl-allylsilane **3.9** and tetrahydrofuran **3.10**. The allylsilane component was prepared from the corresponding aldehyde **3.8** by addition of vinylmagnesium bromide, followed by conversion to the chloride and installation of the $SiMe_3$ component by displacement. In the coupling event, treatment of **3.10** with boron trifluoride diethyl etherate in the presence of allylsilane **3.9** gave intermediate **3.11**, which was subsequently converted to the natural product.

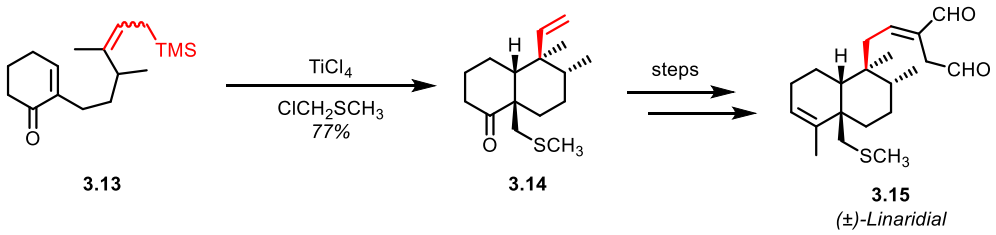
**Scheme 3.3** Allylsilane reaction in the total synthesis of (+)-Tetronomycin




The above example represents an intermolecular reaction of an allylsilane, but they have also been used in an intramolecular sense to prepare natural products as well. In Tokoyorama's synthesis of (±)-Linaridial (**3.15**), the key step is an intramolecular coupling of an allylsilane and an α,β-unsaturated ketone (Scheme 3.4).[11] Intermediate **3.13** was treated with titanium (IV) chloride, initiating a 1,4-addition of the attached allylsilane to the unsaturated ketone. The resulting enolate was trapped with chloromethyl methyl thioether to give **3.14**, the core of the natural product, with complete

control over all 4 contiguous stereocenters. This is also an excellent example of the exquisite selectivity of allylation reactions with allylsilanes; the highly congested product with a quaternary stereocenter is the sole product from this reaction.

**Scheme 3.4** Intramolecular allylsilane reaction in the synthesis of (±)-Linaridial




## 3.1.2 Preparation of Allylsilanes

Considerable attention has been devoted to the preparation of allylsilanes. A complete discussion of allylsilane synthesis would be too extensive for this discussion. Rather, several representative methods will be discussed. An excellent review of the preparation of allylsilanes can be found in *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*.[7] All of the methods and specific reactions discussed here are taken from that review unless another reference is specifically cited. Preparation of allylsilanes from *existing* allylsilanes (i.e. modification of allylsilanes) will not be discussed here.

Allylsilanes contain three main bonds (Figure 1): one C–Si bond, one C–C single bond, and one C–C double bond. The installation of these bonds in the preparation of allylsilanes will form the framework for this portion of the introduction.

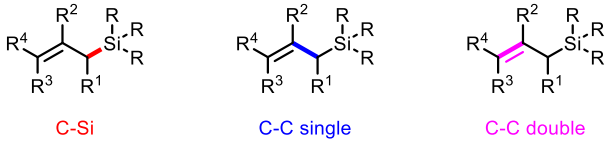
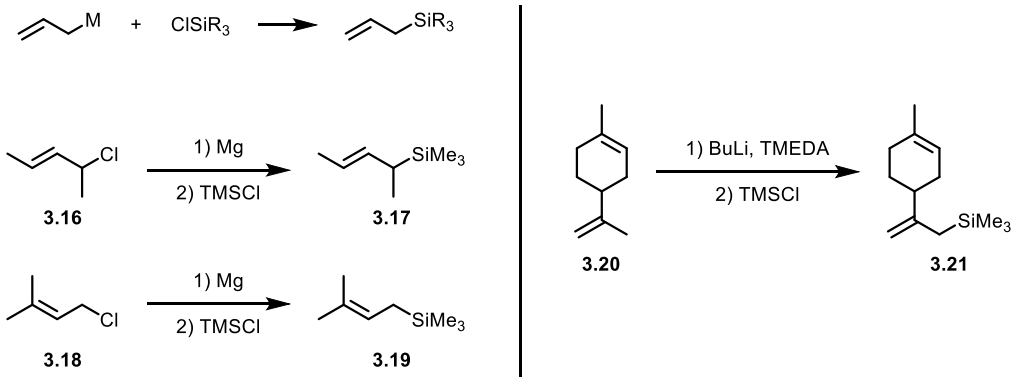



**Figure 3.1** Three allylsilane bonds

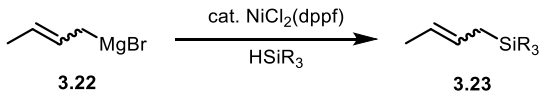
### 3.1.2.1 Preparation of allylsilanes by forming the C–Si bond

Perhaps the most obvious, and simplest, strategy for the preparation of allylsilanes is to use an allylmetal reagent such as a Grignard reagent together with a chlorosilane (Scheme 3.5). This method works well for simple allylsilanes that come from symmetrical allyl halides, or in cases where steric factors bias one regioisomer over the other, such as in the preparation of **3.17** and **3.19**, respectively. This method is not suitable for unsymmetrical allylmetal reagents where the steric environments are similar at the two reactive sites. Direct lithiation of alkenes is another method that can be used to prepare the allylmetal reagent. In this way, terpene **3.20** can be silylated to give **3.21**.

**Scheme 3.5** Allylsilanes by silylation of allylmetal reagents



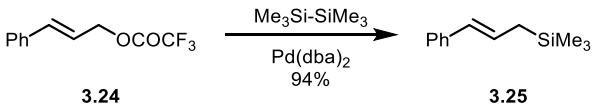

It is also possible to form the C–Si bond of allylsilanes by coupling a Grignard reagent with a hydrosilane (Eq. 3.2). This is typically accomplished with a nickel catalyst, $NiCl_2$(dppf). In general, a large excess of Grignard reagent is required, and thus this transformation is only practical for very simple Grignard reagents.




(Eq. 3.2)

The C–Si bond can be formed from allyl esters and a Pd(0) catalyst *via* the allylpalladium complex and disilanes (Eq. 3.3). The preparation of **3.25** from **3.24**, for

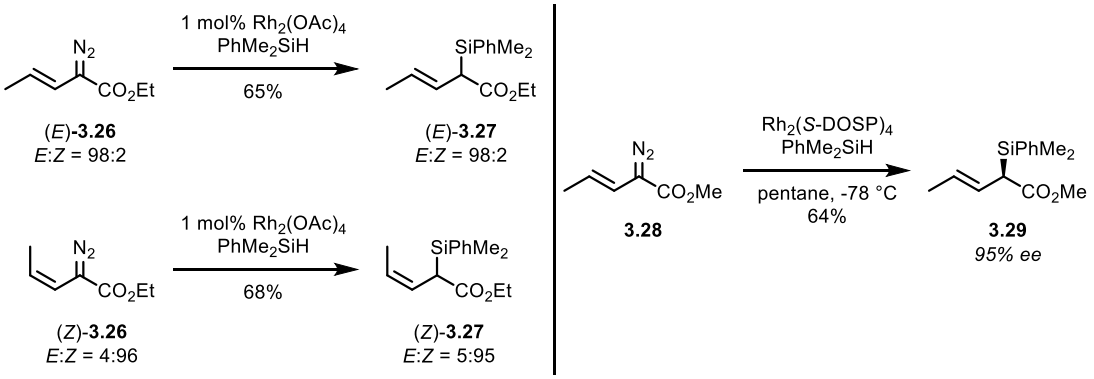
example, offers milder conditions relative to the Grignard approach. A variation of this method uses TMSCl in combination with samarium(II) iodide, and has the advantage of high regioselectivity.




**3.24** **3.25** (Eq. 3.3)

Another method for preparing the C–Si bond of allylsilanes utilizes rhodium(II) carbenes. Allylsilanes can be prepared by rhodium-catalyzed decomposition of vinyldiazo compounds in the presence of silanes (Scheme 3.6), by direct insertion into the Si–H bond. This method allows the preparation of allylsilanes with an ester group under mild conditions. The alkene geometry of the original diazo compound is preserved, as shown in the preparation of **3.27**. With a chiral rhodium catalyst, at low temperatures, the allylsilane products can be prepared enantioselectively, as in the preparation of **3.29** with 95% ee.[12] These enriched products have been used for asymmetric crotylation chemistry.[13,14]

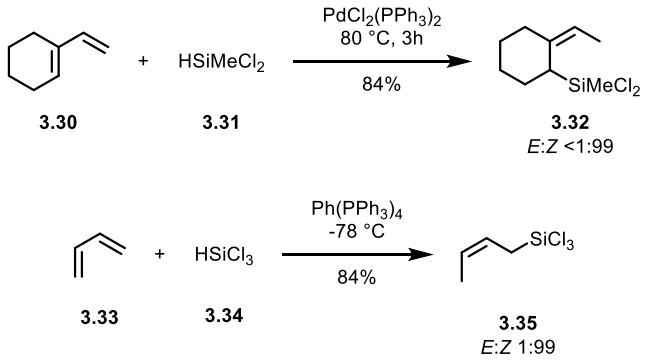
**Scheme 3.6** Rhodium-catalyzed Si–H insertion to prepare allylsilanes




One final, but important, strategy for forming the C–Si bond of allylsilanes is by transition metal catalyzed hydrosilylation of conjugated acyclic dienes (Scheme 3.7). This method allows the preparation of *Z*-allylsilanes with exceptionally high levels of

stereocontrol. Thus, **3.32** and **3.35** can be prepared in good yields as single double bond isomers. With chiral transition metal catalysts, the allylsilanes can be formed asymmetrically, and the levels of stereocontrol are often moderate.[15,16]

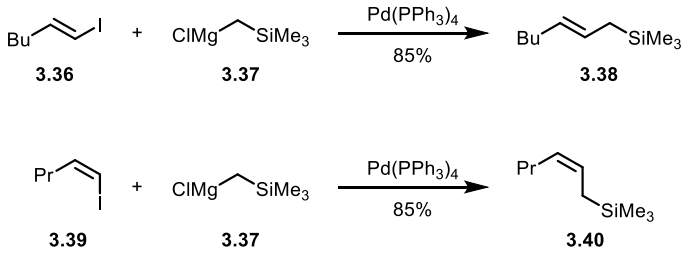
**Scheme 3.7** Hydrosilylation of acyclic conjugated dienes




### 3.1.2.2 Preparation of allylsilanes by forming the C–C single bond

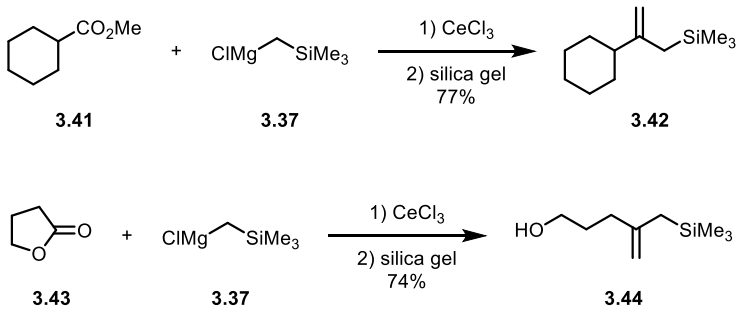
Methods for preparing allylsilanes by forming the C–C single bond typically utilize the silyl portion as a nucleophile and the alkenyl portion as the electrophile. One example of this is the palladium catalyzed coupling between an alkenyl halide and [(trimethylsilyl)methyl]magnesium halides, such as **3.37** (Scheme 3.8). Provided the alkenyl halides can be prepared with a defined geometry, this method allows the preparation of allylsilanes with a predictable stereochemistry.

**Scheme 3.8** Palladium catalyzed coupling of alkenyl halides and silyl Grignard reagents



Another related method is useful for the preparation of 2-substituted allylsilanes (Scheme 3.9). In this method, **3.37** is allowed to react twice with an ester such as **3.41**, and then undergoes a Peterson-type elimination to give the 2-substituted products. Lactones are effective substrates as well, as **3.43** can be used to prepare **3.44**.

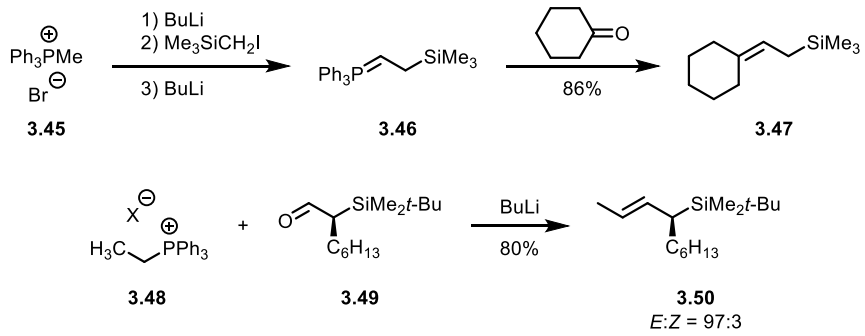
**Scheme 3.9** Allylsilanes by double Grignard addition/Peterson-type elimination




### 3.1.2.3 Preparation of allylsilanes by forming the C–C double bond

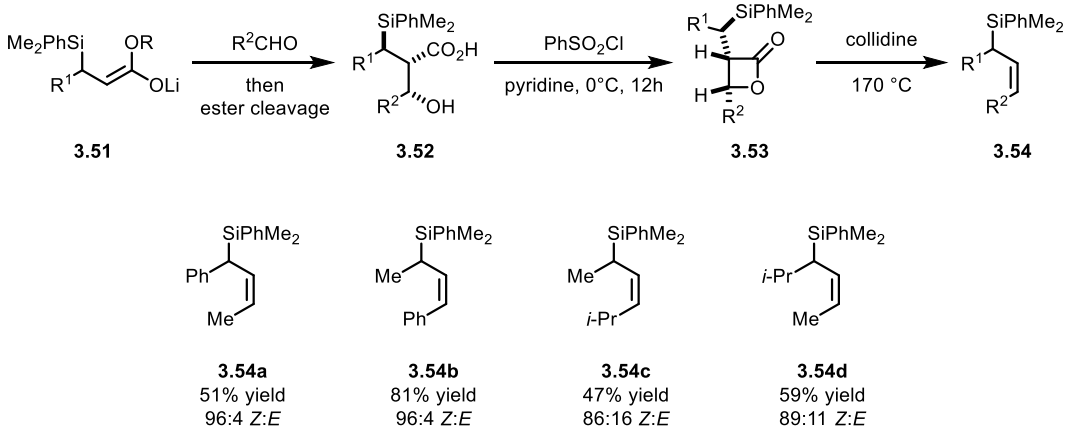
The C–C double bond of allylsilanes can be prepared by a variety of methods. One such method is the classic Wittig reaction (Scheme 3.10). The silane can be a part of either the ylide or the carbonyl component of the reaction, as shown with **3.46** and **3.49**. By reacting with the appropriate partner, these components can be used to prepare **3.47** and **3.50**, respectively. The Wittig reagent **3.46** can be prepared *via* an *in-situ* formed phosphonium salt (as shown) or *via* a pre-formed phosphonium salt. Unfortunately, at times this strategy can make control over the geometry of the resulting alkene challenging. It should also be noted that variations of this reaction based on the Horner-Wadsworth-Emmons and Julia olefination strategies have also been successfully implemented in the preparation of allylsilanes.

**Scheme 3.10** Wittig strategy for allylsilane preparation




Another strategy pertinent to the research discussed in this chapter is shown in Scheme 3.11. This method makes use of β-lactones, **3.53**, prepared from enolates **3.51** and aldehydes, followed by cleavage of the ester and lactonization. Upon heating, these β-lactones rearrange stereospecifically to give *Z*-allylsilanes selectively. A similar method can be used to prepare the corresponding *trans* β-lactones, which form *E*-allylsilanes. Notably, while the β-lactones rearrange stereospecifically (cis → *Z*, trans → *E*), very high temperatures are required.

**Scheme 3.11** Allylsilanes by decarboxylative rearrangement of β-lactones




This method for allylsilane preparation is most similar to the new method discussed in this chapter, in that the products arise from decarboxylation of β-lactones. However,

the method discussed in Scheme 3.11 requires several steps, including a copper catalyzed conjugate addition and aldol reaction.[17,18] Additionally, once the β-lactone **3.53** is formed, the conditions for its rearrangement to the allylsilane product are harsh, requiring 170 °C. This is an important difference between this method and the new method described in this chapter.

#### 3.1.2.4 Preparation of Allylsilanes: Conclusion

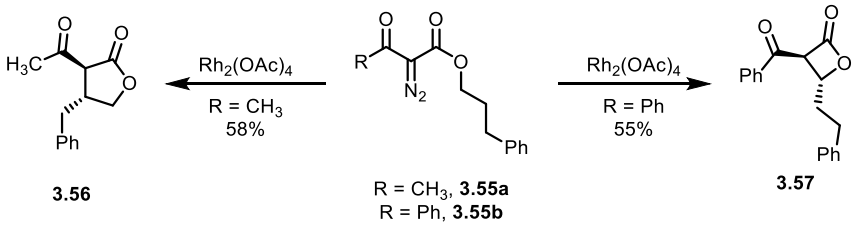
There are many more methods available to prepare allylsilanes than the ones presented here. The previous discussion is not intended to be an exhaustive review, however. Rather, it is intended to set the context for the research that is discussed later in this chapter. With the generality of allylsilanes as mild nucleophilic reagents, their uses are many and varied. As such, the specific allylsilane structure varies greatly from one application to the next. Therefore, it would be expected that no one, or two, methods for their preparation would be sufficiently general for all types of allylsilanes. Indeed, every method has limitations, even those that are, relatively, general. It is in this context that the research discussed later in this chapter is added to the already vast number of methods for allylsilane preparation.

### 3.1.3 β-lactones by Intramolecular C–H Insertion of Diazo Compounds

Since, as will be discussed later, the research in this chapter is presumed to involve the formation of β-lactones by intramolecular C–H functionalization, a brief introduction to that topic is warranted. Intramolecular C–H insertion reactions of diazo compounds typically take place to form five-membered rings.[19–21] However, it has been shown that the structure of the diazo can have a profound effect on the outcome of the reaction

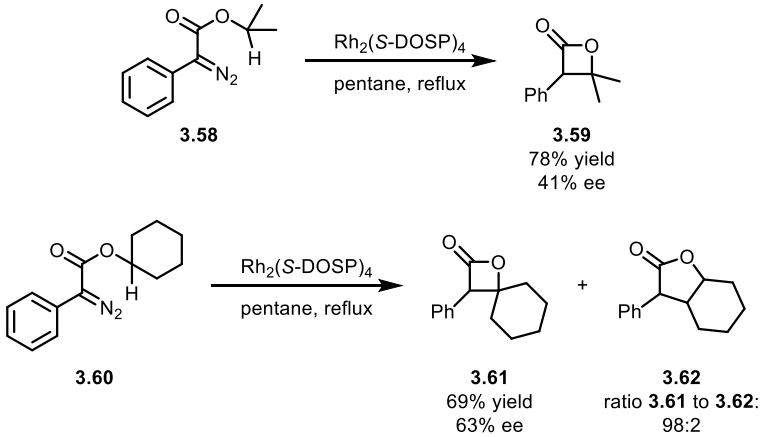
(Scheme 3.12).[22] For example, with acceptor/acceptor diazo **3.55a**, γ-lactone **3.56** is formed preferentially. However, by simply switching to **3.55b**, the β-lactone **3.57** is formed exclusively.

**Scheme 3.12** Formation of γ-lactone and β-lactone by changing diazo structure




In 2001, Doyle reported that using donor/acceptor diazo compounds with a tertiary site for C–H functionalization gave good yields of the corresponding β-lactones. Thus, diazo **3.58** gave β-lactone **3.59** as the only product, in 41% ee with $Rh_2$(*S*-DOSP)$_4$ as the chiral catalyst. Similarly, cyclohexyl diazo **3.60** gave **3.61** almost exclusively over γ-lactone **3.62** (98:2), in 63% ee. Later that year, Doyle showed that a similar intramolecular C–H functionalization was possible in a steroidal system.[23]

**Scheme 3.13** β-Lactone formation by intramolecular methine C–H insertion

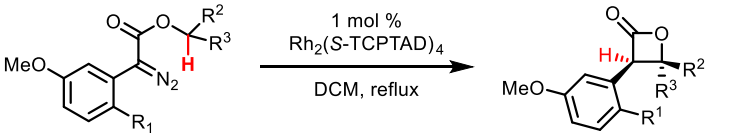


Very recently, Che[24] and Davies[25] showed that β-lactones can be prepared with moderate to good levels of enantioselectivity by intramolecular C–H insertion of diazo compounds (Scheme 3.14). The former used an Ir(III) porphyrin catalyst, and was able to form substituted β-lactones **3.64a** and **3.64b** from C–H insertion at either methine or methylene carbons, respectively. The latter used dirhodium(II) carboxylate catalyst $Rh_2$(*S*-TCPTAD)$_4$ to form β-lactones from insertion at methyl, methylene and methine positions by using an *o*-bromo substituent to sterically disfavor intermolecular chemistry.

**Scheme 3.14** β-lactones by enantioselective C–H insertion


$R^1 = R^2$ = Me, **3.63a**
$R^1$ = H, $R^2$ = Ar, **3.63b**

**3.64a**, 53-86% yield
**3.64b**, 60-88% yield, 39-78% ee




$R^1$ = Br, $R^2$, $R^3$ = H, **3.65a**
$R^1$ = Br, $R^2$ = Ar, $R^3$ = H **3.65b**

**3.66a**, 72% yield, 86% ee
**3.66b**, 71-91% yield, >97% ee

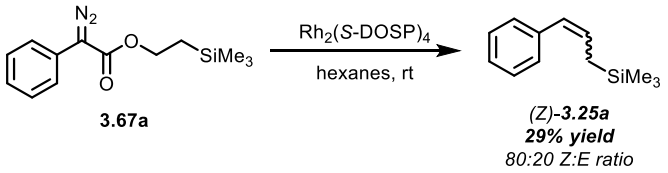
This short discussion of β-lactone formation by intramolecular C–H functionalization shows that the structure of the diazo and the structure of the ester both have an important influence on the outcome of the reaction. Notably, a relatively activated C–H bond (such as tertiary or secondary benzylic), or an *ortho* substituent on the aryl group (**3.65a**,**b**) is required for good yields of the strained 4-membered ring.

## 3.2 Results and Discussion

*Note: This work was conducted together with an undergraduate, Carolyn M. Cohen, whom I mentored during her time in the group. All reactions in this section were conducted by me unless otherwise stated.*

### 3.2.1 Initial Reaction Discovery

This study began as an offshoot of an ongoing program involving cyclopropanation reactions of 2-(trimethylsilyl)ethyl aryldiazoacetates. It was of interest to see if a catalyst and set of conditions could be identified in which these diazoesters would give high yields and enantioselectivities in cyclopropanation reactions of alkenes. This would enable the easy removal of the ester to give the carboxylic acid. While performing a control experiment, diazo **3.67a** was decomposed by $Rh_2$(*S*-DOSP)$_4$ in the absence of a trapping alkene (Eq. 3.4). Interestingly, and unexpectedly, allylsilane **3.25a** was formed in 29% yield. Perhaps even more intriguing was that the allylsilane was formed as an 80:20 mixture of double bond isomers, in favor of the *Z* isomer.




**3.67a**

*(Z)-**3.25a***
***29% yield***
*80:20 Z:E ratio*

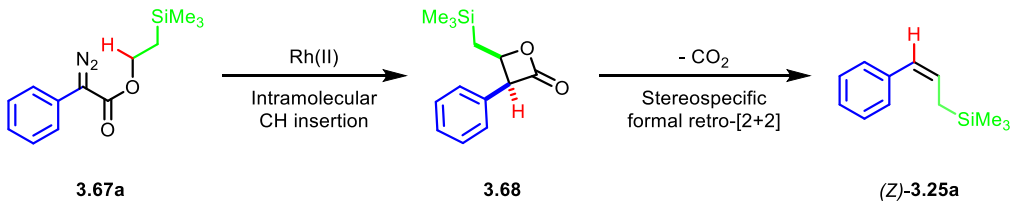
(Eq. 3.4)

### 3.2.2 Forming a Hypothesis for Reaction Optimization

An initial hypothesis was formed as to how the allylsilane product had been produced stereoselectively. The hypothesis consisted of both a mechanism and a stereochemical rationale. The mechanistic hypothesis is shown in Scheme 3.15. It was suggested that, first, the diazo compound undergoes a rhodium catalyzed intramolecular C–H insertion to form β-lactone **3.68**. The lactone then rearranges stereospecifically with extrusion of

$CO_2$ to give the observed product. In this mechanism, the stereochemistry of the final product would be set in the C–H insertion step, as β-lactones are known to rearrange to alkenes stereospecifically (see Scheme 3.11, and select references[18,26,27]). One unanswered question was why this particular β-lactone underwent extrusion of $CO_2$ under these mild conditions.

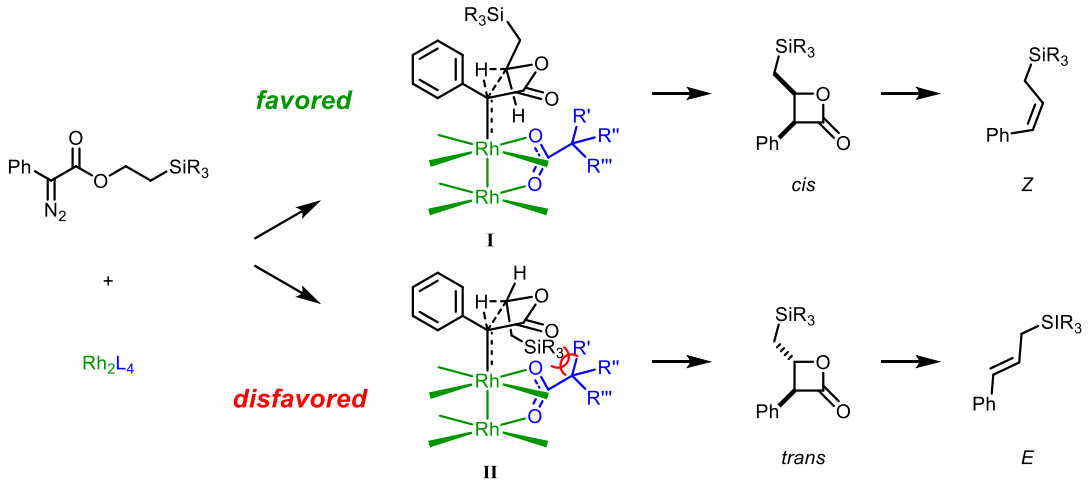
**Scheme 3.15** Mechanistic hypothesis for formation of **3.68a**




**3.67a** **3.68** ***(Z)*-3.25a**

Next, a stereochemical hypothesis was also developed by considering the transition states involved in the C–H insertion step (Scheme 3.16). In what is expected to be the favored transition state (**I**, Scheme 3.16), the silyl group of the ester would be pointing away from the rhodium catalyst. The corresponding diastereomeric transition state, **II**, would presumably place this silyl group near the catalyst and its ligands.

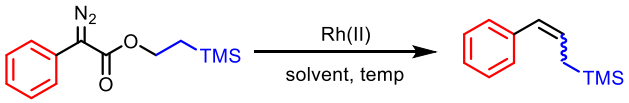
**Scheme 3.16** Hypothesis to explain the stereochemical outcome



Based on the mechanistic and stereochemical hypotheses, a series of experiments were designed in the hopes of improving the reaction. It was expected that, if the hypothesis was correct, the rhodium catalyst would be an important factor in the outcome of the reaction. In particular, it was expected that bulky catalysts would help improve the ratio in favor of the *Z*.

Thus, various rhodium catalysts were screened (Table 3.1). Trifluorotoluene was chosen as the initial solvent since all the rhodium catalysts examined were soluble, and the temperature could be raised to 70 °C. The chiral catalysts examined (entries 1-3) behaved similarly, giving roughly 3:1 to 4:1 *Z*:*E* ratios of **3.25a**. Since the reaction did not generate a chiral center, a variety of achiral catalysts were examined as well. Most achiral catalysts (entries 4-8) gave essentially no preference for either isomer of the alkene, and the electron-deficient catalysts (entries 6 and 7) gave poor yields of the desired product. When the bulky $Rh_2(TPA)_4$ catalyst was used, however, the *Z*:*E* ratio roughly matched that of the chiral catalysts, but with an improved yield (70% yield, entry 9). Lowering the temperature with this catalyst caused a reduction the yield (entry 10). However, switching the solvent to 1,2-dichloroethane proved to be advantageous, as the desired product was formed in 76% yield, and as a 89:11 mixture of isomers in favor of the *Z*.

**Table 3.1** Optimization of rhodium catalyst and conditions



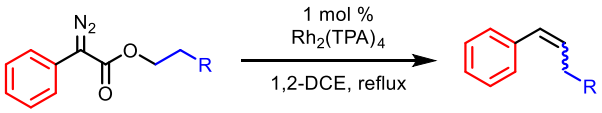

**3.67a** **3.25a**

| entry | Rh(II) | solvent | temp (°C) | *Z*:*E* ratio[a] | yield (%)[b] |
|---|---|---|---|---|---|
| 1[c] | $Rh_2$(*S*-DOSP)$_4$ | $PhCF_3$ | 70 | 80:20 | 57 |
| 2[c] | $Rh_2$(*S*-BTPCP)$_4$ | $PhCF_3$ | 70 | 74:26 | 45 |
| 3[c] | $Rh_2$(*S*-PTAD)$_4$ | $PhCF_3$ | 70 | 83:17 | 42 |
| 4[c] | $Rh_2$(OOct)$_4$ | $PhCF_3$ | 70 | 47:53 | 48 |
| 5[c] | $Rh_2$(Piv)$_4$ | $PhCF_3$ | 70 | 48:52 | 58 |
| 6[c] | $Rh_2$(pfb)$_4$ | $PhCF_3$ | 70 | 50:50 | 17 |
| 7[c] | $Rh_2$(TFA)$_4$ | $PhCF_3$ | 70 | 51:49 | 25 |
| 8[c] | $Rh_2$(esp)$_2$ | $PhCF_3$ | 70 | 46:54 | 42 |
| 9[c] | $Rh_2$(TPA)$_4$ | $PhCF_3$ | 70 | 84:16 | 70 |
| 10[c] | $Rh_2$(TPA)$_4$ | $PhCF_3$ | 40 | 85:15 | 36 |
| 11 | $Rh_2$(TPA)$_4$ | cyclohexane | 81 | 87:13 | 64 |
| ***12*** | ***$Rh_2$(TPA)$_4$*** | ***1,2-DCE*** | ***83*** | ***89:11*** | ***76*** |

[a]Measured by $^1$H NMR of the crude reaction mixture. [b]Isolated yield of the mixture of isomers. [c]Reaction performed by Carolyn M. Cohen under my supervision.

The strong influence of the ligand system on the *Z*:*E* ratio was consistent with the mechanistic and stereochemical hypotheses, which led to a second set of experiments in which the substituents on the silicon atom of the diazo were varied. If the *Z*:*E* ratio was determined by steric interactions between the catalyst ligands and the silicon group during C–H insertion, bulkier silyl groups would be expected to give a higher ratio of the *Z* product. The results of these experiments are shown in Table 3.2. A clear relationship between the size of the silyl group and the *Z*:*E* ratio can be seen for alkyl-substituted silyl groups (entries 1-4), from the smallest trimethylsilyl (entry 1, 89:11) to triisopropylsilyl (entry 4, >97:3). Interestingly, silyl substituents with phenyl groups did not result in improved ratios (entries 5 and 6) until a bulky *t*-Bu group was also added. In this case, the ratio improved to 96:4 (entry 7). Ultimately the triisopropylsilyl group was selected as the best system for exploring the scope of the transformation.

**Table 3.2** Variation of the silyl group




**3.67a-g** **3.25a-g**

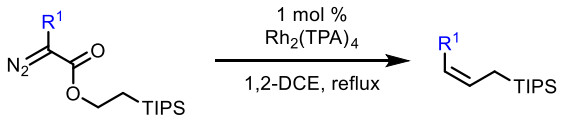
| entry | R | product | Z:E ratio[a] | yield (%)[b] |
|---|---|---|---|---|
| 1 | $SiMe_3$ | **3.25a** | 89:11 | 76 |
| 2 | $SiEt_3$ | **3.25b** | 91:9 | 76 |
| 3 | $SiMe_2$*t*-Bu | **3.25c** | 95:5 | 79 |
| *4* | *Si(i-Pr)$_3$* | ***3.25d*** | *>97:3* | *82* |
| 5 | $SiMe_2Ph$ | **3.25e** | 88:12 | 80 |
| 6 | $SiMePh_2$ | **3.25f** | 89:11 | 70 |
| 7 | $SiPh_2$*t*-Bu | **3.25g** | 96:4 | 68 |

[a]Measured by $^1$H NMR of the crude reaction mixture. [b]Isolated yield of the mixture of isomers.

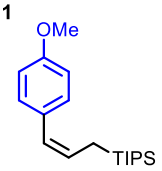
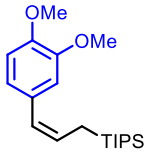
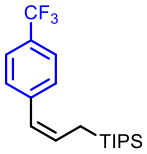
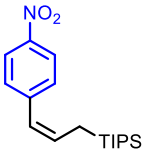
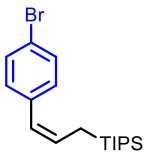
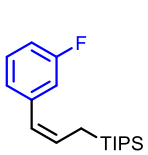
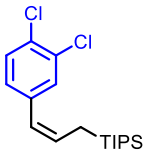
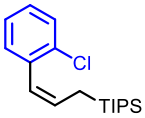
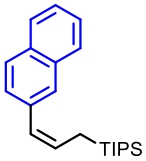
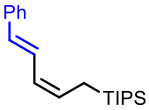
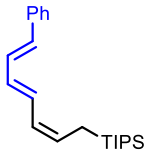
## 3.2.3 Reaction Scope

With the optimized conditions, the scope was then explored. First, the donor group on the diazo was varied (Table 3.3). Electron-rich (entries 1 and 2), electron-deficient (entries 3 and 4), and electron-neutral (entries 5-9) aryl groups worked well in the reaction, typically giving high *Z*:*E* ratios of allylsilanes **3.70a-k**. The ratio dropped slightly with both the *para* nitro substituted diazo **3.69d**, and when *ortho* chloro substituted diazo **3.69h** was used, though the products were still formed in good yields (60-77% yield). The reaction was also extended to the preparation of polyene allylsilane products **3.70j** and **3.70k** from the corresponding vinyl and divinyl diazos **3.69j** and **3.69k** (entries 10 and 11). Even though the yields and *Z*:*E* ratios of these products was lower than for the aryl diazos it is impressive that these allylsilane products could be formed with control over the geometry at each alkene.

**Table 3.3** Scope of the donor group[a,b]




**3.69a-k** **3.70a-k**

| | | | | | |
|---|---|---|---|---|---|
| **1**  **3.70a**, 76% yield >97:3 *Z*:*E* | **2**  **3.70b**, 77% yield 97:3 *Z*:*E* | **3**[c]  **3.70c**, 73% yield >97:3 *Z*:*E* | **4**[c]  **3.70d**, 60% yield 95:5 *Z*:*E* | **5**[c]  **3.70e**, 74% yield >97:3 *Z*:*E* | **6**[c]  **3.70f**, 74% yield >97:3 *Z*:*E* |
| **7**[c]  **3.70g**, 64% yield 97:3 *Z*:*E* | **8**[c]  **3.70h**, 77% yield 94:6 *Z*:*E* | **9**  **3.70i**, 74% yield >97:3 *Z*:*E* | **10**  **3.70j**, 60% yield 95:5 *Z*:*E* | **11**  **3.70k**, 37% yield 93:7 *Z*:*E* | |

[a]*Z*:*E* ratios determined by $^1$H NMR analysis of the crude reaction mixture. [b]Yields refer to isolated yields. [c]Reaction conducted once by David and once by Carolyn.

When the reaction was extended to the formation of trisubstituted alkenes, using diazo **3.71**, the corresponding allysilane **3.72** was isolated as a single *Z* isomer in 36% yield. Interestingly, 1-triisopropylsilyl-2-propanone (**3.73**) was also isolated in 39% yield. While it is not known exactly how this product forms, it is possible the reaction begins with a hydride abstraction during the C–H insertion step, at which point water can quench the positive charge.

The reaction was then explored for the preparation of chiral allylsilanes (Table 3.4). Three different chiral allylsilanes, **3.75a-c**, were prepared from the corresponding diazo compounds in moderate yields. Though these allylsilanes were prepared with the TBS silyl group for ease of preparation (see experimental section for details), they still gave good *Z*:*E* ratios.

**Scheme 3.17** Formation of trisubstituted alkenes and triisopropylsilylacetone

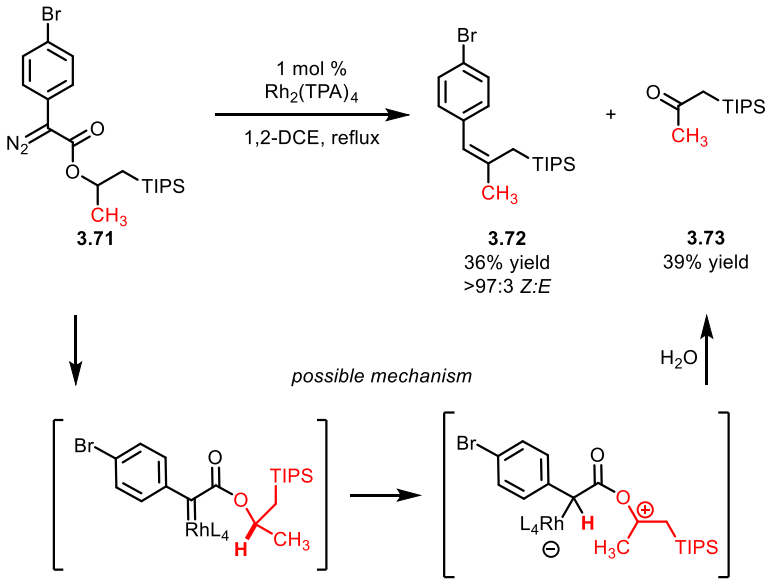
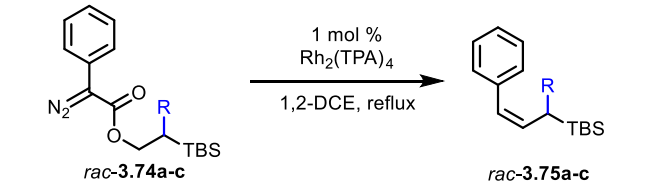
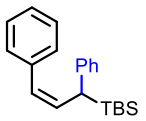
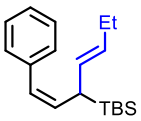
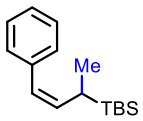



**Table 3.4** Synthesis of chiral allylsilanes[a,b]



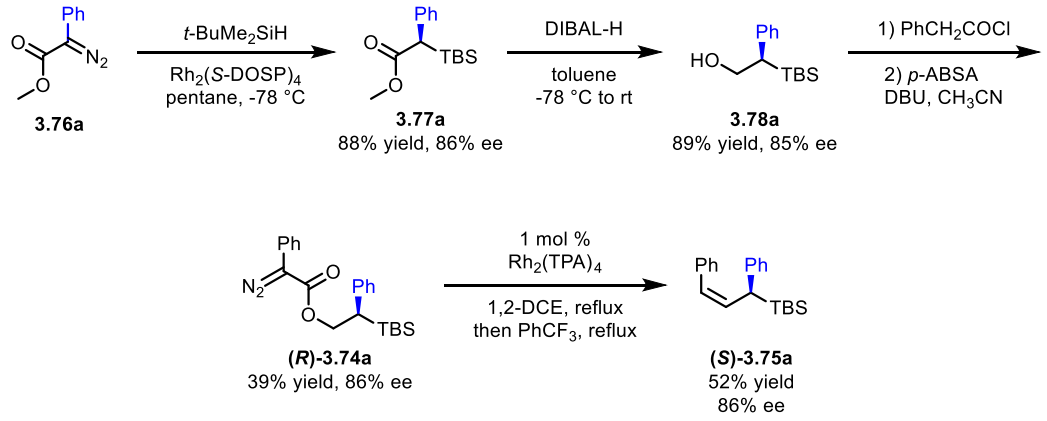

| 1[c] | 2[c] | 3 |
|---|---|---|
|  |  |  |
| **3.75a**, 55% yield<br>>97:3 *Z*:*E* | **3.75b**, 47% yield<br>>97:3 *Z*:*E* | **3.75c**, 68% yield<br>90:10 *Z*:*E* |

[a]*Z*:*E* ratios determined by $^1$H NMR analysis of the crude reaction mixture. [b]Yields refer to isolated yields. [c]After the reaction was complete the solvent was removed and replaced with $PhCF_3$, and heated at reflux for 16h.

Having prepared a variety of chiral allylsilanes, the method was showcased by the preparation of enantioenriched **3.75a**. The general strategy is shown in Scheme 3.18. The necessary diazo **(*R*)-3.74a** was prepared beginning with an enantioselective Si–H insertion reaction using the chiral catalyst $Rh_2$(*S*-DOSP)$_4$ and *tert*-butyldimethylsilane to

give the silyl ester **3.77** in 88% yield and 86% ee. The stereochemistry of this intermediate was assigned tentatively based on a related system.[12] Reduction of this intermediate was accomplished with DIBAL-H, and subsequent esterification and diazo transfer gave the diazo **(*R*)-3.74a**. This diazo was subjected to the same conditions as for the racemic substrate, and the allylsilane product **(*S*)-3.75a** was formed in 52% yield and with complete retention of stereochemical information. This scheme highlights the versatility of this method for the preparation of chiral building blocks.

**Scheme 3.18** Preparation of enantioenriched allysilane **3.75a**

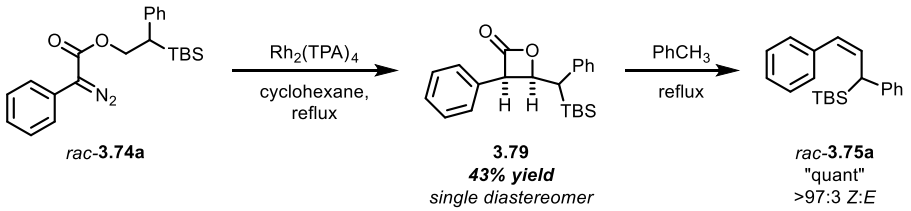



## 3.2.4 Mechanistic Investigation and Control Reactions

A series of reactions were conducted that helped to test the originally proposed hypothesis. First, it was observed that, when the reaction with **3.74a** was conducted at reflux in cyclohexane, β-lactone **3.79** could be isolated in 43% yield. Remarkably, the product was formed as a single diastereomer, with a *cis* relationship between the two lactone substituents. When **3.79** was heated to reflux in toluene, it smoothly decomposed to form **3.75a** as a single isomer. These two results are noteworthy, as this was the first time a β-lactone was isolated from the reaction mixture. This reaction demonstrates that

β-lactones are viable intermediates in the mechanism of the reaction, and demonstrates their stereospecific rearrangement to form the observed allylsilanes.

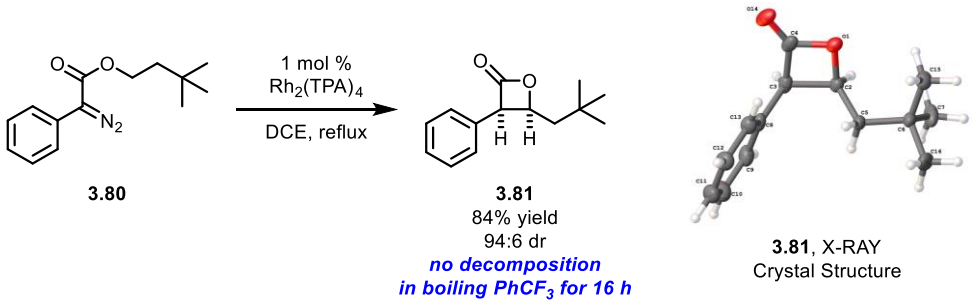
**Scheme 3.19** Isolation of a β-lactone and its stereospecific rearrangement




With strong evidence for β-lactone intermediates in the mechanism, two additional questions were raised: 1) Why were the β-lactones formed so selectively (as opposed to the competing five-membered ring, for example)? and 2) Why did the β-lactones extrude $CO_2$ to form allylsilanes under such mild conditions (while the literature suggests temperatures >150 °C are required)?

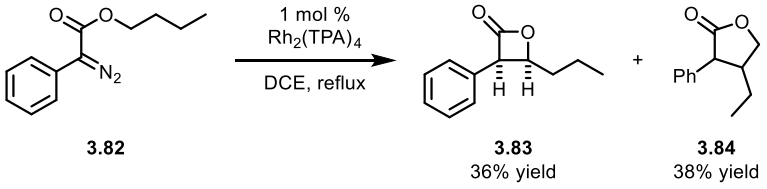
First, diazo **3.80**, with a 3,3-dimethylbutyl ester, was examined under the standard conditions (Scheme 3.20). With this diazo, β-lactone **3.81** was formed, as primarily the *cis* isomer, in 84% yield. The structure of this intermediate was confirmed by X-ray crystallographic analysis. This result suggests that there is a steric factor that governs the site-selective C–H insertion, since only the β-lactone was observed (as opposed to the 5-membered ring). Importantly, **3.81** showed no signs of decomposition in boiling $PhCF_3$ after 16 h.

**Scheme 3.20** Control reaction with 3,3-dimethylbutyl phenyldiazoacetate




When the steric influence of the ester was reduced, however, a different result was observed (Scheme 3.21). With *n*-butyl ester diazo **3.82**, a mixture of the β- and γ-lactones **3.83** and **3.84**, respectively, was formed in about a 1:1 ratio. This result suggests that when the steric influence at the position β to the ester oxygen is removed, C–H insertion at that site becomes competitive. Therefore, it is reasonable to attribute, at least in part, the selective formation of β-lactones in this chemistry to the steric influence of the silyl group. Whether the silicon group is also electronically activating the C–H insertion step (*via* the β-silicon effect) is not clear from these experiments.

**Scheme 3.21** Control reaction with a butyl ester

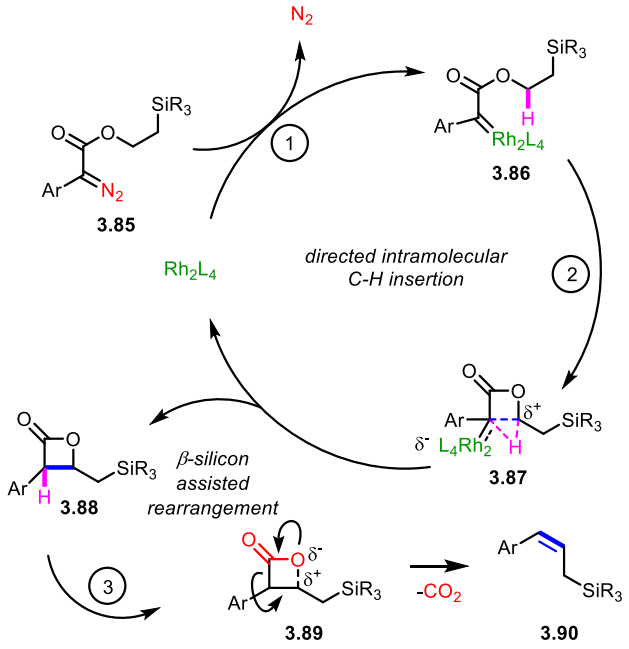



One final observation is that, in nonpolar solvents, the allylsilane is not immediately formed, but rather another intermediate, presumably the β-lactone, can be observed by $^{1}$H NMR analysis of the crude reaction mixture. Upon heating in a more polar solvent (such as $PhCF_3$ or DCE), this intermediate rearranges to the allylsilane. Attempted isolation of this intermediate by silica gel chromatography was not possible; upon addition of the

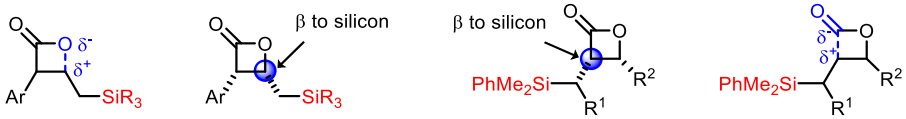
crude mixture to the silica gel, bubbles were observed, and only the allylsilane was isolated.

With these control reactions complete, a more detailed mechanism was proposed that incorporated the observations (Scheme 3.22): First, the diazo **3.85** is decomposed by the catalyst to form the carbene intermediate **3.86**. This then undergoes an intramolecular C–H insertion, directed by the silicon (at least in a steric sense), to form an intermediary β-lactone **3.88**. Based on the fact that the allylsilanes are formed under such mild conditions, and the observations in the preceding paragraph regarding solvent effects, etc., it is proposed that the silicon is destabilizing the β-lactone intermediate by the β-silicon effect (**3.89**, Scheme 3.22). (Note: this effect is not sterically driven (at least not entirely), since β-lactone **3.81** is stable under identical conditions). This causes the β-lactone to rearrange to the allylsilane product under mild conditions. The solvent effects discussed earlier underscore the impact of the subtle electronic effects in this step.

**Scheme 3.22** Proposed mechanism for allylsilane formation



Consider again the related method for allylsilane preparation discussed in Scheme 3.11. It is interesting to note the effect of the structural differences between β-lactone **3.88** and **3.53** (see Figure 3.2). In the former, the position β-to silicon (the position at which the silicon could help stabilize a carbocation) is next to the ester oxygen. In the latter, however, it is next to the ester carbonyl. Since a charge-separated intermediate such as **3.89** is much more reasonable than the corresponding **3.91**, one would expect that, if the silicon is electronically enabling the extrusion of $CO_2$, it would be much more effective in the former case.




**3.89** **3.88** **3.53** **3.91**

**Figure 3.2** Placement of silicon atoms in β-lactones **3.88** and **3.53**

## 3.3 Conclusion

In this chapter, a synthesis of *Z*-allylsilanes from 2-(trialkylsilyl)ethyl aryl- and vinyldiazoacetates has been described. A hypothesis was formed regarding the mechanism and the origin of the selectivity. The hypothesis guided a series of experiments that improved the reaction, allowing the *Z*-allylsilanes to be prepared in ratios of >97:3 over the *E*.

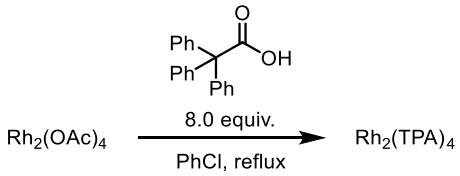
The reaction is general with respect to the donor group. A variety of aryl groups can be used, as well as vinyl and divinyl donor groups. Chiral allylsilanes can also be produced by using the appropriate starting material, and if the diazo is enantioenriched, the chirality can be transferred to the allylsilane products, giving enriched allylsilanes.

A series of reactions was conducted to further test the mechanistic hypothesis. A β-lactone intermediate was isolated, and its stereospecific rearrangement to an allylsilane was demonstrated. Additionally, two other control reactions established that steric bulk is important to avoid C–H insertion α to the silicon, which would form γ-lactones. It was demonstrated that in the absence of the silicon (but with a *t*-Bu group in its place), the β-lactone does not rearrange, suggesting that the silicon is involved electronically in the rearrangement. Finally, a more complete mechanism was proposed that incorporates these observations and conclusions.

The reaction described herein is, admittedly, specific. That is, it allows *Z* allylsilanes to be prepared specifically, but not *E*. Additionally, the reaction is best for preparing allylsilanes that contain a triisopropylsilyl group, as well an aryl group on the alkene. However, as discussed in the introduction, the generality and broad usefulness of allylsilanes has resulted in a wide variety of methods for their preparation, and no single method is useful for all kinds of allylsilanes. So while it is acknowledged that this method is somewhat specific, within its space of allylsilane chemistry (however small), it performs exceptionally.

As a final remark: there are probably other directions this chemistry could go (for example, using alkynyl diazo precursors to prepare enynes). At this point, these options are left open to exploration by others, should the interest arise.

## 3.4 Experimental Section

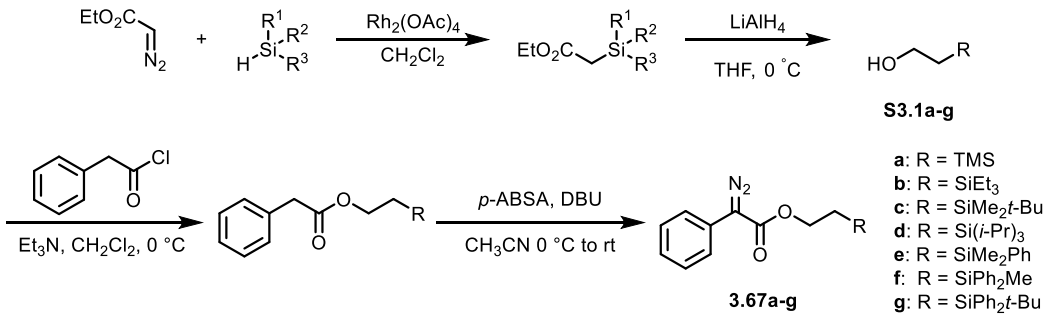



**dirhodium(II) tetrakis(triphenylacetate):** $Rh_2(OAc)_4$ (700 mg, 1.58 mmol, 1.0 equiv.) and triphenylacetic acid (3.6 g, 12.5 mmol, 8.0 equiv.) were dissolved in chlorobenzene (150 mL) in a 250 mL round-bottomed flask equipped with a magnetic stir bar. A soxhlet extractor was attached, containing potassium carbonate, and a reflux condenser. The mixture was heated at reflux overnight (16 hours). $CH_2Cl_2$ (150 mL) was added and the mixture was washed with saturated aqueous sodium bicarbonate solution (2 x 150 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated. The green residue was purified by column chromatography (eluent: $CH_2Cl_2$) to give the product as a green solid. This was dissolved in a minimal quantity of benzene and flash frozen with liquid nitrogen. The frozen solution was freeze-dried on a high vacuum pump overnight to give the product as a fluffy light green solid (1.4 g, 61% yield). The spectral data matched those reported in the literature.[28]

### 3.4.1 Synthesis of Achiral Diazos

Diazo **3.82** was prepared according to a literature procedure.[29] Diazos **3.67a-g** were prepared by direct diazo transfer to the ester according to Scheme 3.23.

**Scheme 3.23** Preparation of diazos **3.67a-g**



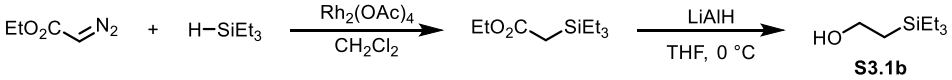

### 3.4.1.1 Preparation of 2-silylethanols

Alcohol **S3.1a** was purchased from Alfa Aesar and used as received. Alcohol **S3.1g** was prepared according to a literature procedure.[30] Alcohols **S3.1b-c** and **S3.1e-f** were prepared by Si-H insertion with ethyl diazoacetate according to Scheme 3.23.

#### *Synthesis of alcohols S3.1b-c and S3.1e-f:*

Alcohols **S3.1b-c** and **S3.1e-f** were prepared by Si-H insertion with ethyl diazoacetate according to Scheme 3.23 above. The procedure for **S3.1b** is shown below. Alcohols **S3.1c**,**e** and **f** were prepared in a manner analogous to **S3.1b**, and spectral data for these compounds were consistent with those reported.[31–33]

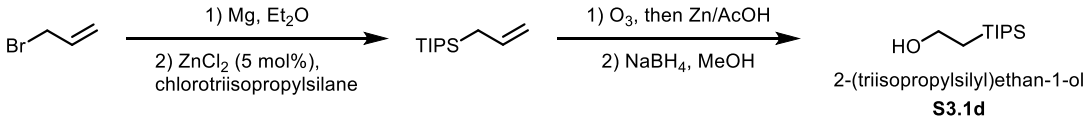
**The synthesis of S3.1b is representative:**




**2-(triethylsilyl)ethanol (S3.1b):** A solution of ethyl diazoacetate (2.5 g, 80% by mass in $CH_2Cl_2$, 17.5 mmol, 1.0 equiv.) in $CH_2Cl_2$ (20 mL) was added dropwise over 4 hours to a solution of triethylsilane (5.7 mL, 35.1 mmol, 2.0 equiv.) and $Rh_2(OAc)_4$ (77 mg, 0.18 mmol, 1 mol %) in $CH_2Cl_2$ (40 mL). The mixture was stirred overnight and the volatiles removed by rotary evaporation. The crude reside was filtered through a short plug of

silica to remove the catalyst, eluting with 95:5 pentane:$Et_2O$. The filtrate was concentrated to give crude ethyl triethylsilylacetate as a pale oil. This oil was dissolved in 15 mL THF and added dropwise to a suspension of lithium aluminum hydride (1.3 g, 35 mmol, 2.0 equiv.) in THF (20 mL) at 0 °C. The mixture was stirred overnight at room temperature. The mixture was cooled again to 0 °C and water added ***carefully*** (1.3 mL), followed by careful dropwise addition of 15% aqueous NaOH (1.3 mL). THF (40 mL) was added to break up the solids, followed by water (4.5 mL). The slurry was stirred vigorously until the gray solids became a white precipitate (approx. 30 mins). The precipitate was removed by filtration, washing with EtOAc. The filtrate was dried over $MgSO_4$ and concentrated to give the crude 2-(triethylsilyl)ethanol (2.3 g, 80% yield over 2 steps), sufficiently pure for the next step. The spectral data were consistent with those previously reported.[34]

### *Synthesis of 2-(triisopropylsilyl)ethanol*




**2-(triisopropylsilyl)ethanol (S3.1d):**

*Synthesis of allyltriisopropylsilane* – by a modified literature procedure[35]: A flame dried, 3-necked, 500 mL round-bottomed flask was fitted with a glass stopper, reflux condenser, addition funnel and magnetic stirring bar. The flask was cooled under a stream of argon, which was then maintained throughout the reaction. The flask was charged with magnesium turnings (15.1 g, 630 mmol, 3.15 equiv.) followed by $Et_2O$ (100 mL). The addition funnel was charged with allyl bromide (51.9 mL, 600 mmol, 3.0 equiv.) and 150 mL $Et_2O$ and stirred until well mixed. While the magnesium suspension was stirred

vigorously, a small portion of the allyl bromide solution (10 mL) was carefully added to the flask. The reaction initiated almost immediately, and the allyl bromide solution was added dropwise at such a rate as to maintain a gentle reflux. When the addition was complete, the mixture was stirred overnight (16 hours) at room temperature. To another flask was added zinc(II) chloride (1.4 g, 10 mmol, 5 mol %) followed by THF (300 mL) and triisopropylchlorosilane (42.8 mL, 200 mmol, 1.0 equiv.). To this solution was carefully added the Grignard solution via cannula, under argon. The solution was stirred 4 hours and quenched carefully by adding water dropwise (10 mL). A solution of HCl (1M, 200 mL) was added, and the layers separated. The organic layer was washed with water (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by passing through a small plug of silica, eluting with hexanes. Allyltriisopropylsilane was collected as a colorless oil (39.1 g, 98% yield). The spectral data matched those in the literature.[35]

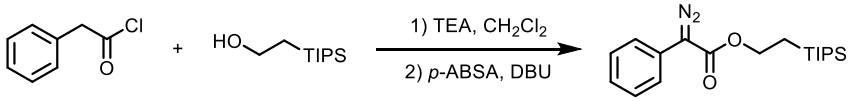
*Synthesis of 2-(triisopropylsilyl)ethanol* (**S3.1d**): allyltriisopropylsilane (20.0 g, 101 mmol, 1.0 equiv.) was dissolved in 300 mL $CH_2Cl_2$ in a 1000 mL graduated cylinder. The solution was cooled to -78 °C and ozone was bubbled through the solution until a blue color persisted. Argon was bubbled through the system until the solution became colorless. The reaction mixture was allowed to warm to room temperature and concentrated. The crude residue was dissolved in AcOH/$H_2O$ 10:1 (150 mL). Zinc dust (7.8 g, 120 mmol, 1.2 equiv.) was added carefully and the mixture stirred for 2 hours. Water (200 mL) was added and the mixture extracted with $Et_2O$ (200 mL). The organic layer was washed with water (100 mL), saturated aqueous sodium bicarbonate (100 mL), and brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give cleanly the

aldehyde (18 g, 89 % yield), which was used without further purification. The aldehyde (10.0 g, 49.9 mmol, 1.0 equiv.) was dissolved in 150 mL of methanol and cooled to 0 °C. Sodium borohydride pellets (2.1 g, 54.9 mmol, 1.2 equiv.) were added and the mixture stirred for 3 hours. Then saturated sodium bicarbonate solution was added (100 mL) followed by $Et_2O$ (150 mL) and the mixture stirred vigorously. Water was added (100 mL) and the layers separated. The aqueous layer was extracted with $Et_2O$ (75 mL). The organic layers were combined and dried ($MgSO_4$), filtered and concentrated. The biphasic crude residue was dissolved in $Et_2O$ (150 mL) and washed with $H_2O$ (2 x 100 mL), brine (100 mL), and dried over $MgSO_4$, filtrated and concentrated to give the alcohol **S3.1d** as a colorless oil (8.3 g, 82% yield). The spectral data were consistent with those previously reported for this compound.[34]

### 3.4.1.2 Preparation of Diazos 3.67a-g

Diazos **3.67a-g** were prepared from the corresponding alcohols (**S3.1a-g**, the preparation of which have been described above) and phenylacetyl chloride, followed by direct diazo transfer with *p*-ABSA and DBU (according to Scheme 3.23).

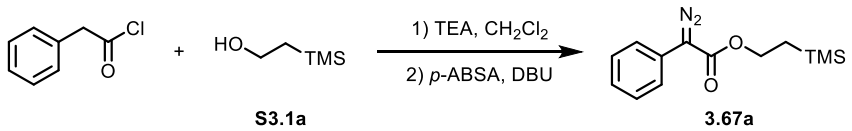
**Preparation of 3.67d is representative:**




S3.1d 3.67d

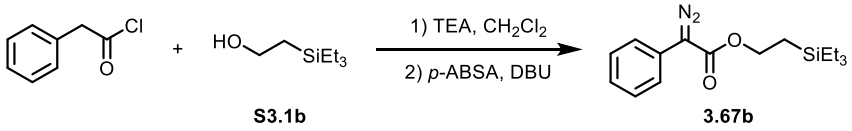
**2-(triisopropylsilyl)ethyl 2-diazo-2-phenylacetate (3.67d):** To a solution of 2-(triisopropylsilyl)ethanol (2.0 g, 9.9 mmol, 1.2 equiv.) and triethylamine (2.3 mL, 16.4 mmol, 2.0 equiv.) in $CH_2Cl_2$ (20 mL) was added phenylacetyl chloride (1.1 mL, 8.2

mmol, 1.0 equiv.) carefully dropwise. The mixture was stirred overnight at room temperature, before it was quenched with 1M HCl (15 mL). The organic layer was separated and washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was passed through a short column of silica gel (3% $Et_2O$ in pentane) to remove the excess alcohol. This gave 2-(triisopropylsilyl)ethyl phenylacetate as a colorless oil (1.7 g, 65% yield), which was used immediately in the next step. This product (1.7 g, 5.3 mmol, 1.0 equiv.) was dissolved in acetonitrile (15 mL) along with *p*-ABSA (1.9 g, 8.0 mmol, 1.5 equiv.) and cooled to 0 °C. Then DBU (1.6 mL, 10.6 mmol, 2.0 equiv.) was added dropwise. The mixture was allowed to warm to room temperature over several hours and then stirred for 48 hours. The mixture was quenched by addition of saturated aqueous $NH_4Cl$ (15 mL) and water (5 mL). The mixture was extracted with $Et_2O$ (20 mL). The organic layer was washed with brine (15 mL) and dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (3% $Et_2O$ in pentane). This gave diazo **3.67d** as a thick orange oil (1.3 g, 72 % yield) that solidified in the freezer (-25 °C). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.53-7.48 (m, 2H), 7.42-7.36 (m, 2H), 7.21-7.16 (m, 1H), 4.47-4.40 (m, 2H), 1.23-1.14 (m, 2H), 1.09 (m, 21H); $^{13}$C NMR (100 MHz, CDCl3) δ 165.6, 129.1, 125.9, 124.2, 63.7, 18.9, 11.4, 11.1 (the resonance resulting from the diazo carbon was not detected); IR (neat): 2939, 2863, 2082, 1697 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{13}H_{30}O_2N_2NaSi$ 369.1969, found 369.1964;




S3.1a 3.67a

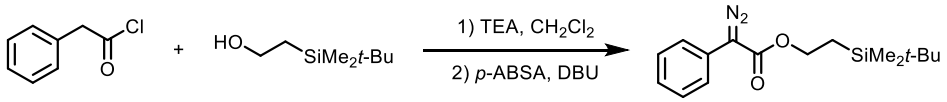
**2-(trimethylsilyl)ethyl 2-diazo-2-phenylacetate (3.67a):** Prepared analogously to **3.67a**. *Step 1*: From phenylacetyl chloride (6.2 mL, 46.6 mmol, 1.1 equiv.), **S3.1a** (5.0 g, 42.3 mmol, 1.0 equiv.) and triethylamine (8.8 mL, 63.5 mmol, 1.5 equiv.). After work-up, the crude was used without purification in *Step 2*: From the crude ester, *p*-ABSA (15.2 g, 63.5 mmol, 1.5 equiv.), and DBU (12.6 mL, 84.6 mmol, 2.0 equiv.). The crude was purified by column chromatography (5% $Et_2O$ in pentane) to give the diazo as a red oil (5.5 g, 50% yield over 2 steps). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.51 (dd, 2H, *J* = 8.5, 1.1 Hz), 7.40 (t, 2H, *J* = 7.9 Hz), 7.19 (m, 1H), 4.43-4.37 (m, 2H), 1.14-1.07 (m, 2H), 0.09 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.5, 129.0, 129.8, 125.9, 124.1, 63.5, 17.8, -1.3 (the resonance resulting from the diazo carbon was not detected); IR (neat): 2954, 2080, 1698, 1150 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{13}H_{18}O_2N_2NaSi$ 285.1029, found 285.1032;




S3.1b 3.67b

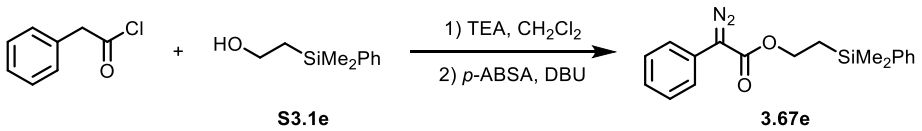
**2-(triethylsilyl)ethyl 2-diazo-2-phenylacetate (3.67b):** Prepared analogously to **3.67d**. *Step 1*: From phenylacetyl chloride (1.6 mL, 11.7 mmol, 1.0 equiv.), **S3.1b** (2.3 g, 14.1 mmol, 1.2 equiv.), and triethylamine (3.3 mL, 23.4 mmol, 2.0 equiv.) to give the ester (1.7 g). *Step 2*: From the ester (1.7 g, 6.0 mmol, 1.0 equiv.), *p*-ABSA (2.2 g, 9.0 mmol, 1.5 equiv.), and DBU (1.8 mL, 12.0 mmol, 2.0 equiv.). The crude was purified by column chromatography (2% $Et_2O$ in pentane) to give the diazo as a red oil (1.2 g, 33% yield

over two steps). $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.51 (dd, 2H, *J* = 8.6, 1.2 Hz), 7.42-7.37 (m, 2H), 7.19 (tt, 1H, *J* = 7.8, 1.2 Hz), 4.41-4.36 (m, 2H), 1.15-1.09 (m, 2H), 0.98 (t, 9H, *J* = 7.9 Hz), 0.58 (q, 6H, *J* = 7.9 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.6, 129.1, 125.9 (2 signals), 124.2, 63.5, 13.1, 7.6, 3.6 (the resonance resulting from the diazo carbon was not detected); IR (film): 2953, 2874, 2080, 1699, 1150 $cm^{-1}$; HRMS (NSI) *m/z*: $[M]^+$ calcd for $C_{16}H_{24}O_2N_2Si$ 304.1602, found 304.1588;



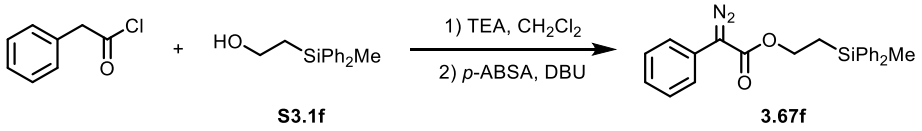

**S3.1c** **3.67c**

**2-(*tert*-butyldimethylsilyl)ethyl 2-diazo-2-phenylacetate (3.67c):** Prepared analogously to **3.67d**. *Step 1*: From phenylacetyl chloride (2.3 mL, 17.7 mmol, 1.1 equiv.), **S3.1c** (2.6 g, 16.1 mmol, 1.0 equiv.) and triethylamine (3.3 mL, 24 mmol, 1.5 equiv.) to give the ester (3.2 g). *Step 2*: From the ester (3.2 g, 11.3 mmol, 1.0 equiv.), *p*-ABSA (4.1 g, 17 mmol, 1.5 equiv.) and DBU (3.2 mL, 22.6 mmol, 2.0 equiv.). The crude was purified by column chromatography (4% $Et_2O$ in pentane) to give the diazo as a red oil (2.3 g, 47% yield over two steps). $^{1}$H NMR (600 MHz; $CDCl_3$) δ 7.51 (dd, 2H, *J* = 8.5, 1.0 Hz), 7.40 (t, 2H, *J* = 8 Hz), 7.19 (t, 1H, *J* = 7.4 Hz), 4.42-4.37 (m, 2H), 1.13-1.09 (m, 2H), 0.92 (s, 9H), 0.03 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.6, 129.1, 125.9 (2 signals), 124.2, 63.8, 26.6, 16.6, 14.1, -5.8 (the resonance resulting from the diazo carbon was not detected); IR (neat): 2953, 2856, 2080, 1699 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{24}O_2N_2NaSi$ 327.1499, found 327.1501;




**S3.1e** **3.67e**

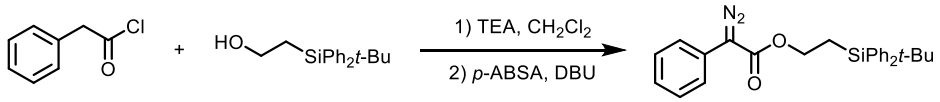
**2-(dimethyl(phenyl)silyl)ethyl 2-diazo-2-phenylacetate (3.67e):** Prepared analogously to **3.67d**. *Step 1*: From phenylaceyl chloride (0.78 mL, 6.0 mmol, 1.0 equiv.), **S3.1e** (1.3 g, 7.2 mmol, 1.2 equiv.), and triethylamine (1.7 mL, 12 mmol, 2.0 equiv.) to give the ester (1.2 g). *Step 2*: From the ester (1.2 g, 3.9 mmol, 1.0 equiv.), *p*-ABSA (1.2 g, 5.9 mmol, 1.5 equiv.) and DBU (1.2 mL, 7.8 mmol, 2.0 equiv.). The crude was purified by column chromatography (3% $Et_2O$ in pentane) to give the diazo as a red oil (870 mg, 46% yield over two steps). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.55-7.50 (m, 2H), 7.47 (d, 2H, *J* = 8.8 Hz), 7.41-7.33 (m, 5H), 7.17 (td, 1H, *J* = 7.4, 1.2 Hz), 4.37 (m, 2H), 1.34 (m, 2H), 0.35 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.5, 138.0, 133.6, 129.4, 129.1, 128.1, 125.9, 125.8, 124.1, 63.2, 17.1, -2.7 (the resonance resulting from the diazo carbon was not detected); IR (film): 2954, 2080, 1697, 1243, 1150 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{20}O_2N_2NaSi$ 347.1186, found 347.1187;




**S3.1f** **3.67f**

**2-(methyldiphenylsilyl)ethyl 2-diazo-2-phenylacetate (3.67f):** Prepared analogously to **3.67d**. *Step 1*: From phenylacetyl chloride (1.0 mL, 7.9 mmol, 1.1 equiv.), **S3.1f** (1.7 g, 7.2 mmol, 1.0 equiv.), and triethylamine (1.5 mL, 10.8 mmol, 1.5 equiv.) to give the ester (2.6 g). *Step 2*: From the ester (2.6 g, 7.2 mmol, 1.0 equiv.), *p*-ABSA (2.6 g, 10.8 mmol, 1.5 equiv.) and DBU (2.0 mL, 14.4 mmol, 2.0 equiv.). The crude was purified by column chromatography (3% EtOAc in hexanes) to give the diazo as a red oil (1.9 g, 68% yield

over two steps). $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.58-7.53 (m, 4H), 7.49-7.44 (m, 2H), 7.43-7.35 (m, 8H), 7.22-7.17 (m, 1H), 4.48-4.41 (m, 2H), 1.71-1.64 (m, 2H), 0.65 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.4, 136.0, 134.5, 129.7, 129.1, 128.2, 125.9, 125.8, 124.1, 63, 15.8, -3.9 (the resonance resulting from the diazo carbon was not detected); IR (neat): 3068, 2955, 2081, 1696, 1150 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{22}O_2N_2NaSi$ 409.1343, found 409.1343;




**S3.1g** **3.67g**

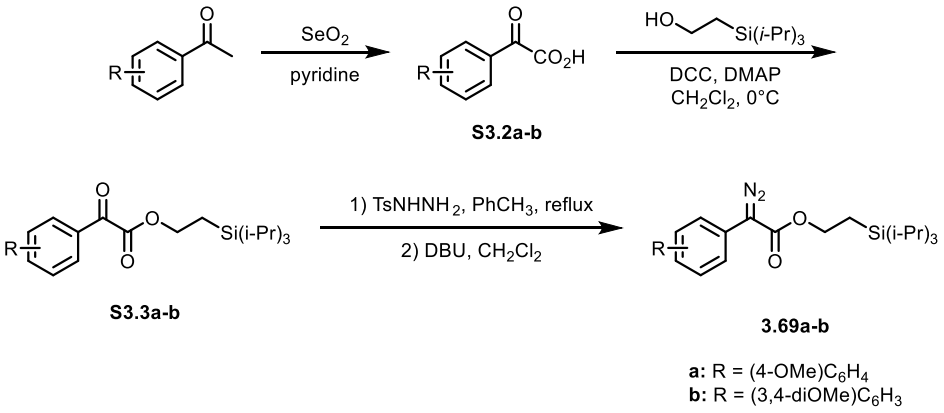
**2-(*tert*-butyldiphenylsilyl)ethyl 2-diazo-2-phenylacetate (3.67g):** Prepared analogously to **3.67d**. *Step 1*: From phenylacetyl chloride (1.9 mL, 14.7 mmol, 1.0 equiv.), **S3.1g** (4.6 g, 16.2 mmol, 1.1 equiv.) and triethylamine (4.5 mL, 32.4 mmol, 2.0 equiv.) to give the ester (4.0 g). *Step 2*: From the ester (4.0 g, 9.9 mmol, 1.0 equiv.), *p*-ABSA (3.6 g, 14.9 mmol, 1.5 equiv.) and DBU (3.0 mL, 19.8 mmol, 2.0 equiv.). The crude was purified by column chromatography (2% $Et_2O$ in pentane) to give the diazo as a thick red oil (2.3 g, 37% yield over two steps). $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.71-7.65 (m, 4H), 7.51-7.36 (m, 10H), 7.23-7.16 (m, 1H), 4.38-4.31 (m, 2H), 1.79-1.72 (m, 2H), 1.09 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.5, 136.0, 133.7, 129.6, 129.1, 128.0, 125.9, 125.9, 124.2, 63.6, 27.8, 18.2, 12.3 (the resonance resulting from the diazo carbon was not detected); IR (neat): 2929, 2856, 2081, 1698, 1149 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{26}H_{28}O_2N_2NaSi$ 451.1812, found 451.1813;

### 3.4.1.3 Preparation of Diazos 3.69a-k

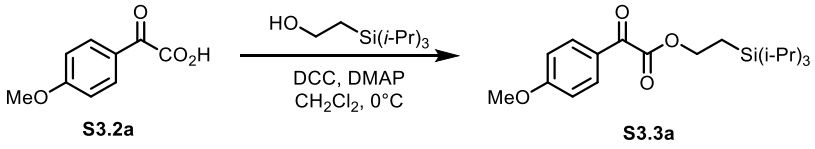
#### *Preparation of Diazos 3.69a-b*

Diazos **3.69a**,**b** were prepared according to Scheme 3.24. Acids **S3.2a-b** were prepared by oxidation of the corresponding acetophenones, according to a literature procedure.[36]

**Scheme 3.24** Preparation of diazos **3.69a-b**

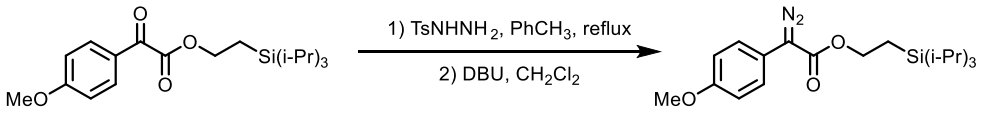



**The preparation of 3.69a is representative:**




**2-(triisopropylsilyl)ethyl 2-(4-methoxyphenyl)-2-oxoacetate (S3.3a):** To a 0 °C solution of acid **S3.2a** (1.1 g, 6.1 mmol, 1.0 equiv.), alcohol **S3.1d** (1.9 g, 9.2 mmol, 1.5 equiv.), and DMAP (74 mg, 0.61 mmol, 0.1 equiv.) in $CH_2Cl_2$ (6 mL) was added a solution of DCC (1.4 g, 6.7 mmol, 1.1 equiv.) in $CH_2Cl_2$ (5 mL). The mixture was stirred overnight, and allowed to warm to room temperature over that time. The precipitate was removed by filtration, washing with copious quantities of $Et_2O$. The filtrate was concentrated by rotary evaporation and purified by column chromatography (5% $Et_2O$ in

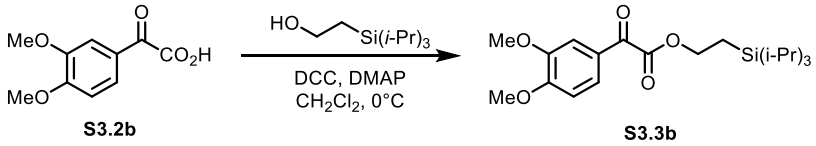
pentane) to give the ester as a colorless oil (1.6 g, 73% yield). $^{1}$H NMR (400 MHz; $CDCl_3$) δ 8.06-8.00 (m, 2H), 7.00-6.96 (m, 2H), 4.56-4.49 (m, 2H), 3.90 (s, 3H), 1.30-1.22 (m, 2H), 1.14-1.03 (m, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 185.2, 165.1, 164.4, 132.8, 125.8, 114.4, 65.1, 55.8, 18.9, 13.2, 11.1; IR (neat): 2941, 2865, 1729, 1675, 1597 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{32}O_4NaSi$ 387.1962, found 387.1966;




**S3.3a** **3.69a**

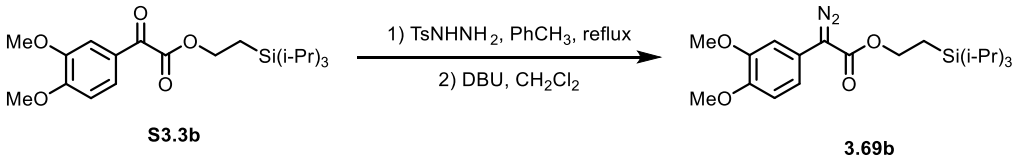
**2-(triisopropylsilyl)ethyl 2-diazo-2-(4-methoxyphenyl)acetate (3.69a):** A solution of the ketone (1.6 g, 4.4 mmol, 1.0 equiv.) and *p*-toluenesulfonyl hydrazide (900 mg, 4.8 mmol, 1.1 equiv.) in toluene (30 mL) was heated to reflux with a dean-stark apparatus overnight. The solution was allowed to cool to room temperature and the toluene removed by rotary evaporation. The crude residue was dissolved in $CH_2Cl_2$ (30 mL) and DBU (2.0 mL, 13.2 mmol, 3.0 equiv.) added. The mixture was stirred at room temperature for 24 hours. The orange solution was quenched with saturated aqueous $NH_4Cl$ (30 mL) and the aqueous phase extracted with $CH_2Cl_2$ (20 mL). The organic extracts were combined and dried over $MgSO_4$, filtered and concentrated. The crude reside was purified by column chromatography (4% $Et_2O$ in pentane) to give the product as a red oil (980 mg, 59% yield). $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.43-7.38 (m, 2H), 6.98-6.92 (m, 2H), 4.45-4.38 (m, 2H), 3.82 (s, 3H), 1.21-1.03 (m, 23H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.2, 158.2, 126.2, 117.3, 114.8, 63.6, 55.6, 18.9, 11.4, 11.2 (the resonance resulting from the diazo carbon was not detected); IR (neat): 2941, 2865, 2077, 1694,

1512 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{32}O_3N_2NaSi$ 399.2074, found 399.2075;




S3.2b S3.3b

**2-(triisopropylsilyl)ethyl 2-(3,4-dimethoxyphenyl)-2-oxoacetate (S3.3b):** Prepared analogously to **S3.3a**. From carboxylic acid **S3.2b** (1.5 g, 7.1 mmol, 1.0 equiv.), alcohol **S3.1d** (1.7 g, 8.5 mmol, 1.2 equiv.), DCC (1.6 g, 7.8 mmol, 1.1 equiv.) and DMAP (87 mg, 0.71 mmol, 0.1 equiv.). The crude was purified by column chromatography (9:1 hexanes:EtOAc) to give the product as a slightly yellow oil (2.1 g, 75% yield). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.67 (dd, 1H, *J* = 8.5, 2.0 Hz), 7.58 (d, 1H, *J* = 2.0 Hz), 6.93 (d, 1H, *J* = 8.5 Hz), 4.57-4.48 (m, 2H), 3.98 (s, 3H), 3.95 (s, 3H), 1.30-1.23 (m, 2H), 1.14-1.05 (m, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 185.3, 164.4, 155.1, 149.5, 126.5, 125.9, 110.9, 110.4, 65.1, 56.4, 56.3, 18.9, 11.1 (2 signals); IR (neat): 2940, 2864, 1729, 1672, 1514 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{21}H_{34}O_5NaSi$ 417.2068, found 417.2072;




S3.3b 3.69b

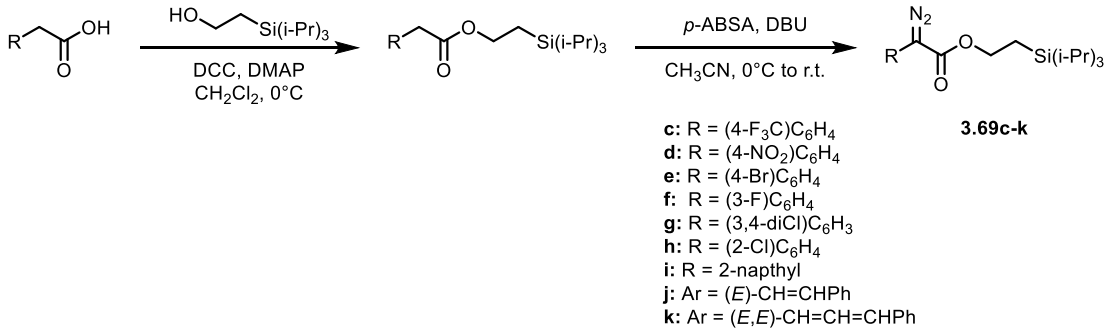
**2-(triisopropylsilyl)ethyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate (3.69b):** Prepared analogously to **3.69a**. From the ketone (2.1 g, 5.3 mmol, 1.0 equiv.), *p*-toluenesulfonyl hydrazide (1.1 g, 5.9 mmol, 1.1 equiv.) and DBU (2.4 mL, 15.9 mmol, 3.0 equiv.). The crude was purified by column chromatography (10-15% $Et_2O$ in pentane) to give the

product as a fluffy red solid (1.3 g, 59% yield). $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.21 (s, 1H), 6.92-6.86 (m, 2H), 4.46-4.37 (m, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 1.20-1.13 (m, 2H), 1.12-1.02 (m, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.1, 149.6, 147.4, 117.8, 116.7, 111.8, 108.5, 63.6, 56.2, 56.1, 18.9, 11.3, 11.2 (the resonance resulting from the diazo carbon was not detected); IR (neat): 2940, 2864, 2077, 1694, 1519 $cm^{-1}$; HRMS (NSI) *m/z*: $[M]^+$ calcd for $C_{21}H_{34}O_4N_2Si$ 406.2282, found 406.2284;

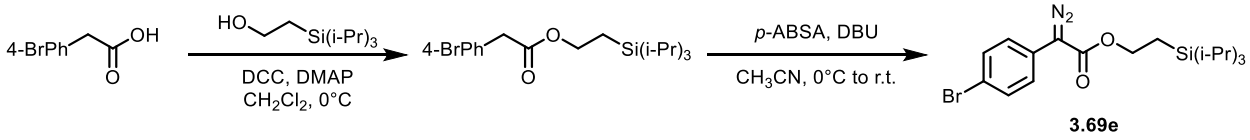
### *Preparation of Diazos 3.69c-k*

Diazos **3.69c-k** were prepared by direct diazo transfer to the ester, according to Scheme 3.25 below:

**Scheme 3.25** Preparation of diazos **3.69c-k**

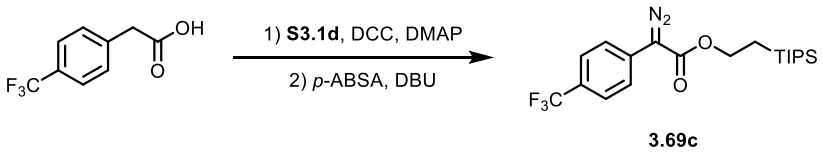



**The preparation of 3.69e is representative:**



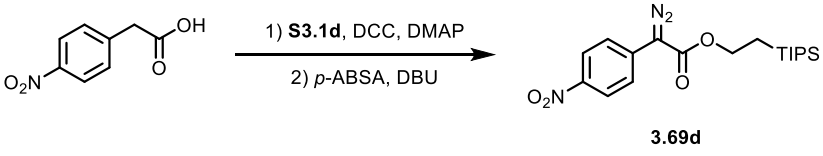

**2-(triisopropylsilyl)ethyl 2-(4-bromophenyl)-2-diazoacetate (3.69e):** A solution of 4-bromophenylacetic acid (1.1 g, 4.95 mmol, 1.0 equiv.), DMAP (60 mg, 0.50 mmol, 10 mol %), and 2-(triisopropylsilyl)ethanol **S3.1d** (1.2 g, 5.9 mmol, 1.2 equiv.) in $CH_2Cl_2$ (4

mL) was cooled to 0 °C. Then a solution of DCC (1.1 g, 5.4 mmol, 1.1 equiv.) in $CH_2Cl_2$ (2 mL) was added over 2 minutes. The mixture was stirred for 3 hours, and the white precipitate was removed by filtration, washing several times with $Et_2O$. The filtrate was concentrated by rotary evaporation and the crude residue purified by column chromatography (5% $Et_2O$ in pentane). The ester intermediate was isolated as a colorless oil (1.8 g) and used immediately in the diazo transfer: The ester (1.8 g, 4.4 mmol, 1.0 equiv.) was dissolved in $CH_3CN$ (10 mL), followed by *p*-ABSA (1.6 g, 6.6 mmol, 1.5 equiv.). The mixture was cooled to 0 °C. Then DBU (1.3 mL, 8.8 mmol, 2.0 equiv.) was added. The mixture was allowed to warm to room temperature and stirred for 72 hours. The reaction was quenched with saturated aqueous $NH_4Cl$ (15 mL) and $H_2O$ (5 mL). The mixture was extracted with $Et_2O$ (20 mL). The ether layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography (2% $Et_2O$ in pentane) to give the diazo **3.69e** as a thick orange/red oil (1.7 g, 79 % yield over two steps), which solidified as an orange solid in the freezer (-25 °C). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.52-7.47 (m, 2H), 7.40-7.36 (m, 2H), 4.46-4.39 (m, 2H), 1.21-1.13 (m, 2H), 1.13-1.02 (m, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.2, 132.2, 125.5, 125.2, 119.4, 63.9, 18.9, 11.4, 11.2 (the resonance resulting from the diazo carbon was not detected); IR (neat): 2939, 2862, 2091, 1690 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{29}O_2N_2BrNaSi$ 447.1074, found 447.1070;




**3.69c**

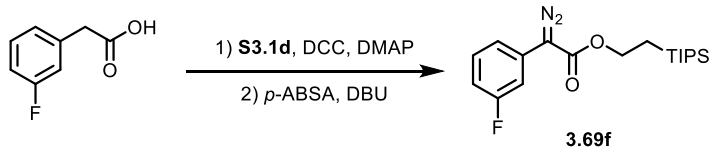
**2-(triisopropylsilyl)ethyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate (3.69c):** Prepared analogously to **3.69e**. *Step 1:* From 4-(trifluoromethyl)phenylacetic acid (1.0 g, 4.9 mmol, 1.0 equiv.), **S3.1d** (1.2 g, 5.9 mmol, 1.2 equiv.), DCC (1.1 g, 5.4 mmol, 1.1 equiv.) and DMAP (72 mg, 0.59 mmol, 0.1 equiv.) to give the intermediate ester (810 mg). *Step 2:* From the ester (0.81 g, 2.1 mmol, 1.0 equiv.), *p*-ABSA (0.77 g, 3.2 mmol, 1.5 equiv.), and DBU (0.59 mL, 4.2 mmol, 2.0 equiv.). The crude was purified by chromatography (2% $Et_2O$ in pentane) to give the product **3.69c** as an orange solid (730 mg, 37% yield over two steps). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.63 (s, 4H), 4.49-4.41 (m, 2H), 1.22-1.15 (m, 2H), 1.11-1.06 (m, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.8, 130.6, 127.6 (q, $J$ = 32.8 Hz), 126 (q, $J$ = 3.7 Hz), 124.3 (q, $J$ = 271.6 Hz), 123.6, 64.1, 18.9, 11.4, 11.2 (the resonance resulting from the diazo carbon was not detected); IR (neat): 2943, 2866, 2087, 1702, 1322 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{29}O_2N_2F_3NaSi$ 437.1843, found 437.1838;




**3.69d**

**2-(triisopropylsilyl)ethyl 2-diazo-2-(4-nitrophenyl)acetate (3.69d):** Prepared analogously to **3.69e**. *Step 1:* From 4-nitrophenylacetic acid (910 mg, 5.0 mmol, 1.0 equiv.), **S3.1d** (1.2 g, 5.9 mmol, 1.2 equiv.), DCC (1.1 g, 5.5 mmol, 1.1 equiv.) and DMAP (61 mg, 0.5 mmol, 0.1 equiv.) to give the ester (1.2 g). *Step 2:* From the ester

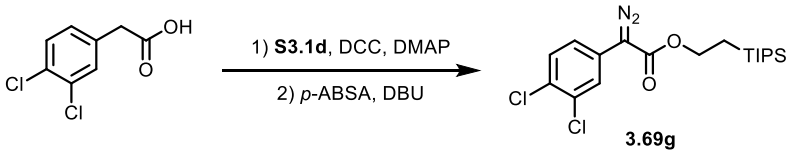
(1.2 g, 3.2 mmol, 1.0 equiv.), *p*-ABSA (1.2 g, 4.8 mmol, 1.5 equiv.) and DBU (0.90 mL, 6.4 mmol, 2.0 equiv.). The crude was purified by column chromatography (2% $Et_2O$ in pentane) to give the diazo as an orange solid (870 mg, 44% yield over two steps). $^1$H NMR (400 MHz; $CDCl_3$) δ 8.23-8.18 (m, 2H), 7.69-7.63 (m, 2H), 4.47-4.40 (m, 2H), 1.20-0.99 (m, 23H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.1, 145.1, 134.4, 124.5, 123.3, 64.4, 18.9, 11.4, 11.1 (the resonance resulting from the diazo carbon was not detected); IR (film): 2942, 2846, 2091, 1697, 1330 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{29}O_4N_2NaSi$ 414.1820, found 414.1815;




**3.69f**

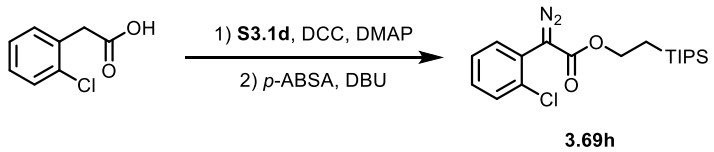
**2-(triisopropylsilyl)ethyl 2-diazo-2-(3-fluorophenyl)acetate (3.69f):** Prepared analogously to **3.69e**. *Step 1:* From 3-fluorophenylacetic acid (760 mg, 4.9 mmol, 1.0 equiv.), **S3.1d** (1.2 g, 5.9 mmol, 1.2 equiv.), DCC (1.1 g, 5.4 mmol, 1.1 equiv.) and DMAP (72 mg, 0.59 mmol, 0.1 equiv.) to give the ester (1.0 g). *Step 2:* From the ester (1.0 g, 3.0 mmol, 1.0 equiv.), *p*-ABSA (1.1 g, 4.5 mmol, 1.5 equiv.) and DBU (0.84 mL, 6.0 mmol, 2.0 equiv.). The crude was purified by column chromatography (1% $Et_2O$ in pentane) to give the diazo as an orange oil (900 mg, 50% yield over two steps). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.41-7.30 (m, 2H), 7.18 (ddd, 1H, $J$ = 8.0, 1.8, 0.9 Hz), 6.86 (tdd, 1H, $J$ = 8.3, 2.5, 0.9 Hz), 4.48-4.40 (m, 2H), 1.25-1.03 (m, 23H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165, 163.4 (d, $^1J_{CF}$ = 245 Hz), 130.5 (d, $^3J_{CF}$ = 8.8 Hz), 128.5 (d, $^3J_{CF}$ = 9.4 Hz), 119 (d, $^4J_{CF}$ = 2.6 Hz), 112.5 (d, $^2J_{CF}$ = 21.3 Hz), 111.3 (d, $^2J_{CF}$ = 25.3 Hz), 63.9, 18.9,

11.4, 11.1; IR (film): 2942, 2865, 2082, 1700, 1244 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{29}O_2N_2FNaSi$ 387.1875, found 387.1879;



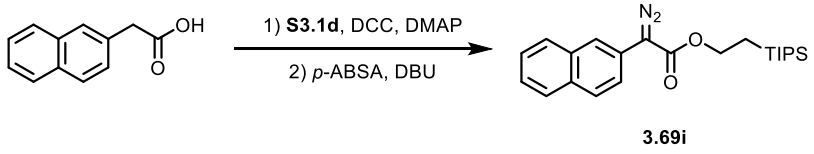

**3.69g**

**2-(triisopropylsilyl)ethyl 2-diazo-2-(3,4-dichlorophenyl)acetate (3.69g):** Prepared analogously to **3.69e**. *Step 1:* From 3,4-dichlorophenylacetic acid (1.0 g, 5.0 mmol, 1.0 equiv.), **S3.1d**, (1.2 g, 5.9 mmol, 1.2 equiv.), DCC (1.1 g, 5.5 mmol, 1.1 equiv.) and DMAP (61 mg, 0.5 mmol, 0.1 equiv.) to give the ester (1.5 g). *Step 2*: From the ester (1.5 g, 3.8 mmol, 1.0 equiv.), *p*-ABSA (1.4 g, 5.7 mmol, 1.5 equiv.) and DBU (1.1 mL, 7.6 mmol, 2.0 equiv.). The crude was purified by column chromatography (0.5% $Et_2O$ in pentane) to give the diazo as an orange solid (1.4 g, 67% yield over two steps). $^1H$ NMR (400 MHz; $CDCl_3$) δ 7.66 (d, 1H, *J* = 2.3 Hz), 7.42 (d, 1H, *J* = 8.6 Hz), 7.30 (dd, 1H, *J* = 8.6, 2.3 Hz), 4.47-4.39 (m, 2H), 1.21-1.04 (m, 23H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 164.7, 133.4, 130.8, 129.4, 126.5, 125.4, 122.8, 64.1, 18.9, 11.4, 11.1; IR (film): 2941, 2865, 2085, 1699, 1159 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{29}O_2N_2Cl_2Si$ 415.1370, found 415.1360; Anal. calcd for $C_{19}H_{28}N_2O_2SiCl_2$: C 54.93, H 6.79, N 6.74, Found C 54.92, H 6.80, N 6.66;




**3.69h**

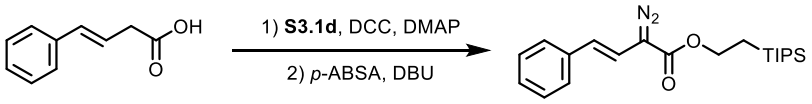
**2-(triisopropylsilyl)ethyl 2-(2-chlorophenyl)-2-diazoacetate (3.69h):** Prepared analogously to **3.69e**. *Step 1*: From 2-chlorophenylacetic acid (850 mg, 5.0 mmol, 1.0 equiv.), **S3.1d** (1.2 g, 5.9 mmol, 1.2 equiv.), DCC (1.1 g, 5.5 mmol, 1.1 equiv.), DMAP (61 mg, 0.5 mmol, 0.1 equiv.) to give the ester (1.2 g). *Step 2*: From the ester (1.2 g, 3.3 mmol, 1.0 equiv.), *p*-ABSA (1.2 g, 5.0 mmol, 1.5 equiv.) and DBU (0.93 mL, 6.6 mmol, 2.0 equiv.). The crude was purified by column chromatography (1% $Et_2O$ in pentane) to give the diazo as a yellow oil (1.1g, 58% yield over two steps). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.55 (dd, 1H, *J* = 7.7, 1.8 Hz), 7.40 (dd, 1H, *J* = 7.9, 1.6 Hz), 7.34-7.22 (m, 2H), 4.42-4.35 (m, 2H), 1.18-1.01 (m, 23H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.9, 133.9, 132.5, 130.2, 129.7, 127.3, 124.3, 64.0, 18.9, 11.4, 11.2; IR (neat): 2941, 2865, 1093, 1698, 1239 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{29}O_2N_2ClNaSi$ 403.1579, found 403.1577; Anal. calcd for $C_{19}H_{29}N_2O_2SiCl$: C 59.90, H 7.67, N 7.35, Found C 60.12, H 7.59, N 7.17;




**3.69i**

**2-(triisopropylsilyl)ethyl 2-diazo-2-(naphthalen-2-yl)acetate (3.69i):** Prepared analogously to **3.69e**. *Step 1*: From 2-naphthylacetic acid (1.2 g, 6.2 mmol, 1.0 equiv.), **S3.1d** (1.5 g, 7.4 mmol, 1.2 equiv.), DCC (1.4 g, 6.8 mmol, 1.1 equiv.) and DMAP (76 mg, 0.62 mmol, 0.1 equiv.) to give the ester (1.6 g). *Step 2*: From the ester (1.6 g, 4.3

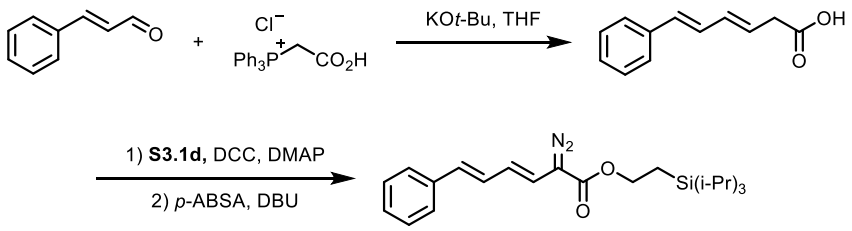
mmol, 1.0 equiv.), *p*-ABSA (1.6 g, 6.5 mmol, 1.5 equiv.) and DBU (1.3 mL, 8.6 mmol, 2.0 equiv.). The crude was purified by column chromatography (1% $Et_2O$ in pentane) to give the diazo as a red oil (1.5 g, 60% yield over two steps) that solidified upon storage in a freezer (-25 °C). $^1$H NMR (400 MHz; $CDCl_3$) δ 8.05 (s, 1H), 7.86 (d, 1H, *J* = 8.7 Hz), 7.85-7.78 (m, 2H), 7.56 (d, 1H, *J* = 8.7 Hz), 7.53-7.41 (m, 2H), 4.51-4.45 (m, 2H), 1.25-1.19 (m, 2H), 1.17-1.04 (m, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.7, 133.8, 131.6, 128.8, 127.8, 127.8, 126.8, 125.9, 123.1, 122.7, 122.1, 63.8, 18.9, 11.4, 11.2 (the resonance resulting from the diazo carbon was not detected); IR (neat): 2962, 2939, 2862, 2083, 1698 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{32}O_2N_2NaSi$ 419.2125, found 419.2125;




**3.69j**

**(*E*)-2-(triisopropylsilyl)ethyl 2-diazo-4-phenylbut-3-enoate (3.69j):** Prepared analogously to **3.69e**. *Step 1*: From *trans*-styrylacetic acid (1.0 g, 6.2 mmol, 1.0 equiv.), **S3.1d** (1.5 g, 7.4 mmol, 1.2 equiv.), DCC (1.4 g, 6.8 mmol, 1.1 equiv.) and DMAP (76 mg, 0.62 mmol, 0.1 equiv.) to give the ester (1.3 g). *Step 2*: From the ester (1.3 g, 3.8 mmol, 1.0 equiv.), *p*-ABSA (1.3 g, 5.2 mmol, 1.5 equiv.) and DBU (1.1 mL, 7.0 mmol, 2.0 equiv.), the reaction mixture was stirred for 3.5 hours before it was quenched. The diazo was purified by chromatography (2% $Et_2O$ in pentane) to give the product as a red oil. This was dissolved in benzene (8 mL), flash frozen with liquid $N_2$, and placed under vacuum (160 mTorr) overnight (16 hours) to furnish the diazo as a red solid (1.1 g, 48% yield over two steps). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.41-7.29 (m, 4H), 7.25-7.17 (m,

1H), 6.52 (d, 1H, *J* = 16.3 Hz), 6.20 (d, 1H, *J* = 16.3 Hz), 4.45-4.38 (m, 2H), 1.20-1.14 (m, 2H), 1.12-1.05 (m, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.5, 137.1, 128.9, 127.2, 126.0, 123.0, 111.8, 64.1, 18.9, 11.4, 11.2 (the resonance resulting from the diazo carbon was not detected); IR (neat): 2937, 2865, 2079, 1698 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{21}H_{32}O_2N_2NaSi$ 395.2125, found 395.2124;




**3.69k**

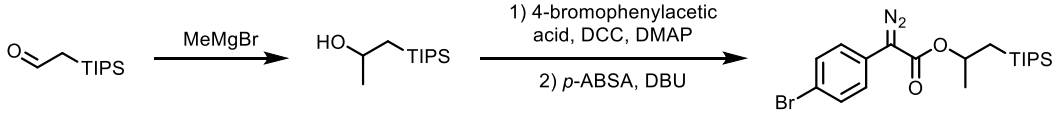
**(3*E*,5*E*)-2-(triisopropylsilyl)ethyl 2-diazo-6-phenylhexa-3,5-dienoate (3.69k):** To a flame-dried, 500 mL round-bottomed flask was added (carboxymethyl)triphenylphosphonium chloride[37] (26.7 g, 72 mmol, 1.2 equiv.). The flask was evacuated under high vacuum and back-filled with argon (2x). Then cinnamaldehyde (7.5 mL, 60 mmol, 1.0 equiv.) and THF (130 mL) were added. The mixture was stirred vigorously and cooled to 0 °C. A solution of KO*t*-Bu (16.8 g, 150 mmol, 2.5 equiv.) in THF (80 mL) was added dropwise over a period of 30 minutes *via* cannula. The mixture was allowed to stir for 2 hours, over which time it warmed to room temperature. The solution was quenched by the addition of saturated aqueous $NH_4Cl$ (150 mL) and $H_2O$ (50 mL). Each of the two layers had become homogenous. The aqueous layer was removed and the organic layer extracted with 0.5 M NaOH (100 mL x 2). The aqueous layer was acidified to pH = 1.0 with concentrated HCl and extracted with $Et_2O$ (200 mL). The ethereal layer was dried over $MgSO_4$ and concentrated. This

gave the crude, impure acid as a sticky reddish oil. A portion of this crude product was used without further purification.

The procedure above for the synthesis of **3.69e** was then followed, using a portion of the crude acid (1.2 g, ~ 6.2 mmol, 1.0 equiv.), **S3.1d** (1.5 g, 7.4 mmol, 1.2 equiv.), DCC (1.4 g, 6.8 mmol, 1.1 equiv.) and DMAP (76 mg, 0.62 mmol, 0.1 equiv.) to give the ester (860 mg). *Step 2*: From the ester (860 mg, 2.3 mmol, 1.0 equiv.), *p*-ABSA (840 mg, 3.5 mmol. 1.5 equiv.) and DBU (0.69 mL, 4.6 mmol, 2.0 equiv.), the reaction mixture was stirred for 3 hours before it was quenched. The crude was purified by column chromatography (2% $Et_2O$ in pentane) to give the diazo as a thick red oil (360 mg, 14% yield over last two steps). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.39 (d, 2H, *J* = 7.6 Hz), 7.32 (dd, 2H, *J* = 7.6, 7.1 Hz), 7.22 (t, 1H, *J* = 7.1 Hz), 6.89 (dd, 1H, *J* = 15.5, 8.8 Hz), 6.47 (d, 1H, *J* = 15.6 Hz), 6.17-6.02 (m, 2H), 4.43-4.36 (m, 2H), 1.19-1.13 (m, 2H), 1.12-1.04 (m, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.4, 137.5, 130.4, 128.8, 128.6, 127.5, 126.4, 124.0, 114.9, 64.1, 18.9, 11.3, 11.1 (the resonance resulting from the diazo carbon was not detected); IR (film): 2941, 2890, 2865, 2072, 1698 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{34}O_2N_2NaSi$ 421.2282, found 421.2291;

### 3.4.1.4 Preparation of Diazos 3.71 and 3.80

Diazo **3.71** was prepared as shown below:



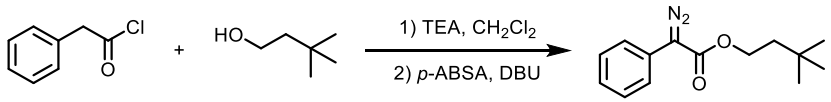

**S3.4**
1-(triisopropylsilyl)propan-2-ol

**3.71**

**1-(triisopropylsilyl)propan-2-ol (S3.4):** To a solution of 2-triisopropylacetaldehyde (see preparation of **S3.1d** above) (2.0 g, 10.0 mmol, 1.0 equiv.) in $Et_2O$ (20 mL) at -78 °C was added methylmagnesium bromide solution (6.7 mL, 3.0 M in $Et_2O$, 20 mmol, 2.0 equiv.) dropwise. The mixture was stirred at this temperature for 1 hour and then quenched with $H_2O$ (3 mL) and allowed to warm to room temperature. 1M aqueous HCl (15 mL) was added and the layers separated. The organic layer was washed with $H_2O$ (10 mL) and brine (10 mL). The organic was dried over $MgSO_4$ and concentrated to give the crude alcohol **S3.4** as a colorless oil (1.9 g, 86% yield), which was used without further purification.

**1-(triisopropylsilyl)propan-2-yl 2-(4-bromophenyl)-2-diazoacetate (3.71):** Prepared analogously to **3.69e**. *Step 1:* From 4-bromophenylacetic acid (1.2 g, 5.8 mmol, 1.0 equiv.), alcohol **S3.4** (1.5 g, 6.9 mmol, 1.2 equiv.), DCC (1.3 g, 6.4 mmol, 1.1 equiv.), and DMAP (71 mg, 0.56 mmol, 0.1 equiv.) to give the ester as a colorless oil (2.0 g). *Step 2:* From the ester (2.0 g, 4.9 mmol, 1.0 equiv.), *p*-ABSA (1.8 g, 7.3 mmol, 1.5 equiv.) and DBU (1.5 mL, 9.8 mmol, 2.0 equiv.). The crude was purified by column chromatography (1% $Et_2O$ in pentane) to give the diazo **3.71** as an orange solid (1.7 g, 68% yield over two steps). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.52-7.47 (m, 2H), 7.41-7.36 (m, 2H), 5.41-5.32 (m, 1H), 1.39 (d, 3H, $J$ = 6.1 Hz), 1.23 (dd, 1H, $J$ = 14.6, 7.0 Hz), 1.11-1.04 (m, 21H), 1.01 (dd, 1H, $J$ = 14.6, 7.5 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ

164.5, 132.1, 125.6, 125.2, 119.3, 71.6, 24.1, 19.0, 19.0, 18.4, 11.5 (the resonance resulting from the diazo carbon was not detected); IR (neat): 2957, 2938, 2862, 2085, 1691 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{31}O_2N_2BrNaSi$ 461.123, found 461.1241;




**3.80**

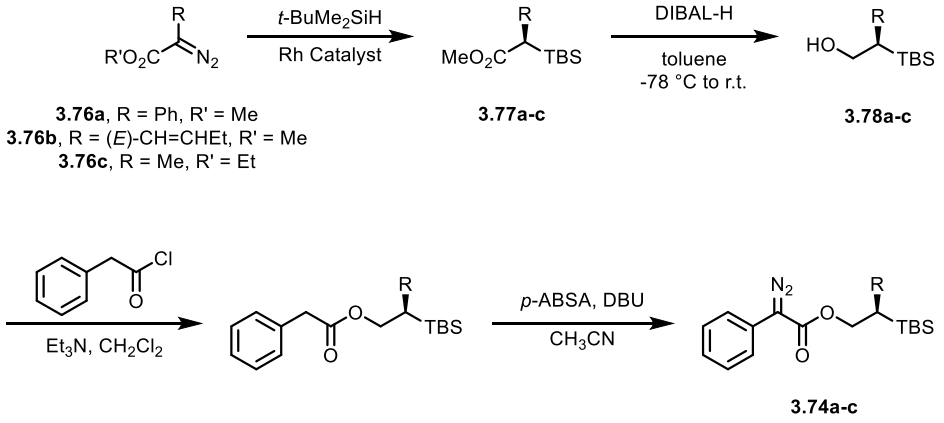
**3,3-dimethylbutyl 2-diazo-2-phenylacetate (3.80):** To a solution of 3,3-dimethyl-1-butanol (1.5 mL, 12 mmol, 1.5 equiv.) and triethylamine (2.3 mL, 16 mmol, 2.0 equiv.) in $CH_2Cl_2$ (20 mL) at 0 °C was added phenylacetyl chloride (1.1 mL, 8.0 mmol, 1.0 equiv.) dropwise slowly. The mixture was stirred overnight and quenched by washing with 1M HCl and dried over $MgSO_4$. The crude mixture was concentrated and used immediately in the next step. To a solution of the crude ester and *p*-ABSA (3.8 g, 15.7 mmol, 2.0 equiv.) in acetonitrile (20 mL) at 0 °C was added DBU (3.1 mL, 20.8 mmol, 2.6 equiv.). The mixture was allowed to warm to room temperature overnight, and quenched with saturated aqueous $NH_4Cl$ (25 mL). The mixture was extracted with $Et_2O$ (20 mL). The ethereal layer was washed with brine (25 mL) and dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography (3% $Et_2O$ in pentane) to give the diazo as a red oil (910 mg, 46% yield over 2 steps). $^1H$ NMR (400 MHz; $CDCl_3$) δ 7.53-7.48 (m, 2H), 7.43-7.37 (m, 2H), 7.19 (tt, 1H, *J* = 7.7, 1.2 Hz), 4.35 (t, 2H, *J* = 7.3 Hz), 1.65 (t, 2H, *J* = 7.3 Hz), 0.98 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 165.6, 129.1, 125.9, 125.8, 124.1, 62.9, 42.1, 30.0, 29.8; IR (neat): 2956,

2867, 2080, 1700, 1240 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{18}N_2O_2Na$ 269.1261, found 269.1259;

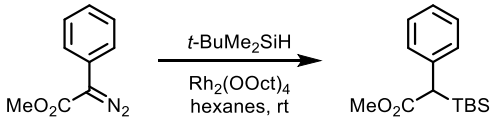
## 3.4.2 Preparation of Chiral Diazos

Chiral diazos **3.74a-c** were synthesized according to the general reaction Scheme 3.26. Diazos **3.76a**[38]**, 3.76b**[39]**,** and **3.76c**[40] were prepared according to known literature procedures.

**Scheme 3.26** Preparation of diazos **3.74a-c**



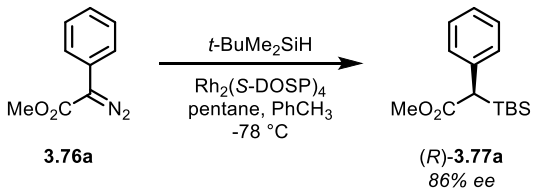

### 3.4.2.1 Synthesis of 3.77a-c




**(*R*/*S*)-methyl 2-(*tert*-butyldimethylsilyl)-2-phenylacetate (*rac*-3.77a):** To a solution of $Rh_2(OOct)_4$ (219 mg, 0.284 mmol, 1 mol %) and *tert*-butyldimethylsilane (9.4 mL, 56.8 mmol, 2.0 equiv.) in hexanes (40 mL) at room temperature was added a solution of **3.76a** (5.0 g, 28.4 mmol, 1.0 equiv.) dropwise over 2 hours. The mixture was allowed to stir at

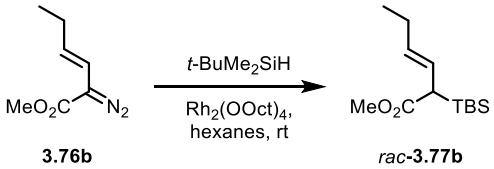
room temperature overnight. The solvent was removed by rotary evaporation and the crude reside purified by column chromatography (3% $Et_2O$ in pentane). The product was isolated as a pale yellow oil (6.7 g, 89 % yield).

**Enantioselective reaction:**



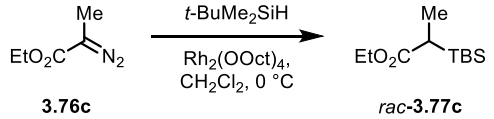

**3.76a** (*R*)-**3.77a** *86% ee*

**(*R*)-methyl 2-(*tert*-butyldimethylsilyl)-2-phenylacetate ((*R*)-3.77a):** *tert*-butyldimethylsilane (15.1 mL, 90.9 mmol, 4.0 equiv.), and $Rh_2$(*S*-DOSP)$_4$ (1.3 g, 0.68 mmol, 3 mol %) were dissolved in a mixture of pentane (135 mL) and toluene (11mL). The green solution was cooled to -78 °C in an acetone/dry ice bath. Diazo **3.67a** (4.0 g, 22.7 mmol, 1.0 equiv.) was dissolved in 75 mL pentane. The orange solution was then added dropwise to the reaction mixture over 2 hours. The mixture was stirred an additional 2 hours before it was allowed to warm to room temperature. The solvent was removed by rotary evaporation and the crude residue purified by column chromatography (3% $Et_2O$ in pentane). The product was isolated as a colorless oil (5.3 g, 88% yield, 86% ee). $[\alpha]_D^{20}$: 15.9 (c. 1.8, $CHCl_3$); $^1$H NMR (400 MHz; $CDCl_3$) δ 7.36 (d, 2H, *J* = 7.5 Hz), 7.26 (dd, 2H, *J* = 7.5, 7.3 Hz), 7.16 (t, 1H, *J* = 7.3 Hz), 3.65 (s, 3H), 3.55 (s, 1H), 0.86 (s, 9H), 0.11 (s, 3H), -0.12 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.0, 137.2, 128.9, 128.3, 125.9, 51.6, 43.1, 26.8, 18.0, -6.3, -6.8; IR (neat): 2951, 2930, 2884, 2858, 1720 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{25}O_2Si$ 265.1618, found 265.1624; The ee was determined by chiral HPLC: OD column, 1 mL/min, 0.5 % iPrOH in hexanes. Major: 4.2 min, Minor: 9.9 min, 86 % ee




**3.76b** *rac*-**3.77b**

**methyl (*E*)-2-(*tert*-butyldimethylsilyl)hex-3-enoate (3.77b):** The diazo **3.76b** (2.9 g, 18.8 mmol, 1.0 equiv.), in pentane (45 mL), was added dropwise over 1 hour to a solution of $Rh_2(OOct)_4$ (145 mg, 0.188 mmol, 1 mol%) and *t*-$BuMe_2SiH$ (9.3 mL, 56.4 mmol, 3.0 equiv.) in 45 mL pentane. The mixture was stirred for 15 minutes and concentrated. The crude mixture was purified by column chromatography (3% $Et_2O$ in pentane). The product **3.77b** was isolated as a colorless oil (3.5 g, 76% yield). $^1H$ NMR (400 MHz; $CDCl_3$) δ 5.61 (ddt, 1H, *J* = 15.3, 10.4, 1.4 Hz), 5.36 (dt, 1H, *J* = 15.3, 6.4 Hz), 3.63 (s, 3H), 2.96 (d, 1H, *J* = 10.4 Hz), 2.07-1.98 (m, 2H), 0.96 (t, 3H, *J* = 7.5 Hz), 0.91 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.5, 132.1, 124.3, 51.3, 41.0, 26.9, 25.9, 18.1, 14.0, -6.5, -6.7; IR (neat): 2958, 2930, 2858, 1721, 1131 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{27}O_2Si$ 243.1775, found 243.1776;

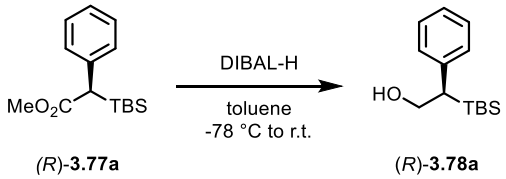



**3.76c** *rac*-**3.77c**

**ethyl 2-(*tert*-butyldimethylsilyl)propanoate (*rac*-3.77c):** *tert*-butyldimethylsilane (19.4 mL, 117 mmol, 3.0 equiv.) and $Rh_2(OOct)_4$ (300 mg, 0.39 mmol, 1 mol %) were dissolved in $CH_2Cl_2$ (100 mL). The mixture was cooled to 0 °C. The diazo **3.76c** (5.0 g, 39 mmol, 1.0 equiv.), as a solution in $CH_2Cl_2$ (100 mL) was added to the reaction mixture dropwise over 3 hours. The reaction mixture was stirred at room temperature overnight (16 hours). The solvent was removed and the crude reside purified by column

chromatography (5% $Et_2O$ in pentane). The product was isolated as a slightly green-tinged oil (7.9 g, 94% yield). $^1$H NMR (400 MHz; $CDCl_3$) δ 4.15-4.01 (m, 2H), 2.14 (q, 1H, *J* = 7.2 Hz), 1.28-1.20 (m, 6H), 0.92 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.1, 59.9, 27.6, 26.9, 17.8, 14.5, 12.7, -6.7, -6.8; IR (neat): 2957, 2931, 2883, 2859, 1717 $cm^{-1}$; HRMS (APCI-methanol) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{25}O_2Si$ 217.1618, found 217.1619;

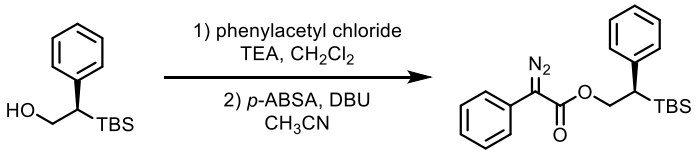
### 3.4.2.2 Synthesis of Diazos 3.74a-c




(*R*)-**3.77a** (*R*)-**3.78a**

**(*R*)-2-(*tert*-butyldimethylsilyl)-2-phenylethanol ((*R*)-3.78a):** To a solution of **(*R*)-3.77a** (4.0 g, 15.1 mmol, 1.0 equiv.) in toluene at -78 °C was added DIBAL-H (38 mL, 1.0 M in toluene, 37.8 mmol, 2.5 equiv.) dropwise slowly. The mixture was stirred at this temperature for 30 minutes, allowed to warm to room temperature, and stirred for 2 hours. The mixture was carefully quenched with MeOH (5 mL), and stirred until the bubbling ceased. A concentrated aqueous solution of Rochelle salt (25 mL) was added followed by $H_2O$ (25 mL) and toluene (25 mL). The biphasic mixture was stirred vigorously overnight. The aqueous phase was drained and the organic phase dried over $MgSO_4$ and concentrated. The crude was passed through a short plug of silica, eluting with 3:1 hexanes:EtOAc. The product was isolated as a colorless oil (3.2 g, 89% yield.). $[\alpha]_D^{20}$: 5.4 (c. 1.2, $CHCl_3$); $^1$H NMR (400 MHz; $CDCl_3$) δ 7.30-7.23 (m, 2H), 7.17-7.09 (m, 3H), 4.08 (ddd, 1H, *J* = 11.7, 11.2, 3.2 Hz), 3.99 (ddd, 1H, *J* = 11.2, 9.0, 4.3 Hz),

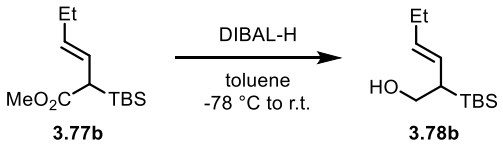
2.58 (dd, 1H, *J* = 11.7, 4.3 Hz), 1.39 (dd, 1H, *J* = 9.0, 3.2 Hz), 0.82 (s, 9H), 0.02 (s, 3H), -0.22 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 141.2, 128.9, 128.6, 125.6, 64.3, 39.1, 27.1, 17.6, -6.1, -6.8; IR (film): 3379, 2954, 2927, 2882, 2856 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{24}ONaSi$ 259.1489, found 259.1490; The ee was determined by chiral HPLC: ADH column, 1 mL/min, 1 % iPrOH in hexanes. Major: 11.5 min, Minor: 13 min, 85 % ee.




(*R*)-**3.78a** (*R*)-**3.74a**

**(*R*)-2-(*tert*-butyldimethylsilyl)-2-phenylethyl 2-diazo-2-phenylacetate ((*R*)-3.74a):** To a solution of alcohol **(*R*)-3.78a** (3.2 g, 13.5 mmol, 1.05 equiv.) and triethylamine (3.6 mL, 25.7 mmol, 2.0 equiv.) in $CH_2Cl_2$ (40 mL) at 0 °C was added phenylacetyl chloride (1.7 mL, 12.9 mmol, 1.0 equiv.) dropwise. The mixture was stirred 4 hours and quenched with saturated $NH_4Cl$ (50 mL). The organic phase was washed with aqueous 1M HCl (30 mL) and saturated aqueous $NaHCO_3$ (30 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified by column chromatography (9:1 hexanes:EtOAc) to give the ester (2.7 g). This ester was immediately dissolved in acetonitrile (35 mL), along with *p*-ABSA (2.7 g, 11.4 mmol, 1.5 equiv.) and cooled to 0 °C. Then DBU (2.3 mL, 15.2 mmol, 2.0 equiv.) was added dropwise. The mixture was allowed to warm to room temperature over a few hours and stirred a total of 36 hours. The mixture was quenched by addition of $NH_4Cl$ (40 mL). The aqueous phase was extracted with $Et_2O$ (30 mL). The ethereal layer was dried over $MgSO_4$ and

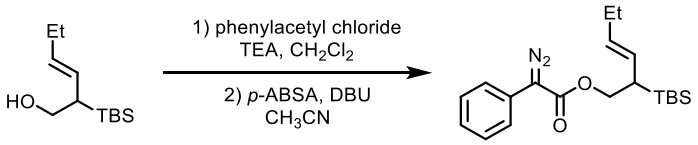
concentrated. The crude material was purified by column chromatography (3% $Et_2O$ in pentane) to give the diazo as an orange oil (1.9 g, 39% yield over two steps). $[\alpha]_D^{20}$: 4.2 (c. 1.4, $CHCl_3$); $^1H$ NMR (400 MHz; $CDCl_3$) δ 7.30-7.22 (m, 6H), 7.17-7.08 (m, 4H), 4.78 (dd, 1H, *J* = 11.2, 4.2 Hz), 4.65 (dd, 1H, *J* = 12.2, 11.2 Hz), 2.76 (dd, 1H, *J* = 12.2, 4.2 Hz), 0.88 (s, 9H), 0.11 (s, 3H), -0.15 (s, 3H); $^{13}C$ NMR (100 MHz, CDCl3) δ 165.8, 141.4, 129.0, 128.6, 128.2, 125.8, 125.7, 125.4, 124.1, 67.2, 35.0, 27.1, 17.6, -6.1, -6.8 (the resonance resulting from the diazo carbon was not detected); IR (film): 2954, 2928, 2882, 2856, 2083, 1698 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{28}O_2N_2NaSi$ 403.1812, found 403.1819; The ee was determined by chiral HPLC: OJ column, 1 mL/min, 0.5 % iPrOH in hexanes. Major: 7.6 min, Minor: 11.5 min, 86% ee.



**3.77b** **3.78b**

**(*E*)-2-(*tert*-butyldimethylsilyl)hex-3-en-1-ol (3.78b):** To a -78 °C solution of the ester **3.77b** (3.5 g, 14.4 mmol, 1.0 equiv.) in toluene (50 mL) was added a solution of DIBAL-H (36 mL, 1.0 M in toluene, 36.0 mmol, 2.5 equiv.) dropwise. The mixture was stirred for 1.5 hours at this temperature, allowed to warm to room temperature and stirred for 1 hour. The mixture was quenched by careful addition of MeOH (5 mL), and stirred until bubbling had ceased. Then toluene (50 mL) and a saturated aqueous solution of Rochelle salt (50 mL) was added. The mixture was stirred vigorously until both layers had become homogenous, about 30 min. The layers were separated and the organic layer dried over $MgSO_4$ and concentrated. This gave the crude alcohol as a colorless oil (3.0 g, 97% yield). $^1H$ NMR (600 MHz; $CDCl_3$) δ 5.51 (dt, 1H, *J* = 15.2, 6.4 Hz), 5.28 (dd, 1H, *J* =

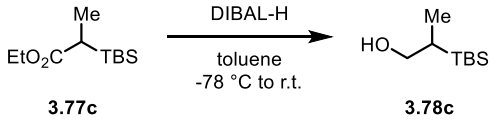
15.2, 10.1 Hz), 3.74 (ddd, 1H, *J* = 10.7, 9.1, 3.8 Hz), 3.58 (ddd, 1H, *J* = 11.6, 10.7, 2.3 Hz), 2.12-2.03 (m, 2H), 1.98 (ddd, 1H, *J* = 11.6, 10.1, 3.8 Hz), 1.65 (dd, 1H, *J* = 9.1, 2.3 Hz), 0.99 (t, 3H, *J* = 7.5 Hz), 0.90 (s, 9H), -0.04 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 134.5, 127.7, 62.6, 36.3, 27.2, 26.1, 17.6, 14.3, -6.7, -6.8; IR (film): 3366, 2957, 2928, 2856, 1248 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{27}OSi$ 215.1826, found 215.1828;




**3.78b** **3.74b**

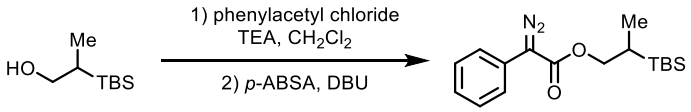
**(*E*)-2-(*tert*-butyldimethylsilyl)hex-3-en-1-yl 2-diazo-2-phenylacetate (3.74b):** To a solution of the alcohol **3.78b** (3.0 g, 14.0 mmol) and triethylamine (3.9 mL, 28.0 mmol, 2.0 equiv.) in $CH_2Cl_2$ (50 mL) at 0 °C was added phenylacetyl chloride (3.0 mL, 22.4 mmol, 1.6 equiv.) dropwise. The mixture was allowed to warm to room temperature overnight and was diluted with $CH_2Cl_2$ (50 mL). The solution was washed with 1M HCl (50 mL) and 1M NaOH (50 mL). The mixture was dried over $MgSO_4$ and concentrated to give the crude ester as a yellow oil (4.6 g). This was immediately dissolved in acetonitrile (55 mL) with *p*-ABSA (5.0 g, 20.7 mmol, 1.5 equiv.) and cooled to 0 °C. DBU (4.1 mL, 2.0 equiv.) was added dropwise, and the mixture allowed to warm to room temperature over several hours, and stirred for a total of 72 hours. The reaction was quenched with saturated aqueous $NH_4Cl$ (70 mL) and extracted with $Et_2O$ (75 mL). The ethereal layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated. The crude material was purified by column chromatography (2% $Et_2O$ in pentane) to give the

diazo as an orange oil (1.6 g, 31% yield over two steps). $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.49 (d, 2H, *J* = 7.5 Hz), 7.38 (dd, 2H, *J* = 7.5, 7.4 Hz), 7.18 (t, 1H, *J* = 7.4 Hz), 5.46-5.28 (m, 2H), 4.53 (dd, 1H, *J* = 10.9, 3.9 Hz), 4.31 (dd, 1H, *J* = 11.6, 10.6 Hz), 2.19 (ddd, 1H, *J* = 11.6, 9.2, 3.9 Hz), 2.09-1.99 (m, 2H), 1.01-0.93 (m, 12H), 0.03 (s, 3H), 0.01 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.7, 132.5, 129.1, 127.6, 126.0, 125.8, 124.1, 66.4, 32.6, 27.3, 26.1, 17.7, 14.3, -6.5, -6.7 (the resonance resulting from the diazo carbon was not detected); IR (neat): 2957, 2929, 2856, 2081, 1699 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H-N_2]^+$ calcd for $C_{20}H_{31}O_2Si$ 331.2088, found 331.2086;




**3.77c** **3.78c**

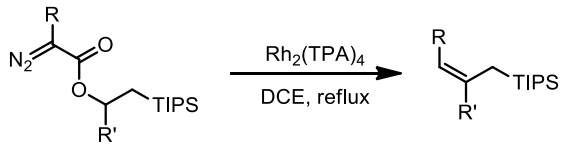
**2-(*tert*-butyldimethylsilyl)propan-1-ol (3.78c):** To a solution of the ester **3.77c** (3.0 g, 13.9 mmol, 1.0 equiv.) in $CH_2Cl_2$ (20 mL) at -78 °C was added a solution of DIBAL-H (35 mL, 1.0 M in $CH_2Cl_2$ 35 mmol, 2.5 equiv.) dropwise. The mixture was stirred for 2 hours, warmed to room temperature, and stirred for 1 hour. The mixture was quenched by careful addition of MeOH (5 mL), and stirred until bubbling ceased. An aqueous solution of Rochelle salt (25 mL) was added followed by $CH_2Cl_2$ (20 mL). The mixture was stirred vigorously for 1 hour. The layers were separated and the organic layer dried over $MgSO_4$ and concentrated. This gave the product as a colorless oil (2.2 g, 92% yield). $^{1}$H NMR (400 MHz; $CDCl_3$) δ 3.89-3.82 (m, 1H), 3.55-3.47 (m, 1H), 1.50-1.43 (m, 1H), 1.17-1.05 (m, 4H), 0.91 (s, 9H), -0.04 (s, 3H), -0.05 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 66.5, 27.4, 22.6, 17.4, 13.1, -6.8, -6.9; IR (neat): 3322, 2954, 2928, 2857 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H-H_2O]^+$ calcd for $C_9H_{21}Si$ 157.1413, found 157.1408;




**3.78c** **3.74c**

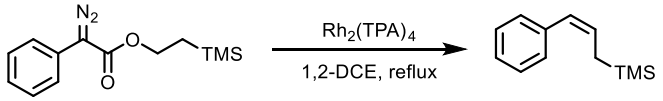
**2-(*tert*-butyldimethylsilyl)propyl 2-diazo-2-phenylacetate (3.74c):** To a solution of the alcohol **3.78c** (1.5 g, 8.6 mmol, 1.2 equiv.) and triethylamine (2.0 mL, 14.4 mmol, 2.0 equiv.) in $CH_2Cl_2$ (30 mL) at 0 °C was added phenylacetyl chloride (0.95 mL, 7.2 mmol, 1.0 equiv.) dropwise. The mixture was allowed to warm to room temperature overnight and quenched by washing with saturated aqueous $NaHCO_3$ (30 mL), and 1M HCl (30 mL). The mixture was dried over $MgSO_4$ and concentrated. The crude mixture was purified by column chromatography (5% $Et_2O$ in pentane) to give the ester as a colorless oil (1.5 g). This was immediately dissolved in acetonitrile (15 mL) with *p*-ABSA (1.9 g, 7.8 mmol, 1.5 equiv.) and cooled to 0 °C. DBU (1.6 mL, 10.4 mmol, 2.0 equiv.) was added dropwise, and the mixture allowed to warm to room temperature over several hours, and stirred for a total of 48 hours. The reaction was quenched with saturated aqueous $NH_4Cl$ (20 mL) and extracted with $Et_2O$ (25 mL). The ethereal layer was washed with brine (20 mL), dried over $MgSO_4$ and concentrated. The crude material was purified by column chromatography (5% $Et_2O$ in pentane) to give the diazo as an orange oil (1.2 g, 52% yield over two steps). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.51 (d, 2H, *J* = 8.6 Hz), 7.39 (dd, 2H, *J* = 8.6, 7.4 Hz), 7.19 (t, 1H, *J* = 7.4 Hz), 4.56 (dd, 1H, *J* = 10.8, 3.7 Hz), 4.15 (app t, 1H, *J* = 10.8 Hz), 1.43-1.32 (m, 1H), 1.11 (d, 3H, *J* = 7.3 Hz), 0.95 (s, 9H), 0.00 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.7, 129.1, 125.9, 125.9, 124.2, 69.4, 27.3, 19.1, 17.4, 13.6, -6.8, -7.0; IR (film): 2953, 2928, 2856, 2080, 1699 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{26}O_2N_2NaSi$ 341.1656, found 341.1660;

## 3.4.3 General Procedure for Allyl Silane Reaction



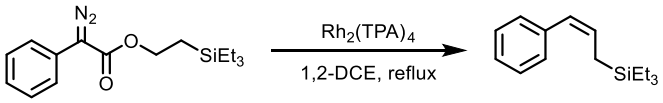

A solution of the diazo (0.3 – 0.5 mmol) in 4 mL 1,2-dichloroethane (DCE) was added dropwise over 2 hours to a solution of $Rh_2(TPA)_4$ (1 mol %) in DCE (2 mL) at reflux. The mixture was stirred at reflux for an additional 30 minutes, cooled to room temperature and concentrated. The crude was purified by chromatography.

## 3.4.4 Experimental Data for Allyl Silanes




**3.67a** **3.25a**

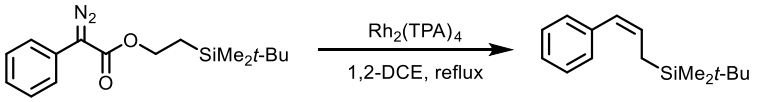
**(*Z*)-trimethyl(3-phenylallyl)silane (3.25a):** The general procedure for allyl silane formation was followed, with **3.67a** (131 mg, 0.5 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (7 mg, 0.005 mmol, 1 mol %), purifying by column chromatography (pentane) to give **3.25a** as a colorless oil (72 mg, 76% yield) as a 89:11 mixture of *Z*:*E* isomers. Both the *Z*[41] and *E*[42] isomers of this compound are known in the literature.




**3.67b** **3.25b**

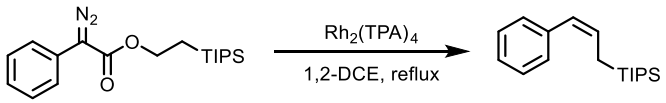
**(*Z*)-triethyl(3-phenylallyl)silane (3.25b):** The general procedure for allyl silane formation was followed, with **3.67b** (152 mg, 0.5 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (7 mg, 0.005 mmol, 1 mol %), purifying by column chromatography (pentane) to give **3.25b**

as a colorless oil (86 mg, 76% yield) as a 91:9 mixture of *Z*:*E* isomers. $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.37-7.31 (m, 4H), 7.25-7.18 (m, 1H), 6.34 (dt, 1H, *J* = 11.6, 1.6 Hz), 5.76 (dt, 1H, *J* = 11.6, 9.1 Hz), 1.89 (dd, 2H, *J* = 9.1, 1.6 Hz), 0.94 (t, 9H, *J* = 7.9 Hz), 0.58 (q, 6H, *J* = 7.9 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 138.4, 129.4, 128.8, 128.3, 126.9, 126.2, 14.8, 7.5, 3.6; IR (neat): 2951, 2909, 2874, 1446 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{25}Si$ 233.1720, found 233.1718;




**3.67c** **3.25c**

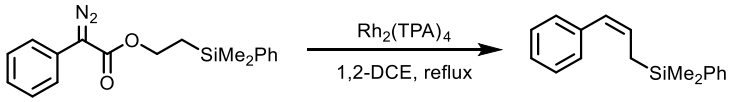
**(*Z*)-*tert*-butyldimethyl(3-phenylallyl)silane (3.25c):** The general procedure for allyl silane formation was followed, with **3.67c** (152 mg, 0.5 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (7 mg, 0.005 mmol, 1 mol %), purifying by column chromatography (pentane) to give **3.25c** as a colorless oil (92 mg, 79% yield) as a 95:5 mixture of *Z*:*E* isomers. $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.37-7.29 (m, 4H), 7.23-7.18 (m, 1H), 6.34 (d, 1H, *J* = 11.6 Hz), 5.75 (dt, 1H, *J* = 11.6, 9.1 Hz), 1.88 (dd, 2H, *J* = 9.1, 1.4 Hz), 0.90 (s, 9H), 0.00 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 138.4, 129.6, 128.8, 128.3, 127.0, 126.2, 26.7, 17.1, 15.7, -6.0; IR (neat): 2952, 2927, 2882, 2855, 1248 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{25}Si$ 233.1720, found 233.1722;




**3.67d** **3.25d**

**(*Z*)-triisopropyl(3-phenylallyl)silane (3.25d):** The general procedure for allyl silane formation was followed, with **3.67d** (173 mg, 0.5 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (7

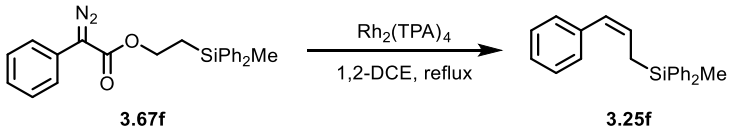
mg, 0.005 mmol, 1 mol %), purifying by column chromatography (pentane) to give **3.25d** as a colorless oil (112 mg, 82% yield). $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.35-7.27 (m, 4H), 7.22-7.15 (m, 1H), 6.29 (dt, 1H, *J* = 11.6, 1.8 Hz), 5.81 (dt, 1H, *J* = 11.6, 8.8 Hz), 1.92 (dd, 2H, *J* = 8.8, 1.8 Hz), 1.11-0.97 (m, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 138.4, 130.0, 128.9, 128.3, 127.0, 126.2, 18.9, 12.1, 11.3; IR (neat): 2940, 2889, 2864, 1462, 881 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{31}Si$ 275.2190, found 275.2186;




**3.67e** **3.25e**

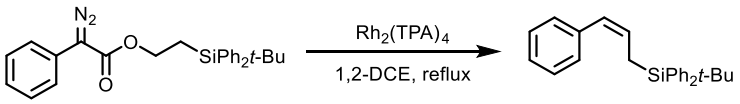
**(*Z*)-dimethyl(phenyl)(3-phenylallyl)silane (3.25e):** The general procedure for allyl silane formation was followed, with **3.67e** (162 mg, 0.5 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (7 mg, 0.005 mmol, 1 mol %), purifying by column chromatography (0.1% $Et_2O$ in pentane) to give **3.25e** as a colorless oil (101 mg, 80% yield) as a 84:16 mixture of *Z*:*E* isomers. The *E* isomer has been characterized previously.[42] Characterization data for *Z* isomer: $^{1}$H NMR (400 MHz; $CDCl_3$) (Note: Aryl hydrogens appeared as groups of multiplets, and the signals resulting from the minor *E* isomer could not be distinguished from those of the *Z*. The other peaks could be easily distinguished by comparison to published spectra for the *E* isomer[42]) δ 7.57-7.52 (m, 2H), 7.42-7.28 (m, 5H), 7.27-7.17 (m, 3H), 6.38 (d, 1H, *J* = 11.6 Hz), 5.73 (dt, 1H, *J* = 11.6, 9.0 Hz), 2.10 (dd, 2H, *J* = 9.0, 1.3 Hz), 0.34 (s, 6H); $^{13}$C NMR (100 MHz, CDCl3) (The peaks for the *Z* isomer could be distinguished from those for the *E* by comparison to the published spectrum for the *E* isomer[42]) δ 138.7, 138.2, 133.8, 129.3, 128.8, 128.5, 128.3, 128.0, 127.7, 126.3, 18.9, -

2.9; IR (neat): 3068, 3008, 2955, 1248, 1112 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{21}Si$ 253.1407, found 253.1411;



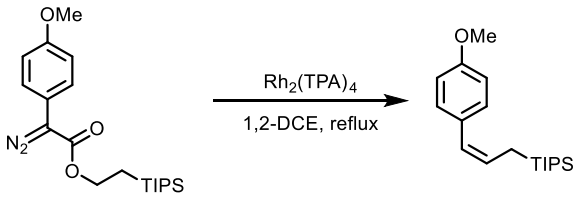

**3.67f** **3.25f**

**(*Z*)-methyldiphenyl(3-phenylallyl)silane (3.25f):** The general procedure for allyl silane formation was followed, with **3.67f** (139 mg, 0.36 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (5 mg, 0.0036 mmol, 1 mol %), purifying by column chromatography (1% $Et_2O$ in pentane) to give **3.25f** as a colorless oil (79 mg, 70% yield) as a 89:11 mixture of *Z*:*E* isomers. The compound was characterized as the mixture of isomers. NMR peaks for the major and minor isomers were tentatively assigned as closely as possible: $^1H$ NMR (400 MHz; $CDCl_3$) δ 7.60-7.51 (m, 4H, major and minor), 7.45-7.15 (m, 11H, major and minor), 6.40 (d, 1H, *J* = 11.6 Hz, major), 6.34 (m, 2H, minor), 5.76 (dt, 1H, *J* = 11.6, 8.8 Hz, major), 2.40 (dd, 2H, *J* = 8.8, 1.6 Hz, major), 2.26 (d, 2H, *J* = 7.1 Hz, minor), 0.62 (s, 3H, minor), 0.60 (s, 3H, major); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 138.1 (major), 136.6 (minor), 134.8 (major), 129.9 (minor), 129.7 (major), 128.9 (major), 128.7 (minor), 128.5 (major), 128.4 (major), 128.2 (major), 127.9 (major, 2 signals), 126.8 (minor), 126.6 (minor), 126.5 (major, 2 signals), 125.9 (minor), 21.8 (minor), -4.2 (major), -4.3 (minor); IR (neat): 3067, 3009, 1427, 1110, 694 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{22}NaSi$ 337.1383, found 337.1386;




**3.67g** **3.25g**

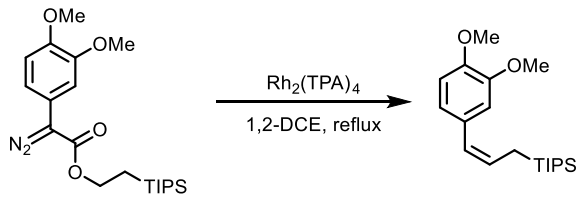
**(*Z*)-*tert*-butyldiphenyl(3-phenylallyl)silane (3.25g):** The general procedure for allylsilane formation was followed, with **3.67g** (154 mg, 0.36 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (5 mg, 0.0036 mmol, 1 mol %), purifying by column chromatography (1% $Et_2O$ in pentane) to give **3.25g** as a colorless oil (87 mg, 68% yield) as a 96:4 mixture of *Z*:*E* isomers. $^1$H NMR (400 MHz; $CDCl_3$) δ 7.62-7.57 (m, 4H), 7.44-7.29 (m, 8H), 7.26-7.17 (m, 3H), 6.32 (d, 1H, J = 11.5 Hz), 5.73 (dt, 1H, *J* = 11.5, 8.4 Hz), 2.47 (dd, 2H, *J* = 8.4, 1.5 Hz), 1.05 (s, 9H); $^{13}$C NMR (100 MHz, CDCl3) δ 138.1, 136.2, 134.3, 129.3 (2 signals), 128.8, 128.4, 128.3, 127.8, 126.4, 28.0, 18.6, 13.3; IR (neat): 3012, 2928, 2856, 1426, 696 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{29}Si$ 357.2033, found 357.2029;




**3.69a** **3.70a**

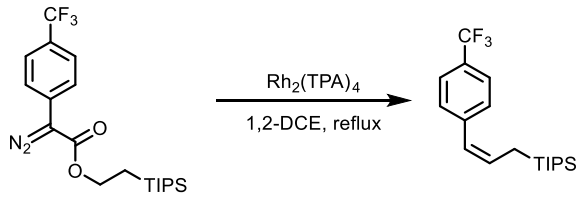
**(*Z*)-triisopropyl(3-(4-methoxyphenyl)allyl)silane (3.70a):** The general procedure for allylsilane formation was followed, with **3.69a** (132 mg, 0.35 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (5 mg, 1 mol %), purifying by column chromatography (1% $Et_2O$ in pentane) to give **3.70a** as a colorless oil (81 mg, 76% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 7.29 (d, 2H, *J* = 8.6 Hz), 6.92-6.86 (m, 2H), 6.25 (d, 1H, *J* = 11.5 Hz), 5.74 (dt, 1H, *J* = 11.5, 8.7 Hz), 3.83 (s, 3H), 1.91 (dd, 2H, *J* = 8.7, 1.8 Hz), 1.12-1.00 (m, 21H); $^{13}$C NMR (150

MHz, $CDCl_3$) δ 157.95, 131.08, 129.98, 128.46, 126.57, 113.73, 55.4, 18.88, 11.9, 11.36; IR (neat): 2940, 2889, 2864, 1509, 1242 $cm^{-1}$; HRMS (APCI) *m/z*: $[M]^+$ calcd for $C_{19}H_{33}OSi$ 304.2217, found 304.2215;




**3.69b** **3.70b**

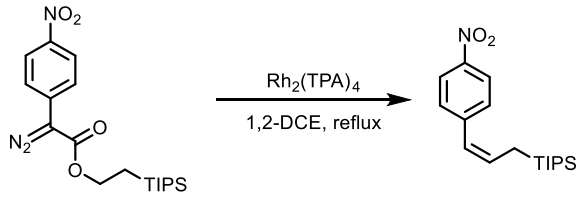
**(*Z*)-(3-(3,4-dimethoxyphenyl)allyl)triisopropylsilane (3.70b):** The general procedure for allyl silane formation was followed, with **3.69b** (122 mg, 0.3 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (4 mg, 0.0035 mmol, 1 mol %), purifying by column chromatography (5% $Et_2O$ in pentane) to give **3.70b** as a colorless oil (77 mg, 77% yield). $^1H$ NMR (400 MHz; $CDCl_3$) δ 6.95-6.81 (m, 3H), 6.23 (d, 1H, *J* = 11.5 Hz), 5.74 (dt, 1H, *J* = 11.5, 8.7 Hz), 3.90 (s, 3H), 3.88 (s, 3H), 1.92 (dd, 2H, *J* = 8.7, 1.7 Hz), 1.13-0.98 (m, 21H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 148.6, 147.4, 131.4, 128.8, 126.7, 121.3, 112.1, 111.0, 56.0, 56.0, 18.9, 12.0, 11.3; IR (neat): 2939, 2864, 1512, 1235 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{35}O_2Si$ 335.2401, found 335.2404;




**3.69c** **3.70c**

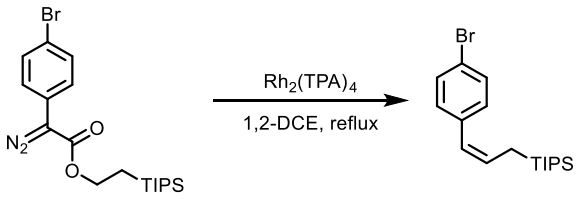
**(*Z*)-(3-(4-(trifluoromethyl)phenyl)allyl)triisopropylsilane (3.70c):** The general procedure for allyl silane formation was followed, with **3.69c** (145 mg, 0.35 mmol, 1.0

equiv.) and $Rh_2(TPA)_4$ (5 mg, 0.0035 mmol, 1 mol %), purifying by column chromatography (pentane) to give **3.70c** as a colorless oil (88 mg, 73% yield). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.59 (d, 2H, *J* = 8.2 Hz), 7.43 (d, 2H, *J* = 8.2 Hz), 6.31 (d, 1H, *J* = 11.7 Hz), 5.94 (dt, 1H, *J* = 11.7, 8.9 Hz), 1.92 (dd, 2H, *J* = 8.9, 1.8 Hz), 1.13-0.98 (m, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 142.1, 132.4, 129.1, 128.2 (q, *J* = 32 Hz), 125.8, 125.3 (q, *J* = 3.7 Hz), 124.6 (q, *J* = 272 Hz), 18.8, 12.5, 11.4; IR (film): 2942, 2866, 1323, 1123 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H-HF]^+$ calcd for $C_{19}H_{29}F_2Si$ 323.2001, found 323.2002;



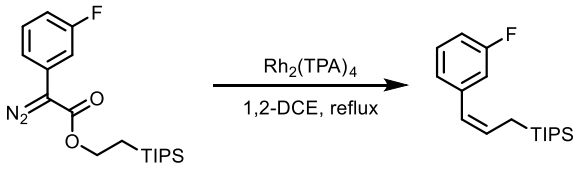

**3.69d** **3.70d**

**(*Z*)-triisopropyl(3-(4-nitrophenyl)allyl)silane (3.70d):** The general procedure for allyl silane formation was followed, with **3.69d** (150 mg, 0.38 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (5 mg, 0.004 mmol, 1 mol %), purifying by column chromatography (1% $Et_2O$ in pentane) to give the allylsilane **3.70d** as a colorless oil (72 mg, 60% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 8.20 (d, 2H, *J* = 8.7 Hz), 7.47 (d, 2H, *J* = 8.7 Hz), 6.32 (d, 1H, *J* = 11.6 Hz), 6.03 (dt, 1H, *J* = 11.6, 9.0 Hz), 1.95 (dd, 2H, *J* = 9.0, 1.8 Hz), 1.12-0.96 (m, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 146.0, 145.5, 134.5, 129.4, 125.0, 123.8, 18.8, 13.0, 11.3; IR (neat): 2941, 2889, 2864, 1514, 1338 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{30}O_2NSi$ 320.2040, found 320.2044;




**3.69e** **3.70e**

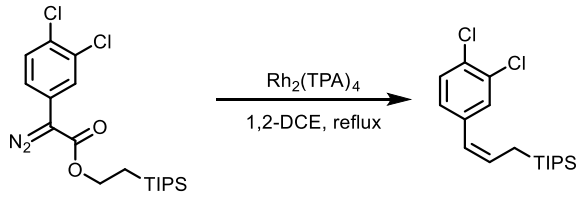
**(*Z*)-(3-(4-bromophenyl)allyl)triisopropylsilane (3.70e):** The general procedure for allyl silane formation was followed, with **3.69e** (149 mg, 0.35 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (5 mg, 0.0035 mmol, 1 mol %), purifying by column chromatography (pentane) to give **3.70e** as a colorless oil (91 mg, 73% yield) $^1$H NMR (400 MHz; $CDCl_3$) δ 7.46-7.40 (m, 2H), 7.21-7.15 (m, 2H), 6.19 (dt, 1H, *J* = 11.6, 1.9 Hz), 5.83 (dt, 1H, *J* = 11.6, 8.8 Hz), 1.86 (dd, 2H, *J* = 8.8, 1.8 Hz), 1.13-0.93 (m, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 137.3, 131.5, 130.9, 130.5, 125.9, 119.9, 18.8, 12.2, 11.3; IR (film): 2940, 2889, 2864, 1486 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{30}BrSi$ 353.1295, found 353.1291;




**3.69f** **3.70f**

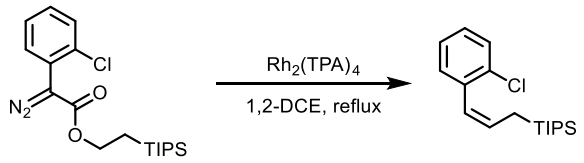
**(*Z*)-(3-(3-fluorophenyl)allyl)triisopropylsilane (3.70f):** The general procedure for allyl silane formation was followed, with **3.69f** (146 mg, 0.4 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (6 mg, 1 mol %), purifying by column chromatography (pentane) to give **3.70f** as a colorless oil (87 mg, 74% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 7.26 (q, 1H, *J* = 7.2 Hz), 7.08 (d, 1H, *J* = 7.7 Hz), 7.02 (d, 1H, *J* = 10.1 Hz), 6.88 (t, 1H, *J* = 8.4 Hz), 6.24 (d, 1H, *J* = 11.6 Hz), 5.88-5.81 (m, 1H), 1.90 (d, 2H, *J* = 8.8 Hz), 1.09-0.98 (m, 21H); $^{13}$C NMR

(150 MHz, $CDCl_3$) δ 163 (d, *J* = 245 Hz), 140.7 (d, *J* = 7.7 Hz), 131.3, 129.7 (d, *J* = 8.4 Hz), 125.9 (d, *J* = 1.7 Hz), 124.6, 115.5 (d, *J* = 21.2 Hz), 113.1 (d, *J* = 21.1 Hz), 18.8, 12.3, 11.3; IR (neat): 2941, 2865, 1580, 880 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{30}FSi$ 293.2095, found 293.2097;



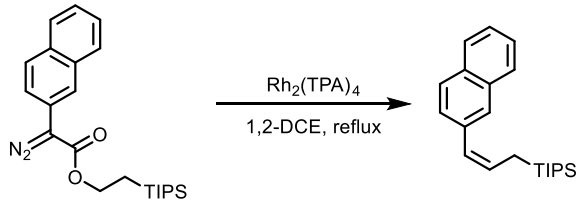

**3.69g** **3.70g**

**(*Z*)-(3-(3,4-dichlorophenyl)allyl)triisopropylsilane (3.70g):** The general procedure for allyl silane formation was followed, with **3.69g** (166 mg, 0.4 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (6 mg, 1 mol %), purifying by column chromatography (pentane) to give **3.70g** as a colorless oil (87 mg, 64% yield). $^1H$ NMR (600 MHz; $CDCl_3$) δ 7.42 (s, 1H), 7.39 (d, 1H, *J* = 8.3 Hz), 7.17 (d, 1H, *J* = 8.3 Hz), 6.18 (d, 1H, *J* = 11.4 Hz), 5.89 (dt, 1H, *J* = 11.4, 8.9 Hz), 1.88 (d, 2H, *J* = 8.9 Hz), 1.12-1.00 (m, 21H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 138.5, 132.3, 132.2, 130.6, 130.3, 129.9, 128.2, 124.7, 18.8, 12.4, 11.4; IR (neat): 2941, 2864, 1470 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{29}Cl_2Si$ 343.1410, found 343.1415;




**3.69h** **3.70h**

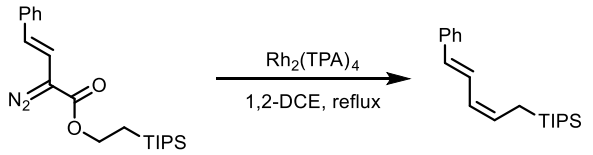
**(*Z*)-(3-(2-chlorophenyl)allyl)triisopropylsilane (3.70h):** The general procedure for allyl silane formation was followed, with **3.69h** (152 mg, 0.4 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (6 mg, 1 mol %), purifying by column chromatography (pentane) to give **3.70h** as a colorless oil (95 mg, 77% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 7.44 (dd, 1H, *J* = 7.6, 1.5 Hz), 7.39 (dd, 1H, *J* = 7.9, 1.2 Hz), 7.24 (td, 1H, *J* = 7.6, 1.2 Hz), 7.17 (td, 1H, *J* = 7.9, 1.5 Hz), 6.36 (d, 1H, *J* = 11.4 Hz), 5.96 (dt, 1H, *J* = 11.4, 8.7 Hz), 1.82 (dd, 2H, *J* = 8.7, 1.7 Hz), 1.14-0.97 (m, 21H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 136.4, 134.0, 131.3, 130.8, 129.7, 127.8, 126.3, 124.4, 18.8, 12.0, 11.3; IR (neat): 2940, 2864, 1469 $cm^{-1}$; HRMS (APCI) *m/z*: calcd for $C_{18}H_{30}ClSi$ 309.1800, found 309.1803;




**3.69i** **3.70i**

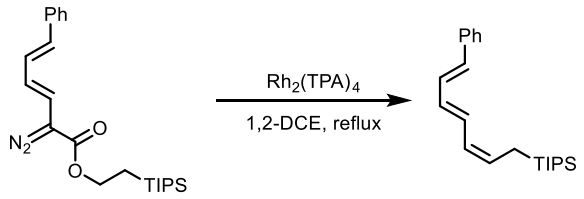
**(*Z*)-triisopropyl(3-(naphthalen-2-yl)allyl)silane (3.70i):** The general procedure for allylsilane formation was followed, with **3.69i** (139 mg, 0.35 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (5 mg, 1 mol %), purifying by column chromatography (pentane) to give **3.70i** as a colorless oil (84 mg, 74% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 7.84-7.77 (m, 4H), 7.52-7.42 (m, 3H), 6.45 (d, 1H, *J* = 11.6 Hz), 5.92 (td, 1H, *J* = 11.6, 8.8 Hz), 2.02 (d, 2H, *J* = 8.8 Hz), 1.14-1.00 (m, 21H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 136.0, 133.7,

132.2, 130.6, 128.0, 127.8, 127.8, 127.6, 127.3, 127.0, 126.1, 125.6, 18.9, 12.4, 11.4; IR (film): 2940, 2888, 2863, 1462 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{33}Si$ 325.2346, found 325.2348;



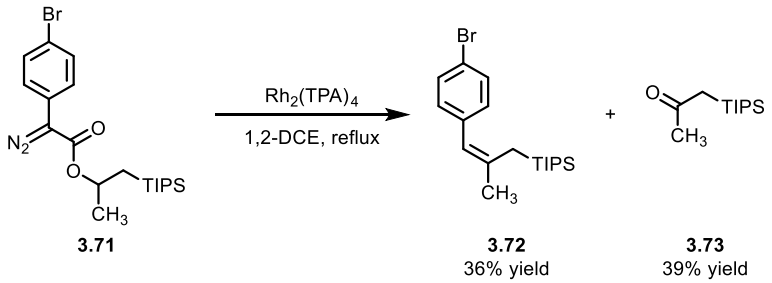

**3.69j** **3.70j**

**triisopropyl((2*Z*,4*E*)-5-phenylpenta-2,4-dien-1-yl)silane (3.70j):** The general procedure for allyl silane formation was followed, with **3.69j** (100 mg, 0.27 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (4 mg, 1 mol %), purifying by column chromatography (pentane) to give **3.70j** as a colorless oil (49 mg, 60% yield). $^1H$ NMR (600 MHz; $CDCl_3$) δ 7.41 (d, 2H, *J* = 7.8 Hz), 7.31 (dd, 2H, *J* = 7.8, 7.3 Hz), 7.20 (t, 1H, *J* = 7.3 Hz), 7.14 (dd, 1H, *J* = 15.5, 11.0 Hz), 6.49 (d, 1H, *J* = 15.5 Hz), 6.06 (dd, 1H, *J* = 11.0, 10.7 Hz), 5.67 (dt, 1H, *J* = 10.7, 9.0 Hz), 1.86 (d, 2H, *J* = 9 Hz), 1.14-1.04 (m, 21H) (Note: The peak at 5.67 appears as a quartet. The coupling between protons at 6.06 ppm and 5.67 ppm was determined by a homonuclear decoupling NMR experiment, irradiating the doublet at 1.86 ppm. In this experiment, the peak at 5.67 is a doublet, with a coupling constant of 10.7 ppm.); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 138.2, 130.9 (2 signals), 128.8, 127.2, 126.6, 126.3, 124.8, 18.9, 12.7, 11.4; IR (neat): 2940, 2889, 2864, 1462 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{33}Si$ 301.2346, found 301.2349;




**3.69k** **3.70k**

**triisopropyl((2*Z*,4*E*,6*E*)-7-phenylhepta-2,4,6-trien-1-yl)silane (3.70k):** The general procedure for allyl silane formation was followed, with **3.69k** (120 mg, 0.3 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (4 mg, 1 mol %), purifying by column chromatography (pentane) to give **3.70k** as a slightly yellow oil (36 mg, 37% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 7.42 (d, 2H, *J* = 7.5 Hz), 7.32 (t, 2H, *J* = 7.7 Hz), 7.22 (t, 1H, *J* = 7.4 Hz), 6.90 (dd, 1H, *J* = 15.5, 10.8 Hz), 6.71 (dd, 1H, *J* = 14.7, 11.4 Hz), 6.54 (d, 1H, *J* = 15.5 Hz), 6.36 (dd, 1H, *J* = 14.7, 10.8 Hz), 6.01 (dd, 1H, *J* = 11.4, 10.5 Hz), 5.66 (dt, 1H, *J* = 10.5, 9.0 Hz), 1.83 (d, 2H, *J* = 9.0 Hz), 1.15-1.05 (m, 21H) (Note: The peak at 5.66 appears as a quartet. The coupling between 6.01 ppm and 5.66 ppm was determined by a homonuclear decoupling NMR experiment, irradiating the doublet at 1.83 ppm. The peak at 5.66 became a doublet, with a coupling constant of 10.5 ppm); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 137.8, 131.7, 131.5, 131.1, 129.9, 129.4, 128.8, 127.4, 126.6, 126.4, 18.9, 12.8, 11.4; IR (neat): 2940, 2888, 2863, 1594, 1461 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{35}Si$ 327.2503, found 327.2504;



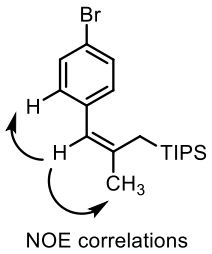

**3.71** **3.72** 36% yield **3.73** 39% yield

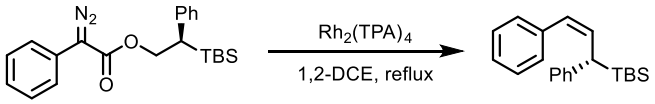
**(*Z*)-(3-(4-bromophenyl)-2-methylallyl)triisopropylsilane (3.72):** The general procedure for allyl silane formation was followed, with **3.71** (132 mg, 0.3 mmol, 1.0 equiv.) and $Rh_2(TPA)_4$ (4 mg, 1 mol %). The two products formed in the reaction were isolated by column chromatography (**3.72**: 100% pentane; 1-(triisopropylsilyl)-2-propanone (**3.73**): 5% $Et_2O$ in pentane) to give **3.72** as a colorless oil (40 mg, 36% yield), and 1-triisopropylsilyl-2-propanone (**3.72**) as a colorless oil (25 mg, 39% yield).

Characterization data for **3.72**: $^1$H NMR (400 MHz; $CDCl_3$) δ 7.42 (d, 2H, *J* = 8.4 Hz), 7.13 (d, 2H, *J* = 8.4 Hz), 6.05 (s, 1H), 1.94 (s, 3H), 1.89 (s, 2H), 1.04-0.97 (m, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 139.6, 138.5, 131.4, 130.6, 122.5, 119.3, 27.8, 18.9, 15.8, 12.1; IR (film): 2941, 2888, 2864, 1485 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{32}BrSi$ 367.1451, found 367.1451;

Characterization data[43] for **3.73**: $^1$H NMR (400 MHz; $CDCl_3$) δ 2.25 (s, 2H), 2.18 (s, 3H), 1.16-1.06 (m, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 208.9, 32.6, 31.4, 18.6, 11.6; IR (neat): 2942, 2866, 1692 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{27}OSi$ 215.1826, found 215.1819.

*The alkene geometry of **3.72** was determined by NOE correlations:*

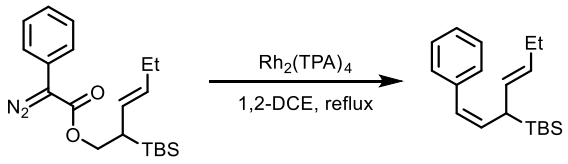



(*R*)-**3.74a** (*S*)-**3.75a**

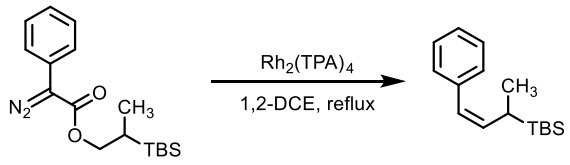
**(*S*,*Z*)-*tert*-butyl(1,3-diphenylallyl)dimethylsilane ((*S*)-3.75a):** The diazo (133 mg, 0.35 mmol, 1.0 equiv.) in 4 mL DCE was added dropwise over 2 hours to a solution of $Rh_2(TPA)_4$ (5 mg, 1 mol %) in 2 mL DCE at reflux. The mixture was allowed to cool to room temperature and the solvent was removed. The solvent was replaced with $PhCF_3$ (5 mL) and the solution heated at reflux overnight. The solution was allowed to cool to room temperature and the solvent removed. The crude residue was purified by column chromatography (pentane) to give the product as a colorless oil (56 mg, 52% yield). The reaction with the racemic diazo was run in an identical manner to give 59 mg of the product (55% yield). $[\alpha]_D^{20}$: 183.7 (c. 1.3, $CHCl_3$); $^1$H NMR (400 MHz; $CDCl_3$) δ 7.37-7.09 (m, 10H), 6.46 (d, 1H, *J* = 11.3 Hz), 6.17 (dd, 1H, *J* = 12.4, 11.3 Hz), 3.67 (d, 1H, *J* = 12.4 Hz), 0.71 (s, 9H), -0.01 (s, 3H), -0.20 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 143.9, 137.9, 132.8, 128.9, 128.7, 128.4, 127.9, 127.7, 126.6, 124.8, 35.6, 27.1, 18.0, -6.4, -7.6; IR (neat): 3022, 2927, 2882, 2855, 1247 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{29}Si$ 309.2033, found 309.2034; The ee was determined by chiral HPLC: OJ

column, 0.5 mL/min, 0 % iPrOH in hexanes, λ = 230 nm. $t_R$: Major: 15.6 min, Minor: 9.3 min, 86% ee.




**3.74b** **3.75b**

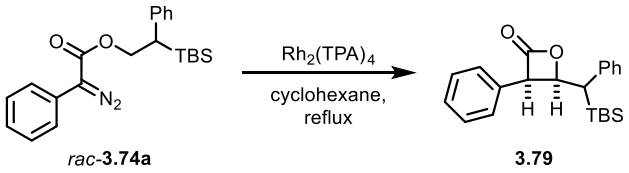
**triisopropyl((1*Z*,4*E*)-1-phenylhepta-1,4-dien-3-yl)silane (3.75b):** The diazo (143 mg, 0.4 mmol, 1.0 equiv.), in 4 mL DCE, was added dropwise over 2 hours to a solution of $Rh_2(TPA)_4$ (6 mg, 1 mol %) in 2 mL DCE at reflux. The solution was allowed to cool to room temperature before the solvent was removed. The crude was dissolved in $PhCF_3$ (5 mL) and heated at reflux for 16 hours. The solvent was again removed and the crude purified by column chromatography (pentane) to give the product as a colorless oil (54 mg, 47% yield). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.33-7.25 (m, 4H), 7.21-7.16 (m, 1H), 6.35 (d, 1H, *J* = 11.5 Hz), 5.73 (dd, 1H, *J* = 12.0, 11.5 Hz), 5.52 (dd, 1H, *J* = 15.3, 7.5 Hz), 5.41 (dt, 1H, *J* = 15.3, 6.2 Hz), 3.24 (dd, 1H, *J* = 12.0, 7.5 Hz), 2.11-2.02 (m, 2H), 0.99 (t, 3H, J = 7.4 Hz), 0.82 (s, 9H), -0.06 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 138.3, 132.7, 129.7, 128.9, 128.7, 128.3, 126.6, 126.4, 32.3, 27.3, 26.2, 18.1, 14.4, -6.8, -7.1; IR (film): 2958, 2928, 2882, 2855 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{31}Si$ 287.2190, found 287.2189;




**3.74c** **3.75c**

**(*Z*)-*tert*-butyldimethyl(4-phenylbut-3-en-2-yl)silane (3.75c):** The diazo (127 mg, 0.4 mmol, 1.0 equiv.), in 4 mL DCE, was added dropwise over 2 hours to a solution of $Rh_2(TPA)_4$ (6 mg, 1 mol %) in 2 mL DCE at reflux. The solution was allowed to cool to room temperature and the solvent removed. The crude residue was purified by column chromatography (pentane) to give the product as a 90:10 mixture of *Z*:*E* alkene isomers (67 mg, 68% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 7.36-7.29 (m, 4H), 7.24-7.20 (m, 1H), 6.31 (d, 1H, *J* = 11.4 Hz), 5.62 (dd, 1H, *J* = 12.3, 11.4 Hz), 2.53 (m, 1H), 1.20 (d, 3H, *J* = 7.2 Hz), 0.87 (s, 9H), -0.02 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 138.5, 137.4, 128.7, 128.3, 126.3, 125.8, 27.4, 20.3, 17.8, 16.8, -7.1, -7.3; IR (neat): 2954, 2928, 2856, 1248 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{27}Si$ 247.1877, found 247.1879;

## 3.4.5 Control Reactions

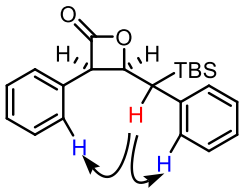



*rac*-**3.74a** **3.79**

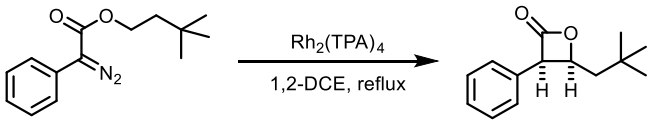
**4-((*tert*-butyldimethylsilyl)(phenyl)methyl)-3-phenyloxetan-2-one (3.79):** The diazo (133 mg, 0.35 mmol, 1.0 equiv.), in 4 mL cyclohexane, was added dropwise over 2 hours to a solution of $Rh_2(TPA)_4$ catalyst (5 mg, 0.0035 mmol, 1 mol %) in 2 mL cyclohexane at reflux. The mixture was allowed to cool to room temperature and the solvent removed. The crude residue was purified by column chromatography (5% $Et_2O$ in pentane) to give the product as a white solid (53 mg, 43% yield). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.25-7.19

(m, 1H), 7.13 (t, 2H, *J* = 7.5 Hz), 6.97-6.90 (m, 3H), 6.78 (d, 2H, *J* = 7.3 Hz), 6.40-6.30 (m, 2H), 5.28 (dd, 1H, *J* = 12.3, 6.1 Hz), 4.94 (d, 1H, *J* = 6.1 Hz), 2.48 (d, 1H, *J* = 12.3 Hz), 0.76 (s, 9H), 0.17 (s, 3H), -0.26 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.2, 138.5, 130.4, 129.6, 128.3 (2 signals), 128.2, 128.1, 125.3, 78.2, 60.7, 34.6, 27.1, 17.7, -5.5, -5.6; IR (neat): 2957, 2927, 2853, 1818, 1122 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{29}O_2Si$ 353.1931, found 353.1933;

The internal *cis* stereochemistry of β-lactone **3.79** was assigned by the diagnostic coupling constant ($J_{cis}$ = 6.1 Hz)[44,45] which was further supported by NOE analysis:




NOE correlations

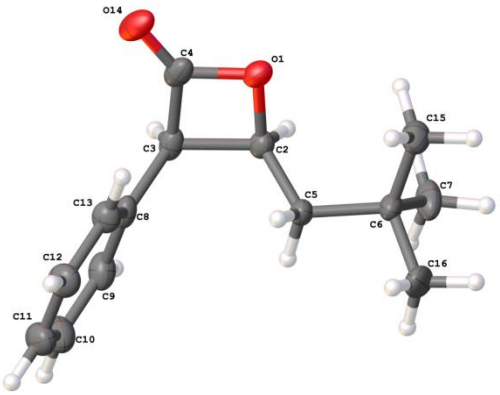


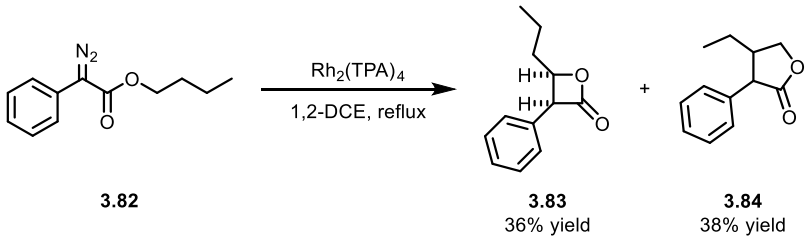

**3.80** **3.81**
94:6 dr

**4-neopentyl-3-phenyloxetan-2-one (3.81):** A solution of the diazo **3.80** (123 mg, 0.5 mmol, 1.0 equiv.) in DCE (4 mL) was added dropwise over 2 hours to a solution of $Rh_2(TPA)_4$ catalyst (7 mg, 0.005 mmol, 1 mol %) in 2 mL DCE at reflux. The mixture was allowed to stir for 20 minutes at reflux before it was allowed to cool to room temperature. The solvent was removed, and the crude mixture was purified by column chromatography (9:1 hexanes:EtOAc) to give the product as a slightly green-tinged solid (92 mg, 84% yield). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.43-7.31 (m, 3H), 7.24-7.19 (m,

2H), 5.06 (d, 1H, *J* = 6.8 Hz), 4.97 (ddd, 1H, *J* = 10.0, 6.8, 2.2 Hz), 1.36 (dd, 1H, *J* = 15.3, 10.0 Hz), 1.15 (dd, 1H, *J* = 15.3, 2.2 Hz), 0.91 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.3, 130.8, 129.1, 129.0, 128.4, 74.9, 59.5, 44.4, 30.3, 29.8; IR (neat): 2953, 2912, 1800, 1143 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{18}O_2Na$ 241.1199, found 241.1198;

The *cis* stereochemistry of β-lactone **3.81** was assigned by the diagnostic coupling constant ($J_{cis}$ = 6.8 Hz) [44,45] and confirmed by X-RAY crystallographic analysis:



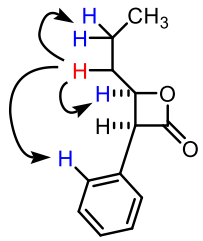

**3.82** **3.83** 36% yield **3.84** 38% yield

***cis*-3-phenyl-4-propyloxetan-2-one (3.83)** and **4-ethyl-3-phenyldihydrofuran-2(3H)-one (3.84).** The diazo (87 mg, 0.4 mmol, 1.0 equiv.) in 4 mL DCE was added dropwise over 2 hours to a solution of $Rh_2(TPA)_4$ (6 mg, 1 mol %) in 2 mL DCE at reflux. The mixture was allowed to heat at reflux for an additional 30 minutes and the solution was cooled. The solvent was removed and the crude mixture was purified by column

chromatography (10-15% EtOAc in hexanes). The two products were isolated separately as slightly green-tinged oils (**3.83**: 27 mg, 36% yield; **3.84**: 29 mg, 38% yield).

Characterization data for **3.83**: $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.41-7.31 (m, 3H), 7.26-7.21 (m, 2H), 5.04 (d, 1H, *J* = 6.7 Hz), 4.80 (ddd, 1H, *J* = 9.1, 6.7, 4.2 Hz), 1.51-1.20 (m, 4H), 0.83 (t, 3H, *J* = 7.1 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.2, 130.7, 129.0, 128.9, 128.3, 76.9, 58.6, 33.2, 18.5, 13.8; IR (neat): 2961, 2874, 1811, 1124 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{15}O_2$ 191.1067, found 191.1068;

The *cis* stereochemistry of β-lactone **3.83** was assigned by the diagnostic coupling constant ($J_{cis}$ = 6.7 Hz),[44,45] which was further supported by NOE analysis:




NOE correlations

Characterization data for **3.84**: $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.41-7.28 (m, 3H), 7.21-7.16 (m, 2H), 4.47 (dd, 1H, *J* = 9.1, 6.8 Hz), 4.15 (dd, 1H, *J* = 9.1, 6.1 Hz), 3.96 (d, 1H, *J* = 8.4 Hz), 2.73-2.62 (m, 1H), 1.21-0.98 (m, 2H), 0.83 (t, 3H, *J* = 7.4 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.8, 133.9, 129.3, 128.9, 127.7, 71.1, 50.3, 43.0, 21.5, 11.9; IR (neat): 2963, 2933, 2877, 1766, 1154 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{15}O_2$ 191.1067, found 191.1068;

The stereochemistry of **3.84** was not assigned.

## 3.4.6 Crystal Structure Data for 3.81

Table 1. Crystal data and structure refinement for **3.81**.

| | | |
|---|---|---|
| Identification code | **3.81** | |
| Empirical formula | C14 H18 O2 | |
| Formula weight | 218.28 | |
| Temperature | 110(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | C 1 2/c 1 | |
| Unit cell dimensions | a = 17.0634(13) Å | α= 90°. |
| | b = 6.0273(5) Å | β= 94.4100(12)°. |
| | c = 24.3906(19) Å | γ = 90°. |
| Volume | 2501.1(3) $Å^3$ | |
| Z | 8 | |
| Density (calculated) | 1.159 $Mg/m^3$ | |
| Absorption coefficient | 0.076 $mm^{-1}$ | |
| F(000) | 944 | |
| Crystal size | 0.647 x 0.46 x 0.19 $mm^3$ | |
| Theta range for data collection | 1.675 to 31.110°. | |
| Index ranges | -24<=h<=24, -8<=k<=8, -35<=l<=35 | |
| Reflections collected | 16250 | |
| Independent reflections | 3997 [R(int) = 0.0241] | |
| Completeness to theta = 26.000° | 100.0 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.7462 and 0.7008 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3997 / 38 / 187 | |
| Goodness-of-fit on $F^2$ | 1.052 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0519, wR2 = 0.1355 | |
| R indices (all data) | R1 = 0.0649, wR2 = 0.1497 | |
| Extinction coefficient | n/a | |
| Largest diff. peak and hole | 0.367 and -0.223 $e.Å^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for **3.81**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 2074(1) | 7530(1) | 9442(1) | 30(1) |
| O(14) | 3117(1) | 9822(2) | 9345(1) | 43(1) |
| C(8) | 3235(1) | 5370(2) | 8559(1) | 25(1) |
| C(2) | 2184(1) | 5136(2) | 9303(1) | 25(1) |
| C(5) | 1586(1) | 4320(2) | 8864(1) | 26(1) |
| C(4) | 2814(1) | 8036(2) | 9312(1) | 30(1) |
| C(13) | 3062(1) | 6976(2) | 8156(1) | 29(1) |
| C(3) | 3027(1) | 5704(2) | 9143(1) | 27(1) |
| C(6) | 748(1) | 3915(2) | 9043(1) | 29(1) |
| C(9) | 3603(1) | 3414(2) | 8415(1) | 33(1) |
| C(12) | 3258(1) | 6624(2) | 7618(1) | 36(1) |
| C(15) | 383(1) | 6043(2) | 9249(1) | 34(1) |
| C(11) | 3626(1) | 4680(2) | 7481(1) | 40(1) |
| C(10) | 3797(1) | 3070(2) | 7879(1) | 41(1) |
| C(7) | 764(1) | 2173(2) | 9504(1) | 42(1) |
| C(16) | 247(1) | 3086(3) | 8540(1) | 54(1) |

Table 3. Bond lengths [Å] and angles [°] for **3.81**.

| | |
|---|---|
| O(1)-C(2) | 1.4978(13) |
| O(1)-C(4) | 1.3600(14) |
| O(14)-C(4) | 1.1939(14) |
| C(8)-C(13) | 1.3950(15) |
| C(8)-C(3) | 1.5070(15) |
| C(8)-C(9) | 1.3933(17) |
| C(2)-C(5) | 1.5036(15) |
| C(2)-C(3) | 1.5560(14) |
| C(5)-C(6) | 1.5466(14) |
| C(4)-C(3) | 1.5175(18) |
| C(13)-C(12) | 1.3941(16) |
| C(6)-C(15) | 1.5277(16) |
| C(6)-C(7) | 1.5365(19) |
| C(6)-C(16) | 1.5244(18) |
| C(9)-C(10) | 1.3899(18) |
| C(12)-C(11) | 1.383(2) |
| C(11)-C(10) | 1.387(2) |
| | |
| C(4)-O(1)-C(2) | 91.59(8) |
| C(13)-C(8)-C(3) | 121.38(10) |
| C(9)-C(8)-C(13) | 118.96(10) |
| C(9)-C(8)-C(3) | 119.66(10) |
| O(1)-C(2)-C(5) | 112.70(9) |
| O(1)-C(2)-C(3) | 88.86(8) |
| C(5)-C(2)-C(3) | 118.88(9) |
| C(2)-C(5)-C(6) | 116.28(9) |
| O(1)-C(4)-C(3) | 95.83(8) |
| O(14)-C(4)-O(1) | 126.28(13) |
| O(14)-C(4)-C(3) | 137.89(12) |
| C(12)-C(13)-C(8) | 120.31(11) |
| C(8)-C(3)-C(2) | 119.81(8) |
| C(8)-C(3)-C(4) | 117.39(9) |
| C(4)-C(3)-C(2) | 83.70(8) |
| C(15)-C(6)-C(5) | 111.69(9) |

| | |
|---|---|
| C(15)-C(6)-C(7) | 108.55(10) |
| C(7)-C(6)-C(5) | 110.45(10) |
| C(16)-C(6)-C(5) | 107.33(9) |
| C(16)-C(6)-C(15) | 108.79(12) |
| C(16)-C(6)-C(7) | 110.02(12) |
| C(10)-C(9)-C(8) | 120.55(11) |
| C(11)-C(12)-C(13) | 120.22(12) |
| C(12)-C(11)-C(10) | 119.83(12) |
| C(11)-C(10)-C(9) | 120.12(13) |

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **3.81**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| O(1) | 32(1) | 29(1) | 27(1) | -4(1) | 2(1) | -9(1) |
| O(14) | 58(1) | 43(1) | 27(1) | -1(1) | 5(1) | -28(1) |
| C(8) | 18(1) | 33(1) | 25(1) | 6(1) | 1(1) | -6(1) |
| C(2) | 25(1) | 27(1) | 22(1) | 1(1) | 4(1) | -6(1) |
| C(5) | 22(1) | 31(1) | 26(1) | -6(1) | 6(1) | -7(1) |
| C(4) | 35(1) | 38(1) | 17(1) | 3(1) | -1(1) | -14(1) |
| C(13) | 29(1) | 32(1) | 25(1) | 5(1) | 2(1) | -2(1) |
| C(3) | 22(1) | 36(1) | 22(1) | 8(1) | -2(1) | -7(1) |
| C(6) | 22(1) | 28(1) | 36(1) | -9(1) | 9(1) | -8(1) |
| C(9) | 27(1) | 34(1) | 39(1) | 10(1) | 6(1) | -2(1) |
| C(12) | 43(1) | 39(1) | 25(1) | 6(1) | 6(1) | -7(1) |
| C(15) | 27(1) | 29(1) | 47(1) | -3(1) | 8(1) | 1(1) |
| C(11) | 45(1) | 43(1) | 34(1) | -3(1) | 16(1) | -11(1) |
| C(10) | 39(1) | 35(1) | 50(1) | -1(1) | 17(1) | -3(1) |
| C(7) | 37(1) | 26(1) | 66(1) | 4(1) | 24(1) | -5(1) |
| C(16) | 28(1) | 81(1) | 55(1) | -33(1) | 9(1) | -22(1) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for **3.81**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(13) | 2810 | 8315 | 8248 | 34 |
| H(9) | 3723 | 2307 | 8686 | 40 |
| H(12) | 3137 | 7723 | 7346 | 43 |
| H(11) | 3762 | 4447 | 7114 | 48 |
| H(10) | 4047 | 1730 | 7784 | 49 |
| H(3) | 3412(7) | 5050(20) | 9404(5) | 28(2) |
| H(2) | 2181(8) | 4310(20) | 9640(5) | 28(2) |
| H(5A) | 1565(8) | 5410(20) | 8557(5) | 28(2) |
| H(5B) | 1802(8) | 2898(19) | 8734(6) | 28(2) |
| H(15A) | 364(11) | 7260(20) | 8967(6) | 53(2) |
| H(7A) | 1040(10) | 790(20) | 9395(7) | 53(2) |
| H(7B) | 211(5) | 1760(30) | 9570(7) | 53(2) |
| H(15B) | 682(9) | 6610(30) | 9591(5) | 53(2) |
| H(15C) | -175(5) | 5750(30) | 9330(8) | 53(2) |
| H(16A) | 453(10) | 1607(18) | 8430(7) | 53(2) |
| H(16B) | -319(5) | 2880(30) | 8610(7) | 53(2) |
| H(16C) | 249(11) | 4200(20) | 8234(6) | 53(2) |
| H(7C) | 1052(10) | 2780(30) | 9847(5) | 53(2) |

Table 6. Torsion angles [°] for **3.81**.

| | |
|---|---|
| O(1)-C(2)-C(5)-C(6) | -74.70(12) |
| O(1)-C(2)-C(3)-C(8) | -117.15(10) |
| O(1)-C(2)-C(3)-C(4) | 0.90(7) |
| O(1)-C(4)-C(3)-C(8) | 119.41(9) |
| O(1)-C(4)-C(3)-C(2) | -0.99(8) |
| O(14)-C(4)-C(3)-C(8) | -60.77(18) |
| O(14)-C(4)-C(3)-C(2) | 178.83(15) |
| C(8)-C(13)-C(12)-C(11) | -0.10(18) |
| C(8)-C(9)-C(10)-C(11) | 0.12(19) |
| C(2)-O(1)-C(4)-O(14) | -178.82(12) |
| C(2)-O(1)-C(4)-C(3) | 1.03(8) |
| C(2)-C(5)-C(6)-C(15) | 61.28(14) |
| C(2)-C(5)-C(6)-C(7) | -59.63(13) |
| C(2)-C(5)-C(6)-C(16) | -179.57(12) |
| C(5)-C(2)-C(3)-C(8) | -1.69(15) |
| C(5)-C(2)-C(3)-C(4) | 116.36(10) |
| C(4)-O(1)-C(2)-C(5) | -122.02(9) |
| C(4)-O(1)-C(2)-C(3) | -1.00(8) |
| C(13)-C(8)-C(3)-C(2) | 83.88(13) |
| C(13)-C(8)-C(3)-C(4) | -15.01(14) |
| C(13)-C(8)-C(9)-C(10) | 0.17(17) |
| C(13)-C(12)-C(11)-C(10) | 0.4(2) |
| C(3)-C(8)-C(13)-C(12) | -179.70(10) |
| C(3)-C(8)-C(9)-C(10) | 179.69(11) |
| C(3)-C(2)-C(5)-C(6) | -176.60(10) |
| C(9)-C(8)-C(13)-C(12) | -0.18(16) |
| C(9)-C(8)-C(3)-C(2) | -95.64(12) |
| C(9)-C(8)-C(3)-C(4) | 165.47(10) |
| C(12)-C(11)-C(10)-C(9) | -0.4(2) |

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# Chapter 4 – Expanding the Scope of Intermolecular Donor/Acceptor Carbene C-H Functionalization

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## Contents

## 4.1 Introduction

Arguably, the grand challenge in C–H functionalization research is to develop the technology to selectively functionalize one C–H bond among the many others present in a given organic molecule. It would be unrealistic to suggest that one "miracle" catalyst or reagent could, alone, fill this need. Therefore, the approach to solving this problem in C–H functionalization is to develop a series, or "toolbox," of reagents and catalysts that gives options to the synthetic chemist. The following research involves efforts to expand the scope of rhodium-carbene C–H functionalization by the design and application new diazo reagents. This section will focus only on intermolecular C–H functionalization.

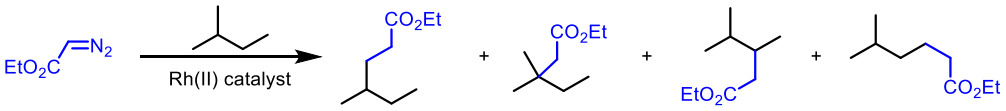
## 4.2 Effect of ester on site-selective C–H functionalization with donor/acceptor diazoacetates

### 4.2.1 Introduction to site-selective C–H functionalization

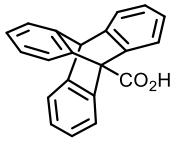
Intermolecular C–H insertion with diazo compounds was typically considered to be of little synthetic utility, since dimerization of the carbene was a complicating byproduct, and regio- and chemoselectivity was often low.[1] A specific example of this is shown in Scheme 4.1. Using acceptor diazo ethyl diazoacetate (**4.1**) and $Rh_2(OAc)_4$ as the catalyst, a mixture of products is formed, with product **4.4** resulting from insertion at the secondary position being formed as the major product. Interestingly, when the bulky catalyst $Rh_2(9\text{-trp})_4$ is used, a sizeable increase in the ratio of primary C–H insertion products **4.2** and **4.5** was observed. Finally, with the use of the electron-deficient catalyst $Rh_2(TFA)_4$, the tertiary (**4.3**) and secondary (**4.4**) products are formed as the major products. Though poor regioselectivity is observed in these reactions, it is an important

example of the effect of catalysts on site-selectivity of rhodium carbene C–H insertion reactions.

**Scheme 4.1** Reaction of ethyl diazoacetate with 2-methylbutane




**4.1** **4.2** **4.3** **4.4** **4.5**

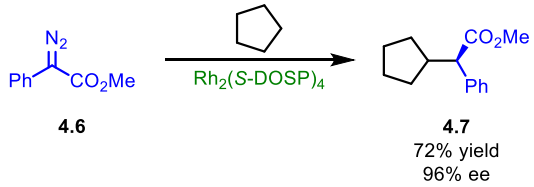



9-triptycenecarboxylic acid (9-trp)

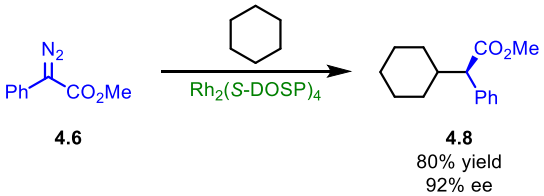
| | | | | |
|---|---|---|---|---|
| $Rh_2(OAc)_4$ | 1 | 8 | 90 | 1 |
| $Rh_2(9\text{-trp})_4$ | 18 | 18 | 27 | 37 |
| $Rh_2(TFA)_4$ | 2 | 25 | 66 | 4 |

Though asymmetric intermolecular C–H insertion reactions of acceptor/acceptor carbenes have been reported,[2,3] they too tend to be fairly non-selective. It was not until the development of donor/acceptor carbenes that intermolecular C–H insertion reactions began to become synthetically useful. Scheme 4.2 shows the reaction of diazo **4.6** with cyclopentane and cyclohexane using the catalyst $Rh_2$(*S*-DOSP)$_4$. The products **4.7** and **4.8** were isolated in good yields and with high levels of enantioselectivity.[4]

**Scheme 4.2** C–H insertion into cycloalkanes with donor/acceptor carbenes



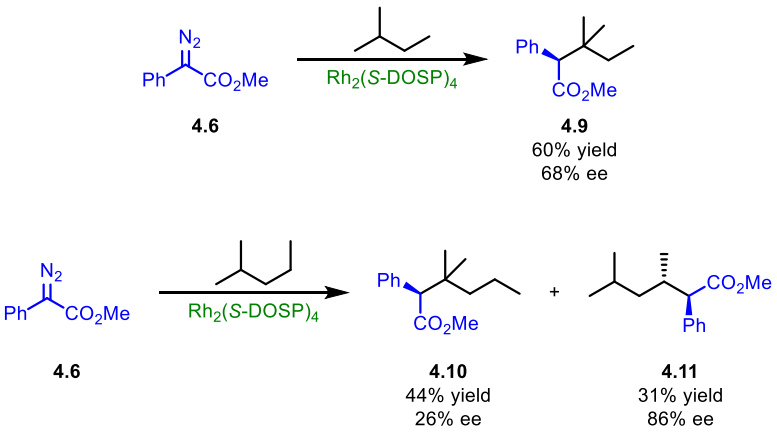

**4.6** **4.7**
72% yield
96% ee




**4.6** **4.8**
80% yield
92% ee

With acyclic alkenes, similar levels of selectivity are also achievable (Scheme 4.3).[4] With 2-methylbutane, the sole product **4.9** comes from C–H insertion at the tertiary site, and is isolated with 68% ee. When compared to the same reaction with ethyl diazoacetate (**4.1**), the differences between donor/acceptor and acceptor carbenes can be clearly seen. When using 2-methyl pentane and diazo **4.6**, however, a mixture of tertiary and secondary C–H insertion products **4.10** and **4.11**, respectively, is formed. These examples highlight the subtle steric and electronic effects that influence the outcome of reactions with donor/acceptor carbenes. Additionally, it is interesting to note that the secondary product, **4.11**, is formed with a much higher level of asymmetric induction than either tertiary product **4.9** or **4.10**.

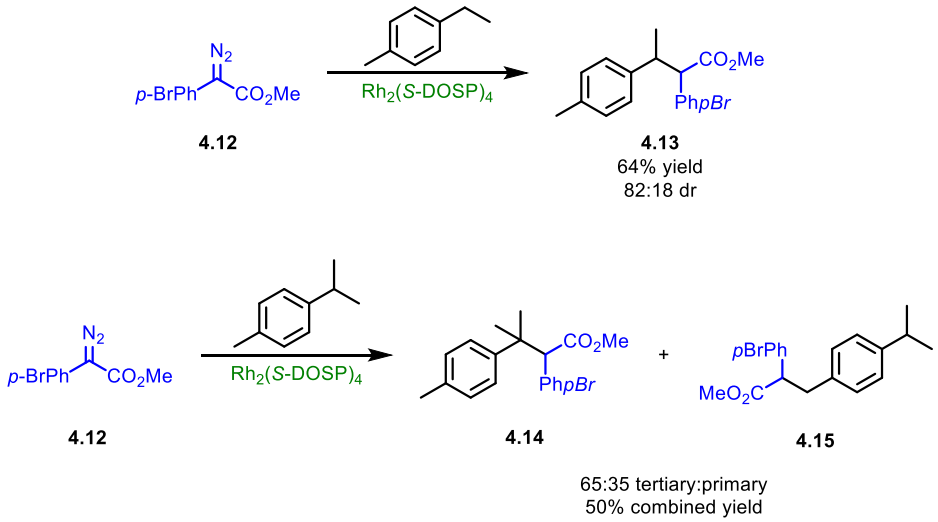
**Scheme 4.3** Reactions of donor/acceptor carbenes with 2-methylbutane and 2-methylpropane



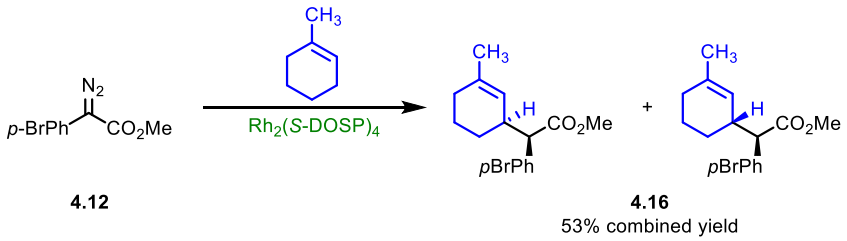

C–H insertion reactions can be carried out selectively in activated systems as well, such as with benzylic C–H bonds (Scheme 4.4).[5] Using 4-ethyltoluene as the substrate, the secondary product **4.13** is formed as the sole regioisomer. With 4-isopropyltoluene, a mixture of products is formed. The products resulting from C–H insertion at the tertiary

(**4.14**) and primary (**4.15**) positions are formed in a 65:35 ratio. Again, the balance between steric and electronic effects can be seen by these examples.

**Scheme 4.4** Site-selective C–H insertion at benzylic positions

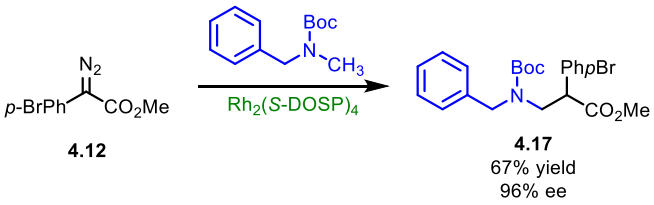



When using 1-methylcyclohexene, the product **4.16** was isolated as the only regioisomer, though as a mixture of diastereomers (Eq. 4.1).[6] This is an excellent example of the subtle steric effects that are at play, since there are two secondary allylic positions in the substrate. Only the secondary allylic C–H bond that is most removed from the methyl group is functionalized.




(Eq. 4.1)

Steric effects can overcome electronic effects with sufficiently activated C–H bonds as well (Eq. 4.2).[7] A primary site α to nitrogen can be selectively functionalized over the more activated position that is also allylic. The results are attributed to the much higher steric requirement of the secondary site over the primary in this system.




(Eq. 4.2)

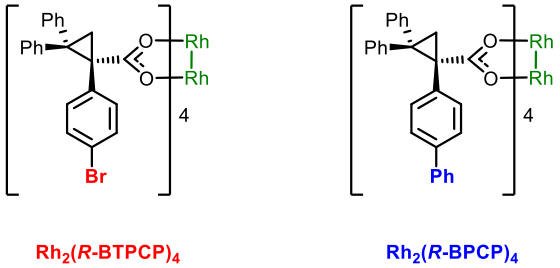
It can be seen from the aforementioned results that site-selectivity with donor/acceptor carbenes is influenced by a subtle combination of steric and electronic effects. With the catalyst $Rh_2$(*S*-DOSP)$_4$ the reaction tends to prefer insertion into secondary C–H bonds. This preference can be overcome, however, in cases where the secondary position is too crowded (such as with 2-methylbutane, Scheme 4.3), or where other positions are significantly activated (such as α to nitrogen, Eq. 4.2).

Of course, if the secondary position is not desired, this could be a serious challenge to using donor/acceptor carbene C–H functionalization methodology. However, as shown in Scheme 4.1, the choice of rhodium catalyst can have a significant influence on the outcome of the reaction. One solution to site-selective C–H insertion at *primary* C–H bonds was the use of a new class of rhodium catalysts: the triarylcyclopropane carboxylate catalysts (see Chapter 1, section 1.1).[8]

The work in this section describes another strategy to influence site-selectivity: the ester portion of donor/acceptor carbenes. Much of this work was conducted with the triarylcyclopropane carboxylate catalysts, and was conducted concurrently with the catalyst study mentioned previously. Where appropriate, results from that study will be mentioned, and the appropriate individual acknowledged.

Before introducing the results, one thing deserves special mention to help avoid confusion. There are two catalysts used primarily in this work (Figure 4.1): $Rh_2$(BTPCP)$_4$ and $Rh_2$(BPCP)$_4$. The former is equipped with a *p*-Br phenyl group, while

the latter has a biphenyl group. As will be seen in the upcoming section, these two catalysts give similar results, and can be easy to confuse.




$Rh_2$(*R*-BTPCP)$_4$ $Rh_2$(*R*-BPCP)$_4$

**Figure 4.1** Two related triarylcyclopropane catalysts

## 4.2.2 Results and Discussion

It was reported previously that, with diazo **4.12a** and $Rh_2$(*S*-DOSP)$_4$ as catalyst, the secondary C–H insertion product **4.13a** was formed as the only product (Table 4.1, entry 1).[5] A former group member, Dr. Changming Qin found that by using the bulkier catalyst, $Rh_2$(*S*-BTPCP)$_4$, a mixture of the primary and secondary C–H functionalization products was formed (entry 2).

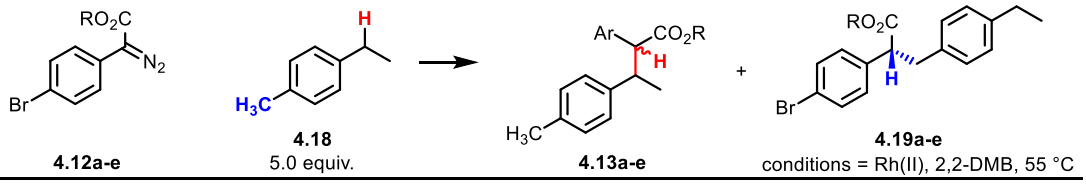
It was known that, with larger ester groups, the asymmetric induction with this catalyst could be improved in cyclopropanation reactions.[9] It was therefore of interest to explore C–H functionalization reactions with larger esters. The anticipated outcome was that, in addition to improved levels of enantioselectivity, a larger ester group might be able to increase the steric demand around the carbene, thereby favoring the smaller methyl C–H bonds. It was hoped that, in combination with the new catalyst, improved regioselectivity could be observed. One of the first ester groups examined was the 2,2,2-trifluoroethyl group, which is slightly larger than the methyl ester. Unfortunately, though this ester caused a degradation in the ratio with $Rh_2$(*S*-DOSP)$_4$, the ratio was essentially unchanged with $Rh_2$(*S*-BTPCP)$_4$. This suggested the need for even bulkier esters.

A concern, however, with the use of bulkier ester groups was the formation of products resulting from intramolecular C–H insertion pathways (such as β-lactones and γ-lactones, see Chapter 3). Thus, the obvious *i*-Pr and *t*-Bu esters were avoided. It was envisioned that β-branching on the ester might provide enough of a steric influence to both improve the regioselectivity while also disfavor intramolecular C–H insertion leading to β-lactones. Thus, diazos **4.12c** and **d** were examined. Though the ratio was improved relative to the methyl ester, the yields were poor. NMR analysis of the crude reaction mixtures suggested that products from intramolecular C–H insertion had indeed formed.

In an attempt to retain the steric influence of these esters while also further disfavoring undesired intramolecular pathways, the 2,2,2-trichloroethyl ester diazo **4.12e** was examined. It was hoped that the electron-withdrawing nature of the chlorine atoms would favor intermolecular reactions. Indeed, the improved ratio relative to the methyl ester was maintained, while improving the yield considerably over the bulky alkyl diazos.

One criticism of rhodium carbene C–H functionalization chemistry is the requirement to use 2,2-dimethylbutane as solvent, which is expensive, and uncommonly used. Since it was known that dichloromethane could be used with $Rh_2(BTPCP)_4$ without depreciation in enantioselectivity,[9] the reaction was examined in this solvent (Table 4.2). For reference, the reaction with DMB as solvent is shown in entry 1. When switching to DCM (entry 2), a good yield was still obtained, but the ratio of the primary product increased. It is not known if this is due to the solvent, the slightly lower temperature of DCM at reflux compared to DMB, or a combination of both factors.

**Table 4.1** Primary vs secondary C–H functionalization of 4-ethyltoluene

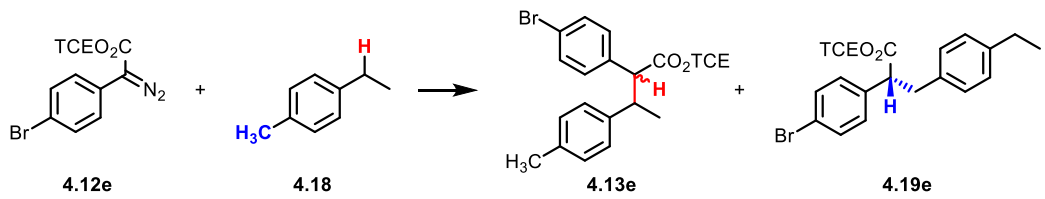



**4.12a-e** | **4.18** 5.0 equiv. | **4.13a-e** | **4.19a-e** | conditions = Rh(II), 2,2-DMB, 55 °C

| entry | catalyst | R | diazo | product | yield (%) | dr of **4.13**[a] | **4.13** : **4.19**[a] |
|---|---|---|---|---|---|---|---|
| 1[b] | $Rh_2$(*S*-DOSP)$_4$ | Me | **a** | **a** | 78% | 2.8 : 1 | >95:5 |
| 2[b] | $Rh_2$(*S*-BTPCP)$_4$ | Me | **a** | **a** | 83% | 2.0 : 1 | 47:53 |
| 3 | $Rh_2$(S-DOSP)$_4$ | $CH_2CF_3$ | **b** | **b** | 73% | 2.3 : 1 | 91:9 |
| 4 | $Rh_2$(*S*-BTPCP)$_4$ | $CH_2CF_3$ | **b** | **b** | 77% | 1.5 : 1 | 48:52 |
| 5 | $Rh_2$(*S*-BTPCP)$_4$ | $CH_2C(CH_3)_3$ | **c** | **c** | 43% | 4.7 : 1 | 38:62[c] |
| 6 | $Rh_2$(*S*-BTPCP)$_4$ | $CH_2TMS$ | **d** | **d** | 38% | 3.3 : 1 | 39:61 |
| **7** | **$Rh_2$(*S*-BTPCP)$_4$** | **$CH_2CCl_3$** | **e** | **e** | **81%** | **3.6 : 1** | **34:66** |

[a]Determined by $^1$H NMR analysis of the crude reaction mixture. [b]Reaction conducted by Dr. Changming Qin. [c]Determined by $^1$H NMR analysis of the purified product.

**Table 4.2** Solvent and temperature study with TCE aryldiazoacetate **4.12e**




**4.12e** | **4.18** 5.0 equiv. | **4.13e** | **4.19e**

conditions = $Rh_2$(*S*-BTPCP)$_4$

| entry | solvent | temp (°C) | combined yield | dr of **4.13e** | ratio **4.19:4.13**[a] |
|---|---|---|---|---|---|
| 1 | DMB | 50 | 81% | 3.6 : 1 | 34:66 |
| 2 | DCM | 40 | 80% | 2.3 : 1 | 17:84 |
| **3** | **DCM** | **23** | **77%** | **3.0 : 1** | **14:86** |
| 4 | $PhCF_3$ | 23 | 70% | 3.2 : 1 | 37:63 |
| 5 | pentane | 36 | - | 1.0 : 1 | 24:76 |
| **6** | **DCM** | **0** | **61%** | **2.0 : 1** | **11:89** |

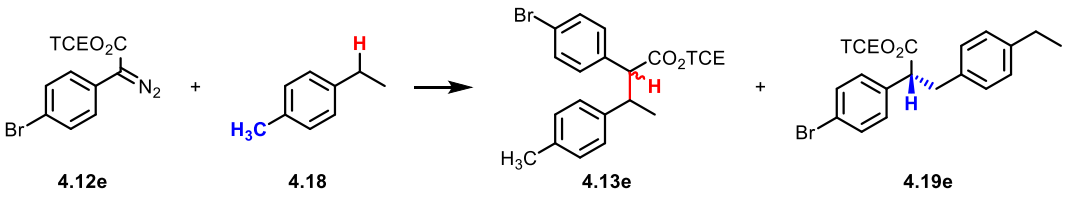
[a]Determined by $^1$H NMR analysis of the crude reaction mixture.

One observation that was made during these studies was the remarkable cleanliness of the reactions with the 2,2,2-trichloroethyl diazo **4.12e**. Wondering whether this diazo would be amenable to C–H functionalization at lower temperatures, and whether this would improve the ratio, the reaction was conducted at room temperature and the ratio improved slightly (entry 3). Using other solvents such as $PhCF_3$ or pentane did not favor

the desired primary product over DCM. When the reaction in DCM was conducted at 0 °C, however, the best ratio yet was observed, 89:11 in favor of the primary product.

Another criticism of this chemistry is that often the substrates must be used in large excess or as solvent to obtain good yields. The effect of changing the stoichiometry of the reagents was therefore examined in this system (Table 4.3). It was found that the stoichiometry of the substrate **4.18** could be reduced to 1.2 equivalents without impacting the yield or the ratio of primary:secondary insertion products.

**Table 4.3** Stoichiometry study with **4.12e**




**4.12e** **4.18** **4.13e** **4.19e**

conditions = $Rh_2$(*S*-BTPCP)$_4$, DCM, reflux

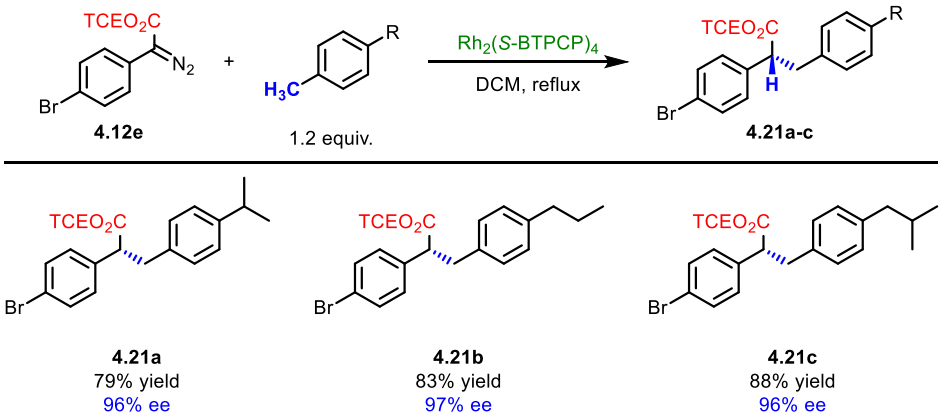
| entry | equiv. **4.18** | yield **1**+**2** | dr of **4.13e** | ratio **4.13:4.19**[a] |
|---|---|---|---|---|
| 1 | 1:5 | 80% | 2.3 : 1 | 16:84 |
| 2 | 1:3 | 75% | 1.6 : 1 | 17:83 |
| 3 | 1:2 | 73% | 2.7 : 1 | 17:83 |
| 4 | 1:1.2 | 76% | 2.5 : 1[b] | 17:83 |

[a]Determined by $^1$H NMR analysis of the crude reaction mixture. [b]Determined by $^1$H NMR analysis of the purified product.

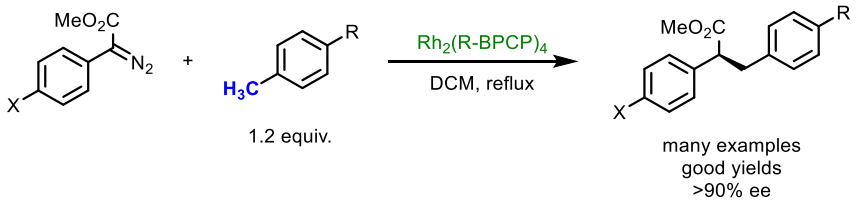
At this point, the enantioselectivity of the reaction had not been examined, since an inseparable mixture of products was being formed. Therefore, the reaction was conducted with a different substrate to get a sense of the levels of enantioinduction possible in these reactions (Scheme 4.5). With 1.2 equivalents of *p*-cymene (4-isopropyltoluene) in DCM at reflux, using $Rh_2$(*S*-BTPCP)$_4$ as catalyst, the primary C–H functionalization product **4.21a** was isolated in 79% yield and 96% ee. Analysis of the crude reaction mixture suggested the primary product was formed in a ratio of >20:1 over the corresponding tertiary regioisomer. The reaction was conducted with two other

substrates as well, demonstrating some generality with regards to the products that can be formed. Thus, products **4.21b** and **4.21c** were formed in 83% and 88% yield, respectively, and in 97% and 96% ee, respectively. In all cases, the product resulting from C–H insertion at the primary position was formed with >95% selectivity.

**Scheme 4.5** Site-selective C–H functionalization of toluene derivatives




At this time, Dr. Changming Qin found that, with the related catalyst $Rh_2$(*R*-BPCP)$_4$, and using the conditions developed here, good regiocontrol could be obtained with a variety of 4-substituted toluene derivatives using a simple methyl ester (Eq. 4.4).[8] The use of the derivative catalyst, $Rh_2$(*R*-BPCP)$_4$, improved levels of enantioselectivity and site-selectivity in these reactions with the methyl ester. The absolute stereochemistry of benzylic C–H functionalization products in this chapter is assigned based on the findings in that report.

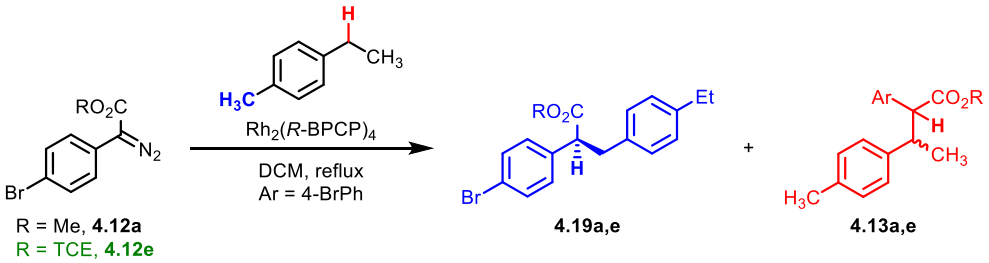



(Eq. 4.4)

As a result of that study, this catalyst was considered in combination with the TCE ester. The reaction of the methyl aryldiazoacetate **4.12a** (conducted by Dr. Changming

Qin)[8] gave a 83:17 mixture of **4.19a** and **4.13a** (note the improvement over the nearly 50/50 mixture formed with $Rh_2$(*S*-BTPCP)$_4$, Table 4.1, entry 2), and the former was made with 92% ee. With the trichloroethyl diazo **4.12e**, however, ratio of primary:secondary insertion products was 93:7. Furthermore, the enantioselectivity improved, with the primary product **4.19e** being formed in 99% ee. These results demonstrated that, though the reactions with the methyl ester were impressive, there was room for improvement, especially for substrates that were not ideal in this chemistry.

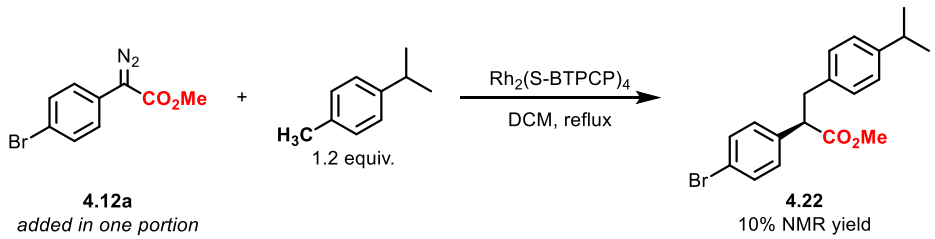
**Scheme 4.6** Reactions of ethyltoluene using $Rh_2$(*R*-BPCP)$_4$



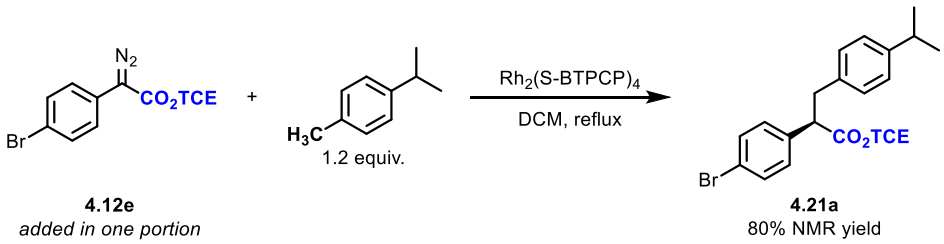

| R | **4.19**:**4.13** | yield (%) | ee of **4.19** (%) | |
|---|---|---|---|---|
| Me | 83:17 | 74 | 92 | (ref. 8) |
| **TCE** | **93:7** | **75** | **99** | |

As mentioned previously, it had been observed that the reactions with the trichloroethyl aryldiazoacetates were remarkably clean. It was hypothesized that this might be because the carbenes formed from these reagents were more robust, and less prone to side products, including diazo dimers[4] and β-lactones formed from intramolecular C–H functionalization.[10–12] Rhodium carbene chemistry is often conducted by slow addition of the diazo, using syringe pump techniques, into the catalyst/substrate solution. This is done to avoid a high concentration of diazo and keep dimerization to a minimum. Therefore, to test the hypothesis that the TCE esters make the carbene less prone to dimerization, the reaction was conducted by fast addition of the

diazo to the solution of catalyst and substrate. First, a control reaction was conducted with the methyl aryldiazoacetate **4.12a**. Under these conditions, this diazo resulted in a low 10% yield of the C–H insertion product, as analyzed by $^{1}$H NMR of the crude mixture. When this experiment was conducted with diazo **4.12e**, however, the desired product was formed in 80% yield. These results clearly demonstrate the improved efficiency of the trichloroethyl diazo over the methyl, and suggest that this may be due, at least in part, to a lower propensity for dimerization.




(Eq. 4.5)




(Eq. 4.6)

## 4.2.3 Conclusion

The work in this section has demonstrated that diazo compounds with trichloroethyl esters are excellent reagents for C–H functionalization of primary, benzylic C–H bonds in combination with $Rh_2(BPCP)_4$ or $Rh_2(BTPCP)_4$. The reactions generally give higher levels of enantioselectivity than those conducted with methyl esters, and the site-selectivity appears to be improved as well. The application of this diazoester to new systems will be discussed in later sections of this chapter.

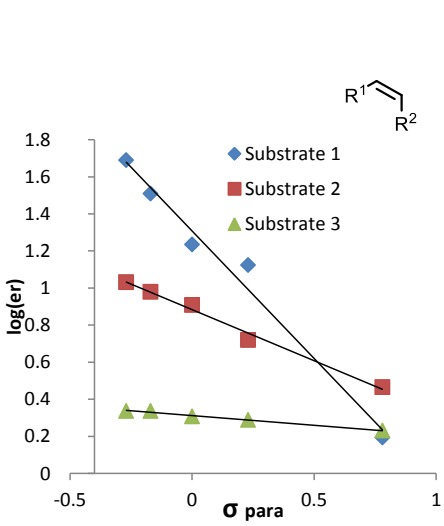
# 4.3 Developing a predictive model for site-selective C–H functionalization

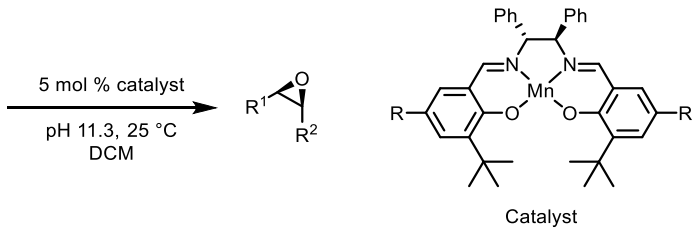
## 4.3.1 Introduction

In the data presented in the previous section, some interesting qualitative trends can be observed. Most notable is the effect of the ester on the site-selectivity of C–H functionalization of 4-substituted toluene derivatives. In that dimension, the trends observed appear to be largely steric in nature, but of course that does not rule out more subtle electronic factors. It was envisioned that this chemistry might be more relevant if the important steric and electronic factors governing site-selectivity could be quantized, giving end users a means of predicting how their substrate might react before going to the bench. Therefore, a collaborative effort was initiated with Professor Matthew Sigman (University of Utah), an expert in the field of relating measured ratios to physical organic parameters.

Modern applications of Linear Free Energy Relationships (LFERs) have typically been in the area of asymmetric catalysis, relating the effect of catalyst modulation to enantioselectivity.[13] An early report of using LFERs in this manner was made by Jacobsen, within the context of asymmetric epoxidation reactions (Scheme 4.7).[14–16] A relationship was observed between the electronics of the catalyst substituents and enantioselectivity. When the measured enantioselectivities were plotted against Hammet $\sigma_{para}$ values, a linear relationship was observed. Interestingly, the electronics of the substrate was also correlated to the magnitude of the effect.

**Scheme 4.7** Hammet correlations of enantioselectivity in Mn(salen) epoxidations

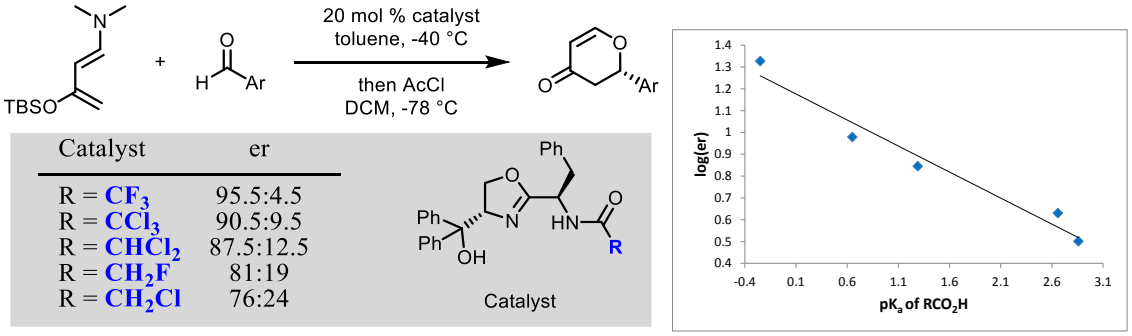



| Catalyst | | | |
|---|---|---|---|
| R = OMe | er = 98:2 | er = 91.5:8.5 | er = 68.5:31.5 |
| R = Me | 97:3 | 90.5:9.5 | 68.5:31.5 |
| R = H | 94.5:5.5 | 89:11 | 67:33 |
| R = Cl | 93:7 | 84:16 | 66:34 |
| R = $NO_2$ | 61:39 | 74.5:25.5 | 63:37 |

In 2007, Sigman and Jensen reported a similar analysis in the context of an asymmetric hetero-Diels–Alder (HDA) reaction (Scheme 4.8).[17] In this report, the authors describe their discovery that the electronic nature of the amide catalysts used in this chemistry[18] had a profound influence on the enantioselectivity of the transformation. In particular, the pronounced effect was related to the R-substitution of the amide. It was found that the enantioselectivities correlated nicely with the $pK_a$ values for the corresponding acetic acid derivatives. The more electron-withdrawing substituents (giving more acidic catalysts) gave the highest levels of enantioselectivity. The authors attribute this to a greater degree of hydrogen-bonding in the Diels–Alder transition state, resulting in tighter catalyst/substrate interactions.

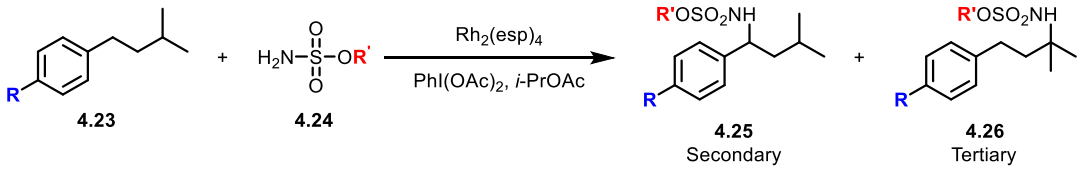
**Scheme 4.8** Effect of R-substitution on enantioselectivity in a HDA reaction.




Enantioselectivity has been related to other physical organic parameters as well, such as polarizability[19] and Charton steric values.[20] However, the field has not been relegated to simply correlating enantioselectivity, but site-selectivity as well. In 2014, Du Bois and Sigman reported a model to predict the site-selectivity of $Rh_2(esp)_4$-catalyzed C–H amination reactions of isoamylbenzene substrates with various sulfamate esters (Scheme 4.9).[21] In an initial screen of sulfamate esters, the authors could identify no obvious qualitative relationship between the steric/electronic factors and the observed site-selectivity. For this reason, it was considered that a simple linear free energy relationship would be inadequate for describing the system mathematically. Therefore, a more complex analysis was performed in which various elements of the system were parameterized, combined, and mathematically narrowed *via* a stepwise linear regression analysis. In this way, the most important elements for describing the site-selectivity were exposed. It was discovered that 3 factors were necessary to accurately describe the system: the Hammet value $\sigma^+$ of the R group, the calculated IR C–O frequency of the sulfamate ester, and the calculated IR O–S–N asymmetric stretching intensity of the sulfamate ester. The model was used to predict the secondary:tertiary ratios of several

sulfamate esters expected to give higher ratios of the secondary product. The measured ratios with these sulfamate esters closely matched the predicted values, lending credence to the accuracy of the model.

**Scheme 4.9** Analysis of site-selectivity in C–H amination reactions of isoamylbenzenes




R = OMe, *t*-Bu, H, Br, $CF_3$
R' = Me, Et, *n*-Pr, $Cl(CH_2)_2$, $Cl(CH_2)_3$, $(ClCH_2)_2CH$, $Cl_3CH_2$, $(CH_3)_2CH$, $CyCH_2$, *t*-$BuCH_2$, *i*-$PrCH_2$, etc.

Model for site selectivity:

$$\Delta\Delta G^{\ddagger} = -0.01 - 0.86(\sigma^{+}) - 0.11(\nu_{CO})(\sigma^{+}) + 0.17(\nu_{CO}) + 0.26(I_{OSN})$$

$\sigma^{+}$ = Hammet value $\sigma^{+}$
$\nu_{CO}$ = calculated IR C–O frequency
$I_{OSN}$ = calculated O-S-N asymmetric stretching intensity

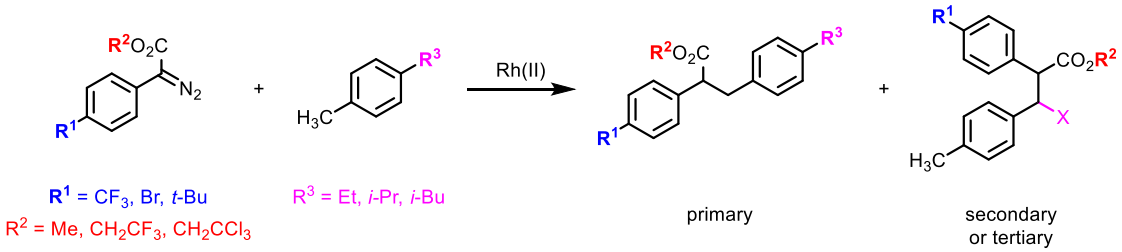
Similar to this amination case, the site-selectivity of the carbene C–H insertion reactions discussed in section 4.2 seems to be governed by a variety of factors. Some of the potential factors include the catalyst, the steric and electronic elements of the ester, and the electronic nature of the carbene aryl group. Like the amination reaction, modeling the carbene C–H insertion reaction using a simple LFER is likely to be unsuccessful. The success of the amination model, however, suggests a similar model might be possible with the carbene system.

## 4.3.2 Results and Discussion

*The results in this section were collected by Elizabeth N. Bess (University of Utah, Sigman group) and me. Experimental data was collected by me unless otherwise stated. Computational and mathematical modeling work was conducted by Elizabeth. Both Elizabeth and I analyzed, interpreted, and discussed the data.*

The reaction of interest, site-selective C–H functionalization of 4-substituted toluene derivatives, is shown in Scheme 4.10. To develop a model for this reaction, three variables were considered interesting for systematic variation: the diazo ester, the diazo aryl substituent, and the 4-substituted toluene substrate. For diazo aryl substituents, only 4-substituted aryldiazo compounds were considered, so as to best model electronic effects apart from the steric effects that might be important with *meta* or *ortho* substituents. For each variable was chosen 3 unique and disparate groups (Scheme 4.10) in the hopes that the variability in electronic and steric properties would result in a range of ratios of (primary)/(secondary or tertiary). Mathematically speaking, three substituents for each of three variables makes for 27 unique diazo/substrate combinations (Figure 4.2a). It was not considered necessary to measure site-selectivity ratios for all 27 of these reactions to develop a model, as long as systematic modification of the variables is present. With this in mind, a reduced set of 15 combinations was selected (Figure 4.2b). These 15 combinations will be referred to as the "training set."

**Scheme 4.10** Analyzing site-selectivity based on a range of steric and electronic properties



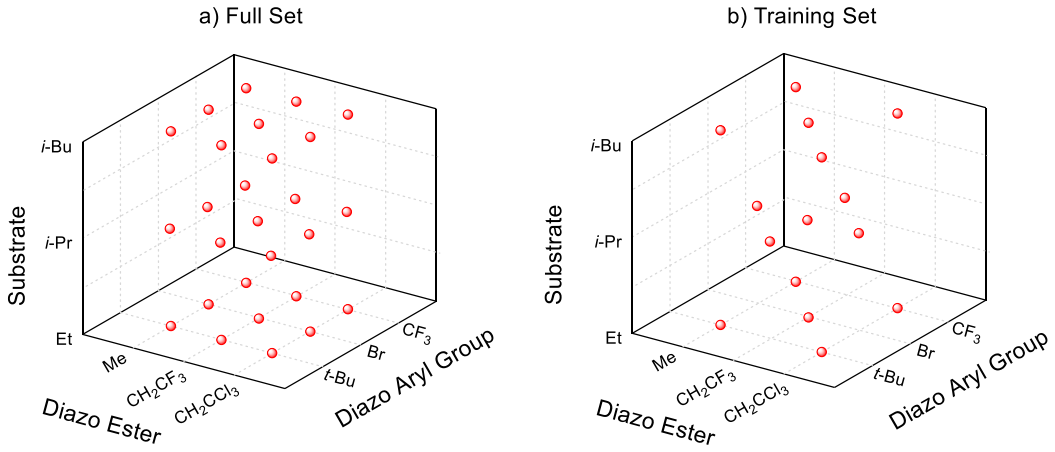
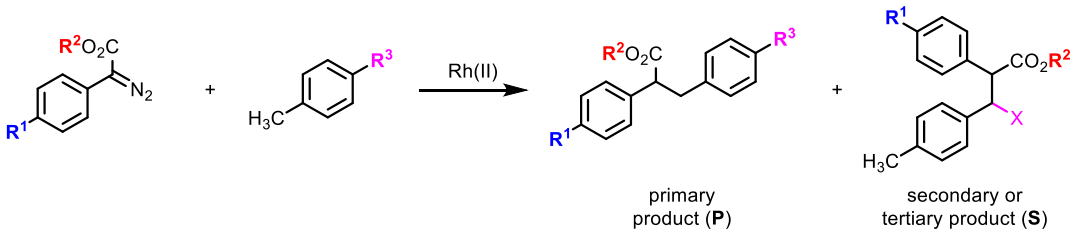



**Figure 4.2** Full set of combinations and training set for developing a model

Having selected the diazo/substrate combinations for the training set, the catalysts to use for the model were selected next. Since it is known that $Rh_2(DOSP)_4$ and $Rh_2(BPCP)_4$ have very different effects on site-selectivity in these reactions,[8] it was concluded that both of these catalysts would be modeled for comparison purposes. The site-selectivity ratios for both the $Rh_2(S\text{-DOSP})_4$ and $Rh_2(R\text{-BPCP})_4$ systems are shown in Table 4.4 for the substrates 4-ethyltoluene and 4-isopropyltoluene. Ratios are reported for the DOSP reaction as secondary or tertiary/primary (S/P), while for BPCP the ratios are reported as primary/secondary or tertiary (P/S). Some initial observations with regards to qualitative trends can be made from this data. First, as expected, DOSP prefers to undergo secondary or tertiary C–H insertion over primary, while the opposite is true of BPCP. Interestingly, the factors that erode selectivity with DOSP (towards primary) seem to improve the selectivity with BPCP (towards primary). In general, larger esters and more electron-deficient aryl groups favor the primary product, while smaller esters and more electron-rich aryl groups favor the secondary or tertiary product.

**Table 4.4** Measured ratios for site-selectivity with ethyltoluene and isopropyltoluene[a]

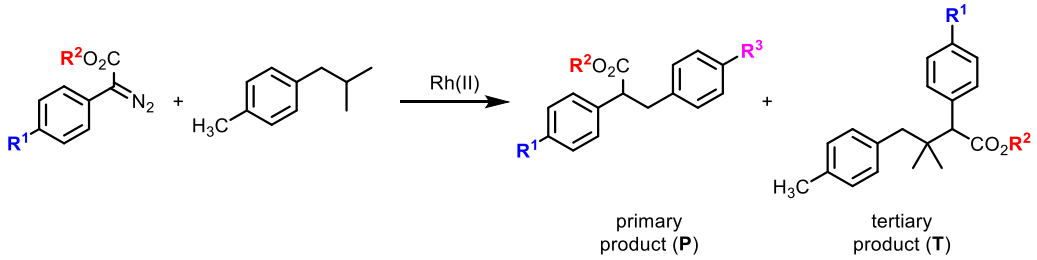



| entry | Ester ($R^1$) | Aryl Group ($R^2$) | $R^3$ | $Rh_2$(*S*-DOSP)$_4$ (**S**/**P**)[b] | $Rh_2$(*R*-BPCP)$_4$ (**P**/**S**)[c] |
|---|---|---|---|---|---|
| 1 | OMe | *t*-Bu | Et | 20 | 3.8 |
| 2 | OMe | $CF_3$ | Et | 10 | 5.2 |
| 3 | $CH_2CF_3$ | Br | Et | 11 | 5.1 |
| 4 | $CH_2CCl_3$ | *t*-Bu | Et | 9.0 | 10 |
| 5 | $CH_2CCl_3$ | $CF_3$ | Et | 4.8 | 14 |
| 6 | OMe | Br | *i*-Pr | 1.9 | 95 |
| 7 | $CH_2CF_3$ | *t*-Bu | *i*-Pr | 4.4 | 101 |
| 8 | $CH_2CF_3$ | Br | *i*-Pr | 1.8 | 182 |
| 9 | $CH_2CF_3$ | $CF_3$ | *i*-Pr | 1.4 | 213 |
| 10 | $CH_2CCl_3$ | Br | *i*-Pr | 0.48 | 610 |

[a]Conditions: Reaction with $Rh_2$(*S*-DOSP)$_4$ was run at reflux in 2,2-DMB. Reaction with $Rh_2$(*R*-BPCP)$_4$ was run at reflux in DCM. The diazo compound (0.2 mmol), in 2.5 mL of the solvent, was added dropwise over 1.5 hours to a solution of the catalyst and substrate (3.0 equiv.) at reflux. The excess starting material was removed by filtering through a short (5 cm) silica plug with hexanes, followed flushing out the product mixture with DCM. [b]Ratio of secondary or tertiary product to primary product. Determined by $^1$H NMR analysis of the crude reaction mixture after removal of the starting material. [c]Ratio of primary product to secondary or tertiary product. Determined by $^1$H NMR analysis of the crude reaction mixture after removal of the starting material.

An interesting result was obtained when isobutyltoluene was used, however. In the crude reaction mixtures with this substrate, none of the expected product from functionalization at the secondary benzylic position was observed. Instead, the mixture seemed to be composed of the expected primary product (P) and the tertiary product (T) as shown in table 4.5.

**Table 4.5** Ratios with 4-isobutyltoluene[a]



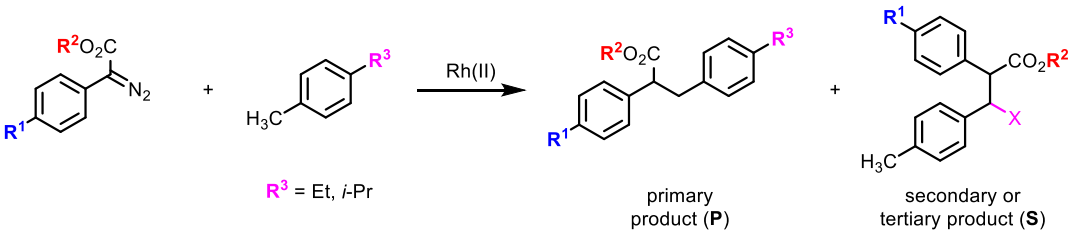

| entry | Ester ($R^1$) | Aryl Group ($R^2$) | $Rh_2$(*S*-DOSP)$_4$ (**T**/**P**)[b] | $Rh_2$(*R*-BPCP)$_4$ (**P**/**T**)[c] |
|---|---|---|---|---|
| 1 | OMe | t-Bu | 0.10[d] | only **P**[d] |
| 2 | OMe | $CF_3$ | 0.067[d] | only **P**[d] |
| 3 | $CH_2CF_3$ | Br | 0.14[d] | only **P**[d] |
| 4 | $CH_2CCl_3$ | t-Bu | 0.10 | only **P** |
| 5 | $CH_2CCl_3$ | $CF_3$ | 0.034 | only **P** |

[a]Conditions: Reaction with $Rh_2$(*S*-DOSP)$_4$ was run at reflux in 2,2-DMB. Reaction with $Rh_2$(*R*-BPCP)$_4$ was run at reflux in DCM. The diazo compound (0.2 mmol), in 2.5 mL of the solvent, was added dropwise over 1.5 hours to a solution of the catalyst and substrate (3.0 equiv.) at reflux. The excess starting material was removed by filtering through a short (5 cm) silica plug with hexanes, followed flushing out the product mixture with DCM. [b]Ratio of the tertiary product to primary product. Determined by $^1$H NMR analysis of the crude reaction mixture after removal of the starting material. [c]Ratio of primary product to tertiary product. Determined by $^1$H NMR analysis of the crude reaction mixture after removal of the starting material. [d]Reaction conducted by Mr. Kuangbiao Liao, NMR data processed by me.

Since the unexpected product mixture with isobutyltoluene was anticipated to unnecessarily complicate the modeling process, only the results in Table 4.4 were used to develop a model. Our collaborators in the Sigman group found that there were several important parameters that could be used to describe the system mathematically (Scheme 4.11). These parameters can be seen in the equations shown in Scheme 4.3. The Hammet σ constant for $R^1$, the parameter B5 for $R^2$ (a measure of size), the calculated IR frequency of the diazo $\nu_{diazo}$, and the point charge for the bulkier C–H bond of $R^3$, $q_{C2}$ were all used to describe the system. Using this model, the measured and predicted energies were plotted against one another. As can be seen from charts a and c in Scheme

4.3, the predicted values correspond well with the measured values for both the DOSP and BPCP systems. A leave-one-out (LOO) analysis was also performed to ensure robustness of the model, in which each data point is left out of the model in turn. A new model is then generated for each of those new data sets, and then the "left-out" point is predicted based on that model.

**Scheme 4.11** Model for describing the system based on the training set

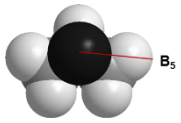


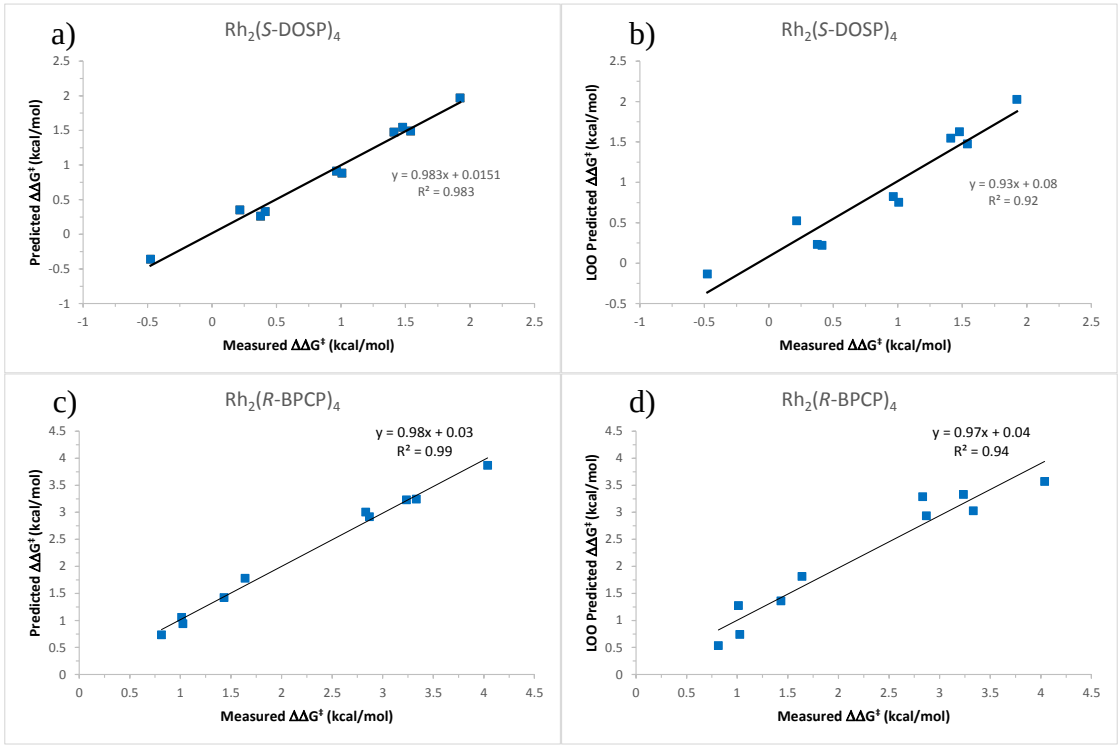

Models for site-selectivity:

For $Rh_2$(*S*-DOSP)$_4$
$\Delta\Delta G^{\ddagger} = -1.06(\sigma_{R^1}) - 1.26(B5_{R^2}) + 1.28(\nu_{diazo}) - 0.87(q_{C2})$

For $Rh_2$(*R*-BPCP)$_4$
$\Delta\Delta G^{\ddagger} = 0.46(\sigma_{R^1}) + 0.71(B5_{R^2}) - 0.60(\nu_{diazo}) + 0.95(q_{C2})$

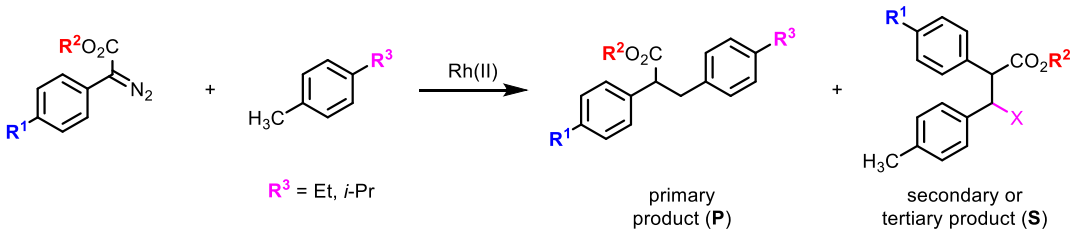
$\sigma_{R^1}$ = Hammet σ value
$B5_{R^2}$ = maximum radius of ester
$\nu_{diazo}$ = diazo IR frequency
$q_{C2}$ = point charge



With a model in place, the next step was to validate it using diazo compounds and/or substrates that were not used to create the model. Five diazo/substrate combinations were chosen that were expected to give a range of site-selectivity ratios for each catalyst (Table 4.6). The reactions were run and the P/S or S/P ratios were measured in the same manner as before.

**Table 4.6** External validations[a]




| entry | Ester ($R^1$) | Aryl Group ($R^2$) | $R^3$ | $Rh_2$(*S*-DOSP)$_4$ (**S**/**P**)[b] | $Rh_2$(*R*-BPCP)$_4$ (**P**/**S**)[c] |
|---|---|---|---|---|---|
| 1 | OMe | Cl | Et | 13 | 3.8 |
| 2 | $CH_2CH_3$ | Br | Et | 12 | 4.4 |
| 3 | $CH_2CBr_3$ | Br | Et | 5.8 | 14 |
| 4 | OMe | OMe | *i*-Pr | 4.7 | - |
| 5 | $CH_2CCl_3$ | OMe | *i*-Pr | 1.3 | 55 |
| 6 | $CH_2CCl_3$ | F | *i*-Pr | - | 437 |

[a]Conditions: Reaction with $Rh_2$(*S*-DOSP)$_4$ was run at reflux in 2,2-DMB. Reaction with $Rh_2$(*R*-BPCP)$_4$ was run at reflux in DCM. The diazo compound (0.2 mmol), in 2.5 mL of the solvent, was added dropwise over 1.5 hours to a solution of the catalyst and substrate (3.0 equiv.) at reflux. The excess starting material was removed by filtering through a short (5 cm) silica plug with hexanes, followed flushing out the product mixture with DCM. [b]Ratio of the secondary or tertiary product to primary product. Determined by $^1$H NMR analysis of the crude reaction mixture after removal of the starting material. [c]Ratio of primary product to secondary or tertiary product. Determined by $^1$H NMR analysis of the crude reaction mixture after removal of the starting material.

Unfortunately, however, when these reactions were predicted using the model, the predicted ratios were not in good agreement with the experimental values (Figure 4.3). With the exception of the diazo/substrate combination in entry 1 (Table 4.6), the

predictions were relatively far from the original trendline for the training set. It is not yet clear whether this is reflective of experimental error or model inaccuracy.

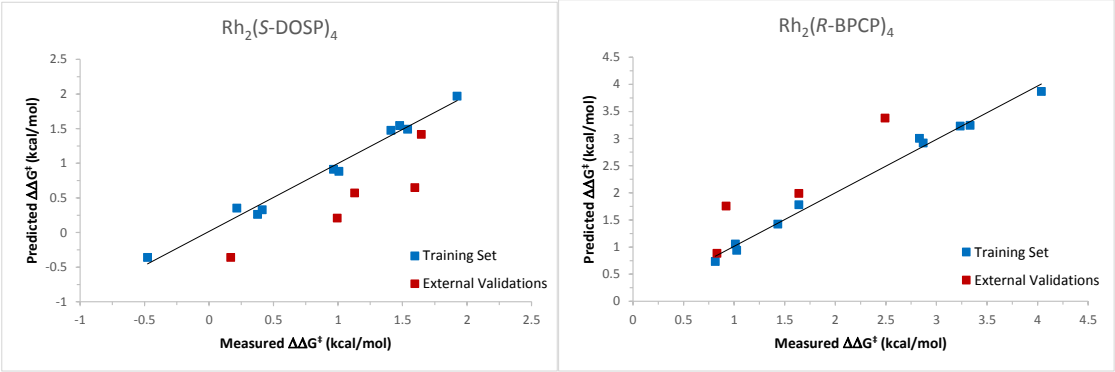



**Figure 4.3** External validations

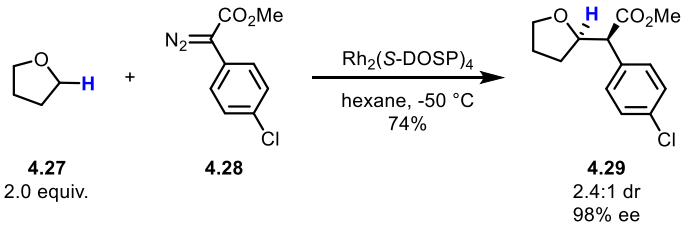
## 4.3.3 Conclusion

Current efforts with this project are centered on determining if a new, more accurate, model is necessary, or if experimental error is to blame. Also, additional validation reactions will need to be performed. When an effective model is developed, it will then be used to predict the site-selectivity expected for new substrates.

# 4.4 Asymmetric C–H functionalization of methyl ethers

## 4.4.1 Introduction to C–H functionalization of methyl ethers

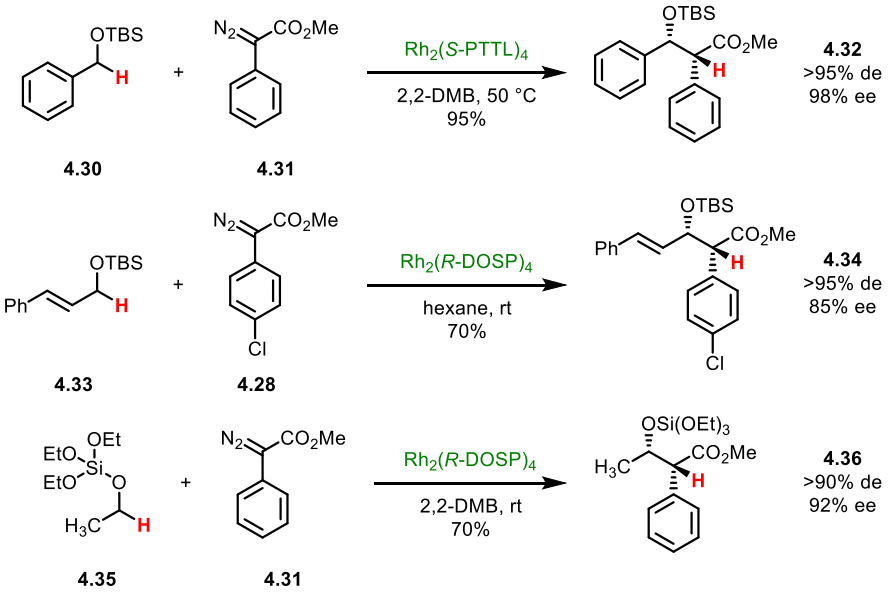
C–H functionalization with donor/acceptor carbenes α to oxygen is a relatively facile process. For example, tetrahydrofuran can undergo C–H insertion to give 4.29 in 74% yield, and the reaction could be conducted with only 2 equivalents of THF at -50 °C. Under these conditions a modest 2.4:1 dr was obtained, though the the major diastereomer was formed in 98% ee.




(Eq. 4.7)

Despite the fact that this is a favorable process, asymmetric C–H functionalization reactions of carbenes α to oxygen have been mostly limited to reactions of secondary C–H bonds.[2,4,22–25] In many systems, impressive levels of diastereo- and enantioselectivity can be achieved (Scheme 4.12). For example, insertion into silyl benzyl ethers[25] gives products like **4.32** in good yields and very high levels of enantioselectivity. Similarly, insertion into allyic silyl ethers[22] gives *syn*-aldol products such as **4.34** with very high diastereocontrol, and good levels of enantioselectivity. A third example is the preparation of *syn*-aldol products from tetraalkoxysilanes, such as **4.35**, which undergoes C–H functionalization with diazo **4.31** to give **4.36** in 70% yield, 92% ee, and as a single diastereomer.

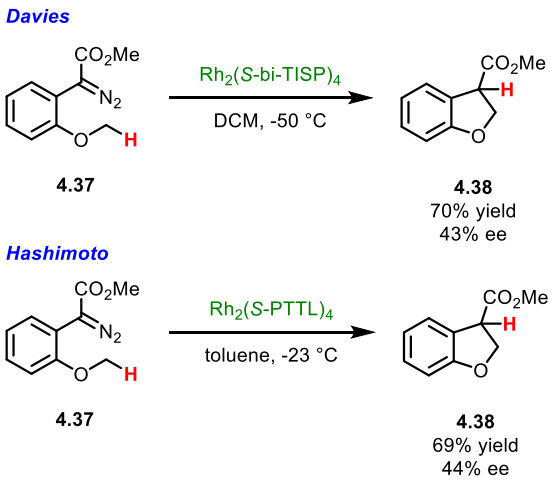
**Scheme 4.12** C–H insertion of ethers applied to the synthesis of aldol producs



Despite these impressive examples, C–H insertion reactions of methyl ethers have been relatively unexplored. An early example of methyl ether functionalization by a rhodium carbene used ethyl diazoacetate.[26] Though insertion into the methyl ether of methyl *tert*-butyl ether was observed with the catalyst $Rh_2(OAc)_4$, the yield was poor (<40%). In that report, much higher yields were obtained when insertion α to oxygen was conducted intramolecularly (and at secondary positions).

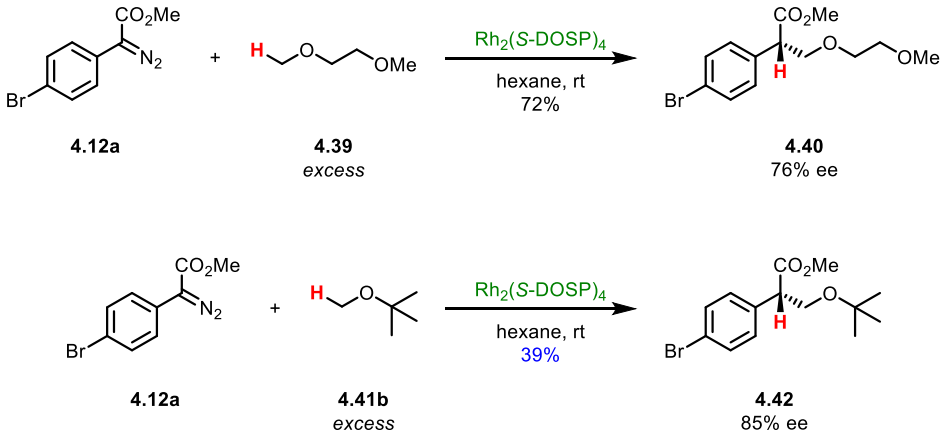
Asymmetric C–H functionalization of methyl ethers was achieved, however, with the use of donor/acceptor rhodium carbenes. Intramolecular functionalization of methyl ethers was used to prepare enriched dihydrobenzofuran derivatives (Scheme 4.13). With the diazo compound **4.37**, both Davies[27] and Hashimoto[28] showed that, with their catalysts $Rh_2$(*S*-bi-TISP)$_4$ and $Rh_2$(*S*-PTTL)$_4$, respectively, the dihydrobenzofuran **4.38** could be prepared in good yields, though with generally low levels of enantioselectivity. In both the Davies and Hashimoto reports, the reactions were much more selective when insertion took place at secondary positions.

**Scheme 4.13** Intramolecular C–H functionalization of methyl ethers



In 2003, the Davies group reported an asymmetric, intermolecular functionalization of methyl ethers.[29] A surprising, failed attempt to functionalize a crown ether led to the exploration of dimethoxyethane (**4.39**) as a substrate for C–H functionalization (Scheme 4.14). With diazo **4.12a** and $Rh_2$(*S*-DOSP)$_4$, the C–H functionalization product **4.40** was isolated in 72% yield and 76% ee. The reaction with DME was conducted with a range of diazo compounds, but levels of enantioselectivity were typically less than 80%. The preference for reaction at the methyl group in this system was attributed to a deactivating inductive effect from the β oxygen present at the secondary sites. The reaction was extended to *tert*-butyl methyl ether (**4.41b**), but this substrate was less apt at undergoing C–H functionalization. Though **4.42** was formed with 85% ee, the yield was only 39%.

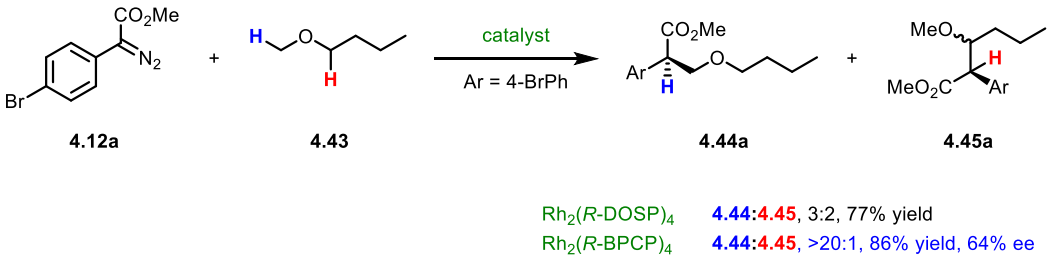
**Scheme 4.14** Intermolecular C–H functionalization of methyl ethers




These results show some serious limitations with the $Rh_2$(*S*-DOSP)$_4$ system. Namely, to achieve site-selective functionalization of methyl ethers, the secondary site must be electronically deactivated or methyl functionalization must be the only reaction that can occur. Even with these constraints on the substrates, the yields and levels of enantioselectivity are moderate. Furthermore, the substrates are used in large excess.

With the application of the triarylcyclopropane carboxylate catalysts to methyl C–H functionalization, it was considered as a potential solution to these problems (Scheme 4.15).[8] With butyl methyl ether (**4.43**) and diazo **4.12a**, for example, $Rh_2$(*R*-DOSP)$_4$ results a 3:2 ratio of primary to secondary C–H functionalization products. However, with $Rh_2$(*R*-BPCP)$_4$, though the primary insertion product **4.44a** was isolated as the sole product, the level of asymmetric induction (64% ee) with this substrate was significantly decreased relative to benzylic methyl groups.

**Scheme 4.15** C–H Functionalization of butyl methyl ether




Since the methyl aryldiazoacetate **4.12a** gave **4.44a** with only a moderate level of enantioselectivity, and since it had been shown in the previous section that the trichloroethyl ester results in improved asymmetric induction, it was considered whether the TCE aryldiazoacetate could improve the reaction with methyl ethers.

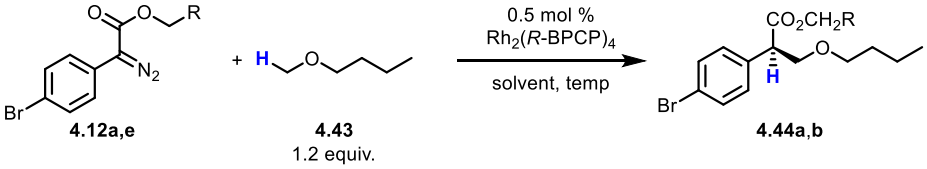
## 4.4.2 Results and Discussion

### 4.4.2.1 Optimization of Methyl Ether Functionalization

In an attempt to find optimal conditions for the C–H functionalization of methyl ethers, the reaction with butyl methyl ether (**4.43**) was re-examined (Table 4.7). When the reaction was conducted with the methyl aryldiazoacetate **4.12a** below room temperature, an increase in the enantioselectivity was observed, giving **4.44a** in 76% ee, but a diminished 59% yield. With the trichloroethyl diazo **4.12e**, at reflux in DCM, the

product was isolated in 82% yield and 84% ee. Decreasing the temperature to 0 °C improved the enantioselectivity to 88% without adversely affecting the yield. The level of enantioselectivity could be improved to 90% ee by conducting the reaction at -40 °C, but the efficiency suffered in this case, and a decrease in the yield was observed (entry 4). The reaction could also be conducted in hydrocarbon solvents at reflux (entries 5 and 6), though without significant improvements in the levels of enantioselectivity. Therefore, to avoid the use of expensive 2,2-DMB and potentially reactive pentane, the optimal conditions were chosen to be DCM as solvent at 0 °C with the trichloroethyl ester.

**Table 4.7** Optimization of butyl methyl ether C–H functionalization



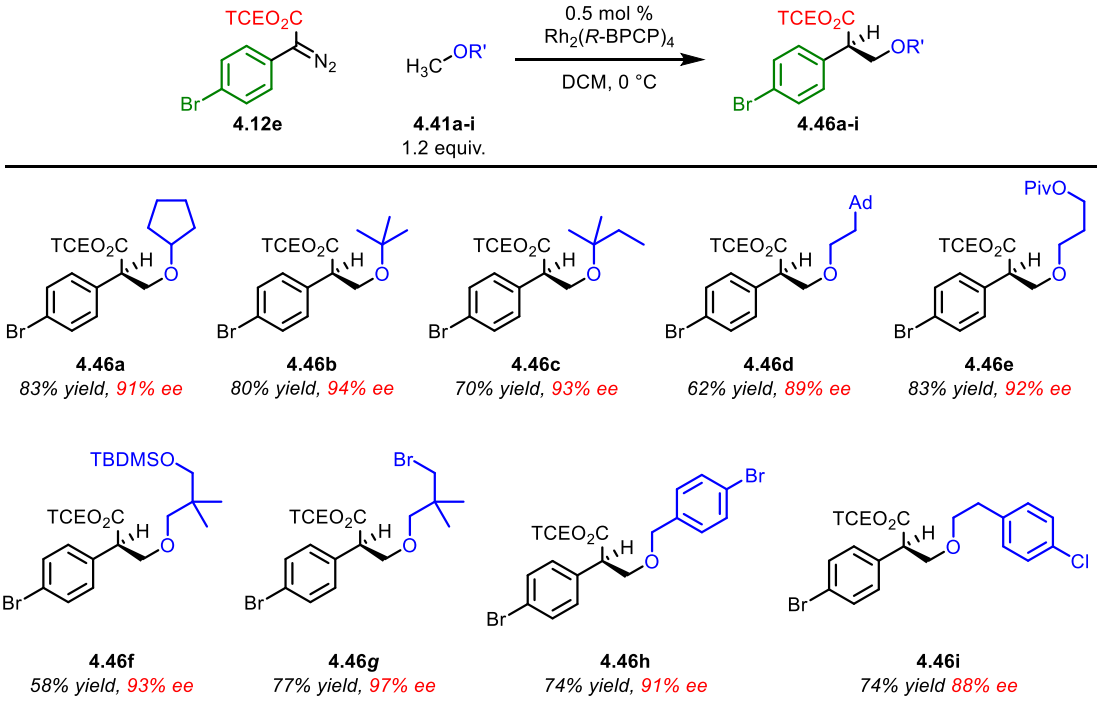

| entry | solvent | R | temp (°C) | yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | DCM | H | 0 | 59 | 76 |
| 2 | DCM | $CCl_3$ | 40 | 82 | 84 |
| **3** | **DCM** | **$CCl_3$** | **0** | **78** | **88** |
| 4 | DCM | $CCl_3$ | -40 | 61 | 90 |
| 5 | 2,2-DMB | $CCl_3$ | 50 | 77 | 88 |
| 6 | pentane | $CCl_3$ | 36 | 74 | 88 |

### 4.4.2.2 Reaction Scope

With optimal conditions determined, the scope of the reaction was explored with a variety of substrates (Scheme 4.16). In all cases, the product from functionalization of the methyl group was formed as the only observable regioisomer, and the yields and levels of enantioselectivity were generally high. Cyclopentyl methyl ether underwent site-selective functionalization at the methyl group over the alternative tertiary C–H bond to give product **4.46a** with 91% ee. Both *tert*-butyl and *tert*-amyl methyl ether gave the corresponding products in good yields and with good levels of enantioselectivity.

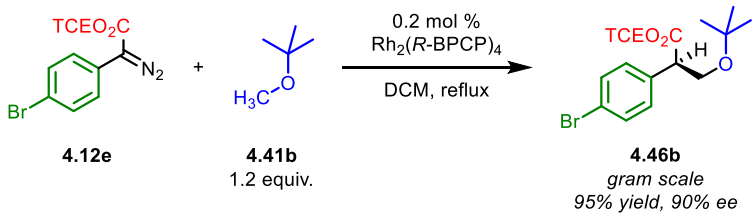
Several other substrates with potentially competitive secondary C–H bonds also underwent site-selective methyl functionalization to give products **4.46d-g** in good yields and with levels of enantioselectivity ranging from 89-97% ee. Especially noteworthy are the reactions of benzyl and phenethyl ethers **4.46h** and **4.46i**. The former substrate has both the methyl ether and the "doubly activated" secondary benzylic positions that could undergo functionalization. The latter has 3 unique sites for functionalization (two α to oxygen, and one benzylic). With both of these substrates, however, only products arising from functionalization at the methyl ether were observed, and isolated in good yields, with ee's ranging from 88-91%.

**Scheme 4.16** Substrate scope of methyl ether C–H functionalization




To demonstrate the potential utility of this chemistry, the reaction with *tert*-butyl methyl ether was conducted at reflux on a gram scale (Eq. 4.8). The catalyst loading could be lowered to 0.2 mol %, and under these conditions the product **4.46b** was isolated

in 95% yield and 90% ee. It is presumed that the lower enantioselectivity in this reaction relative to the one in Scheme 4.8 is due to the increase in temperature rather than the decreased catalyst loading. Indeed, it has been shown that catalyst loadings as low as 0.1 mol % can be used in C–H functionalization of benzylic methyl groups without adversely affecting the asymmetric induction.[8]

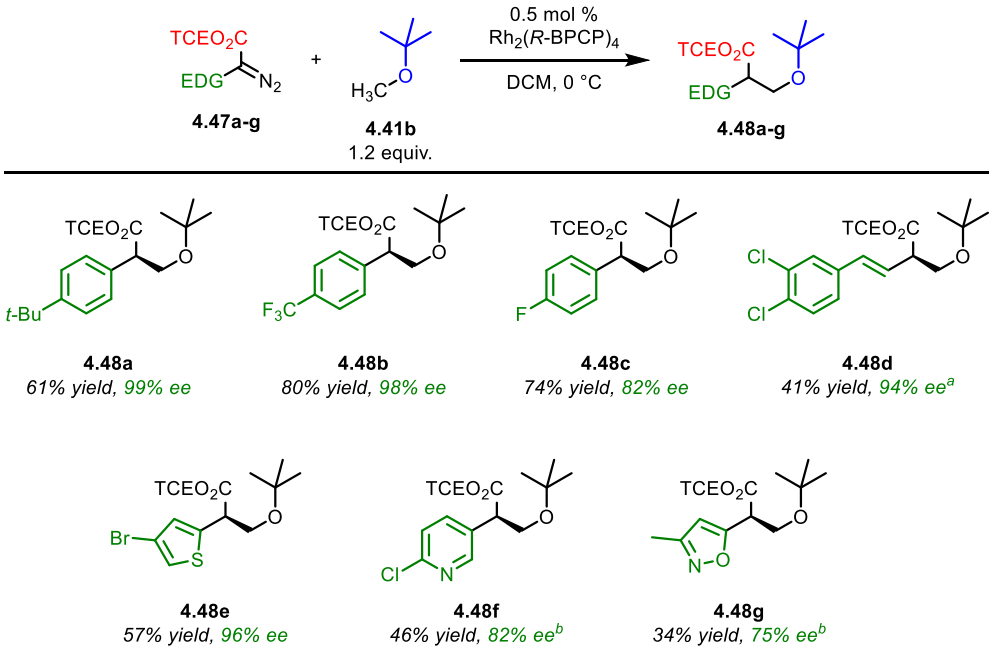



**4.12e** **4.41b** 1.2 equiv. **4.46b** *gram scale* *95% yield, 90% ee*

(Eq. 4.8)

The reaction was also conducted with a variety of donor groups on the diazo compound (Scheme 4.17). Both electron-rich and electron-deficient diazo groups worked well in the reaction, giving **4.48a** and **4.48b** in good yields and with exceptionally high levels of enantioselectivity (98-99% ee). The enantioselectivity dropped to 82% ee with a *p*-fluoro group on the aryl ring, though the yield was still high. The reaction could be extended to styryl diazoacetates as well, giving **4.48d** in a moderate 41% yield but with 94% ee. Particularly impressive, however, are the reactions of heteroaryldiazo compounds **4.47e-g**. The resulting C–H functionalization products were isolated in moderate yields (34-57%), and moderate to excellent levels of enantioselectivity (75-96% ee).

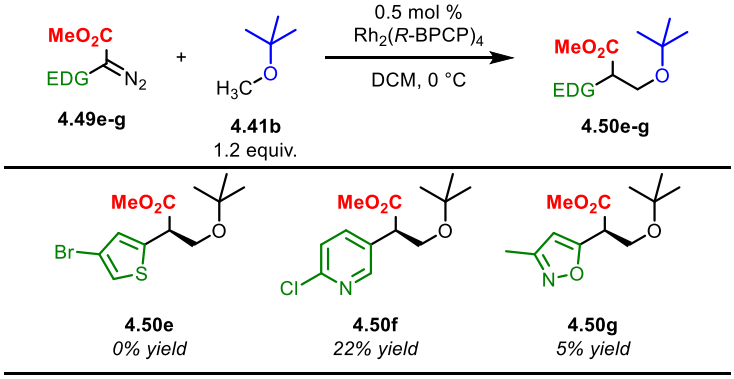
**Scheme 4.17** Scope of diazo compounds




[a]Reaction conducted with 1 mol % $Rh_2$(*R*-BPCP)$_4$. [b]Reaction conducted at reflux.

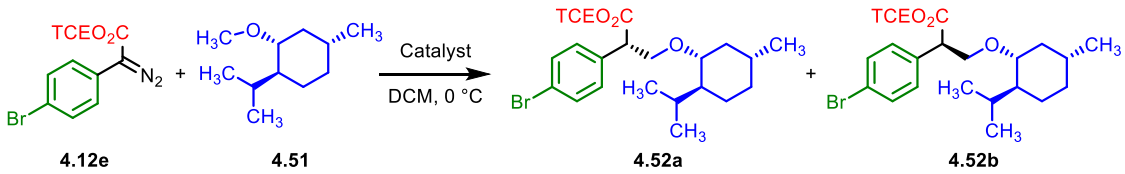
Though the yields are only moderate, the formation of the C–H functionalization products from the trichloroethyl heteroaryldiazoacetates is especially significant since, with the "usual" methyl ester, the products were either not observed, or formed in very low yields (Scheme 4.18). This underscores the value and importance of the trichloroethyl ester in rhodium carbene C–H functionalization reactions.

**Scheme 4.18** C–H Functionalization with methyl heteroaryldiazoacetates



To demonstrate the potential utility of this chemistry for functionalization of complex, chiral substrates, the reaction was conducted with the methyl ether of menthol (**4.51**). The inherent bias of the substrate towards one diastereomer can be seen from the reaction with achiral catalyst $Rh_2(TPA)_4$, in which **4.52a** is formed preferentially, with a dr of 3.6:1. When the reaction was conducted with $Rh_2$(*R*-BPCP)$_4$, the products **4.52a** and **4.52b** were formed with a dr of 1:23, in favor of **4.52b**, the diastereomer opposite to the inherent substrate bias. When using the other enantiomer of the catalyst, $Rh_2$(*S*-BPCP)$_4$, diastereomer **4.52a** was formed predominately, with a dr of >30:1. These results demonstrate a slight match/mismatch effect with this catalyst, though both diastereomers were prepared with good control over the orientation of the newly formed chiral center.

**Scheme 4.19** Functionalization of a chiral substrate



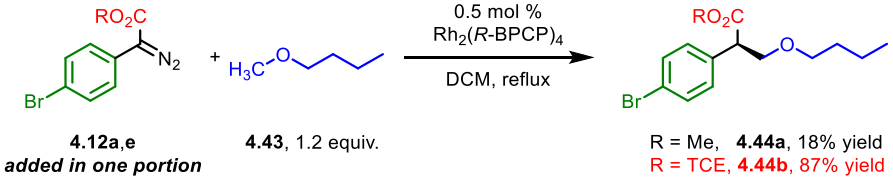

**4.12e** **4.51** **4.52a** **4.52b**

| Catalyst | dr (**a**:**b**) | yield (%) |
|---|---|---|
| $Rh_2(TPA)_4$ | 3.6:1 | 55 |
| $Rh_2$(*R*-BPCP)$_4$ | 1:23 | 62 |
| $Rh_2$(*S*-BPCP)$_4$ | >30:1 | 52 |

### 4.4.2.3 Advantages of the Trichloroethyl Ester in Methyl Ether C–H Functionalization

The unique advantages of the trichloroethyl ester have already been seen in some cases, and these advantages were demonstrated in the context of C–H functionalization reactions of methyl ethers as well. The propensity of the carbene to undergo C–H functionalization rather than formation of dimers is shown for the reaction of **4.12** with butyl methyl ether (**4.43**) in Eq. 4.9. When the methyl ester was added in one portion to a

solution of the catalyst and substrate at reflux in DCM, the product was formed in 18% yield as measured by $^1$H NMR. With the trichloroethyl ester, however, the product was formed in 87% yield.




**4.12a**,**e**
***added in one portion***

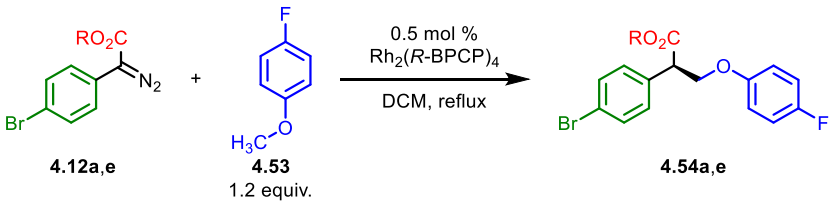
**4.43**, 1.2 equiv.

R = Me, **4.44a**, 18% yield
R = TCE, **4.44b**, 87% yield

(Eq. 4.9)

Having demonstrated the more robust nature of carbenes formed with the TCE ester in the context of methyl ether C–H functionalization, a more challenging substrate was investigated. The oxygen atom of an anisole derivative is expected to be less activating than an alkyl methyl ether, since its electrons are delocalized within the aryl ring. Indeed, when the reaction was conducted with 4-fluoroanisole (**4.53**), the yield was low with the methyl ester (15%). With the trichloroethyl ester, however, the product was formed in 65% yield. A pure sample of **4.54e** isolated for characterization was found to have 97% ee.

**Scheme 4.20** Functionalization of 4-fluoroanisole




**4.12a**,**e**

**4.53**
1.2 equiv.

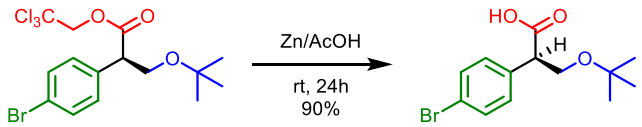
**4.54a**,**e**

| R | yield (%)[a] | ee (%) |
|---|---|---|
| Me | 15 | n.d. |
| TCE | 65 | 97 |

[a]Determined by $^1$H NMR analysis using trichloroethylene as an internal standard.

One final advantage of the trichloroethyl ester that will be considered is its ease of removal under mild conditions. This carboxylate protecting group was originally

developed by Woodward in his total synthesis of Cephalosporin C,[30] and its removal was intended to be tolerant of sensitive functionality in the late stage of the synthesis. In the case of the methyl ether C–H functionalization product **4.46b**, treatment with Zn/AcOH afforded the deprotected carboxylic acid **4.55** in 90% yield without erosion of the chiral information.



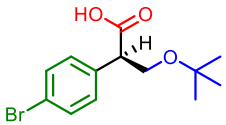

**4.46b**
*90% ee*

**4.55**
*90% ee*

(Eq. 4.10)

The absolute configuration of **4.55** was determined by X-ray crystallography (Figure 4.4). The configuration of all other methyl ether functionalization products was tentatively assigned by analogy (including **4.52a** and **4.52b**, from the functionalization of **4.51**, Scheme 4.11). The sense of asymmetric induction seen in this work was consistent with that observed for C–H functionalization of toluene derivatives.[8]

X-ray Crystal Structure
of **4.55**




**4.55**

**Figure 4.4** X-ray crystal structure of **4.55**

## 4.4.3 Conclusion

The new trichloroethyl ester diazo compounds have been successfully applied to the C–H functionalization of methyl ethers. By using this ester, a significant improvement in enantioselectivity is achieved over the typical methyl ester. Additionally, the trichloroethyl ester enables the use of heteroaryl diazoacetates for C–H functionalization,

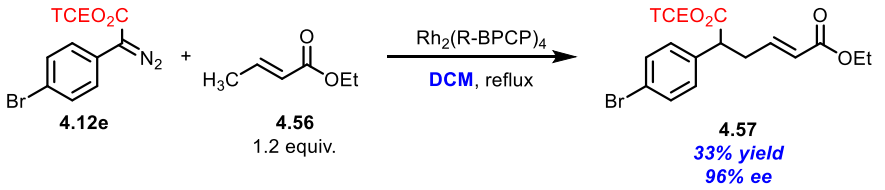
which occurs with the methyl ester in considerably lower yields. Relatedly, with the TCE ester, the reaction can be conducted without slow addition of the diazo compound. A chiral substrate was shown to be suitable, with good catalyst control over the diastereoselectivity. Finally, the trichloroethyl ester can be deprotected smoothly in good yields, without racemization of the chiral center.

## 4.5 Asymmetric functionalization of electron-deficient substrates

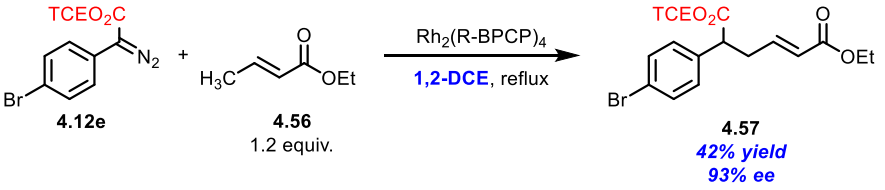
The growing evidence that the trichloroethyl ester results in a more robust, efficient carbene has prompted an effort to extend C–H functionalization to more challenging substrates. In particular, substrates with electron-withdrawing groups were considered interesting targets for functionalization. The electron-deficient nature of such substrates would typically preclude them from consideration. However, in the interest of determining the limits of the trichloroethyl ester for undergoing functionalization of challenging substrates, this section deals with functionalization of these substrates.

### 4.5.1 Results and Discussion

The initial reaction with an electron-deficient substrate was conducted between diazo **4.12e** and ethyl crotonate (**4.56**). In dichloromethane, at reflux, the product **4.57** was formed in 33% yield and 96% ee (Eq. 4.11). At a higher temperature, in dichloroethane, the product was formed in slightly higher yield (42%), though the enantioselectivity was diminished (Eq. 4.12).



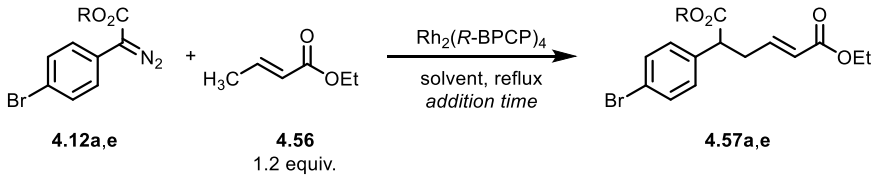

(Eq. 4.11)




(Eq. 4.12)

With the proof of principle that an electron-deficient substrate could undergo C–H functionalization, an optimization study was performed (Table 4.8). As expected, the methyl ester was found to be inadequate for the transformation (entries 1-3). With the trichloroethyl ester, diazo addition time was found to be an important factor (entries 4-6), and slower addition times were necessary to encourage reaction with the more challenging substrate. Both an increase in the catalyst loading to 1.0 mol %, as well as doubling the concentration of the reactants served to improve the yield to as high as 63% (entries 7-8). Using both of these strategies did not result in an improvement (entry 9). By doubling the concentration of the reactants again while maintaining the catalyst loading at 0.5 mol %, the yield of the desired product improved to 71% (entry 10). The enantioselectivity of the product under these conditions was found to be 95% ee. A final improvement in the yield was observed when the reaction was conducted with 2.0 equiv. of the substrate (entry 11), with the desired product formed in 86% yield and 95% ee. A brief examination of 1,2-dichloroethane (entries 12-13) revealed no significant improvement in yield over similar conditions with dichloromethane (compare entry 12 with 5, and entry 13 with 7).

**Table 4.8** Optimization of the reaction with ethyl crotonate




**4.12a,e** **4.56** 1.2 equiv. **4.57a,e**

| entry | R | solvent | relative conc.[b] | catalyst loading (mol %) | time (h)[c] | yield (%)[d] | ee (%)[e] |
|---|---|---|---|---|---|---|---|
| 1 | Me | DCM | 1.0 | 0.5 | 1.5 | 5 | - |
| 2 | Me | DCM | 1.0 | 0.5 | 3.0 | 11 | - |
| 3 | Me | DCM | 1.0 | 0.5 | 6.0 | 16 | - |
| 4 | TCE | DCM | 1.0 | 0.5 | 1.5 | 35 | - |
| 5 | TCE | DCM | 1.0 | 0.5 | 3.0 | 51 | - |
| 6 | TCE | DCM | 1.0 | 0.5 | 6.0 | 48 | - |
| 7 | TCE | DCM | 1.0 | 1.0 | 4.0 | 62 | - |
| 8 | TCE | DCM | 2.0 | 0.5 | 4.0 | 63 | - |
| 9 | TCE | DCM | 2.0 | 1.0 | 3.0 | 64 | - |
| 10 | TCE | DCM | 4.0 | 0.5 | 3.0 | 71 | 95 |
| **11**[f] | **TCE** | **DCM** | **4.0** | **0.5** | **3.0** | **86** | **95** |
| 12 | TCE | 1,2-DCE | 1.0 | 0.5 | 3.0 | 45 | - |
| 13 | TCE | 1,2-DCE | 1.0 | 1.0 | 3.0 | 52 | - |

[a]Reaction conditions for entry 11: The diazo (0.8 mmol) in 1.2 mL DCM was added over 3 hours to a solution of the substrate (2.0 equiv.) and catalyst in 0.5 mL DCM at reflux. [b]Relative concentration (see experimental section for details). [c]Addition time of diazo. [d]Determined by $^1$H NMR using trichloroethylene as an internal standard. [e]Determined by chiral HPLC of the isolated product. [f]Reaction conducted with 2.0 equiv. of substrate.

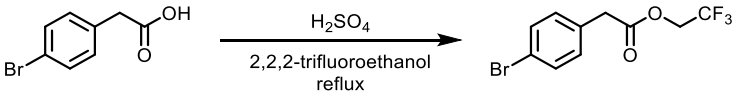
## 4.5.2 Conclusion

With these optimization studies, the groundwork has been laid for an exploration of a variety of electron-deficient, primary C–H bonds. One could imagine a variety of interesting substrates otherwise too unreactive for C–H functionalization with rhodium carbenes. Additionally, the reactions of electron-deficient secondary C–H bonds could be considered with $Rh_2(DOSP)_4$, opening up even more substrates. These reactions will be left for further study.

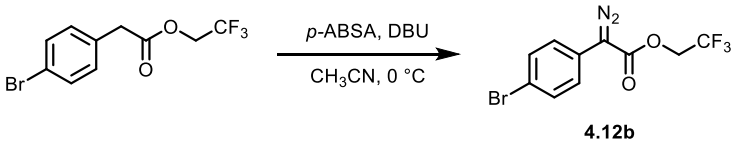
# 4.6 Experimental Section

## 4.6.1 Site Selective C–H Functionalization

### 4.6.1.2 Preparation of Diazo Compounds



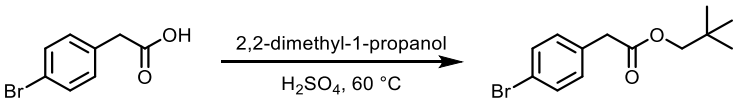

**2,2,2-trifluoroethyl 2-(4-bromophenyl)acetate:** The carboxylic acid (10.0 g, 46.5 mmol, 1.0 equiv.) was dissolved in 2,2,2-trifluoroethanol (100 mL) and several drops of concentrated sulfuric acid were added. The mixture was heated to reflux for 4 hours and then cooled to room temperature. Anhydrous potassium carbonate was added and the mixture stirred for 10 minutes. Solution filtered and concentrated, dissolved in $Et_2O$ (100 mL), dried over $MgSO_4$, and concentrated, giving the product as a colorless oil (10.2 g, 74% yield). This was used immediately without further purification:



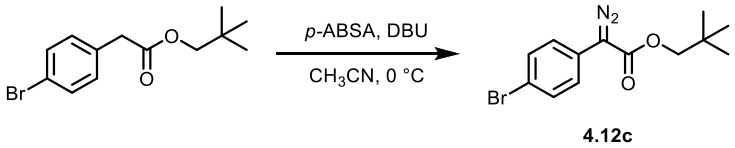

**4.12b**

**2,2,2-trifluoroethyl 2-(4-bromophenyl)-2-diazoacetate (4.12b):** The ester from the previous step (2.0 g, 6.7 mmol, 1.0 equiv.) and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (2.4 g, 10.1 mmol, 1.5 equiv.) were dissolved in acetonitrile (15 mL) and cooled to 0 °C. DBU (2.0 mL, 13.4 mmol, 2.0 equiv.) was added dropwise and the mixture was stirred overnight. The solution was quenched by addition of saturated aqueous ammonium chloride (20 mL) and the mixture was extracted with $Et_2O$ (25 mL). The organic layer was dried over $MgSO_4$ and concentrated. The crude residue was purified by column chromatography to give the product as a fluffy yellow solid. (2.0 g, 91% yield).

$^1$H NMR (400 MHz; $CDCl_3$) δ 7.56-7.51 (m, 2H), 7.38-7.33 (m, 2H), 4.66 (q, 2H, *J* = 8.3 Hz); $^{13}$C NMR (100 MHz; $CDCl_3$) δ IR (neat): 2973, 2092, 1698, 1140 $cm^{-1}$; HRMS (NSI) *m/z*: $[M]^+$ calcd for $C_{10}H_6O_2N_2F_3Br$ 321.9559, found 321.9563;



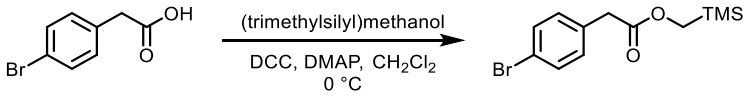

**neopentyl 2-(4-bromophenyl)acetate:** The carboxylic acid (5.0 g, 23.3 mmol, 1.0 equiv.) and neopentyl alcohol (20 mL) were added to a flask. The mixture was placed in a 60 °C oil bath until the solids melted to form a homogenous solution. Concentrated sulfuric acid (several drops) was added and the mixture stirred at 60 °C overnight. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (50 mL). The biphasic mixture was extracted with $Et_2O$ (50 mL). The ethereal layer was washed with saturated aqueous sodium bicarbonate, water and brine (50 mL each), dried over $MgSO_4$, and concentrated by rotary evaporation (bath set at 50 °C to remove excess alcohol). This gave the desired product as a colorless oil (6.4 g, 97% yield). This was used immediately in the next reaction without further purification:



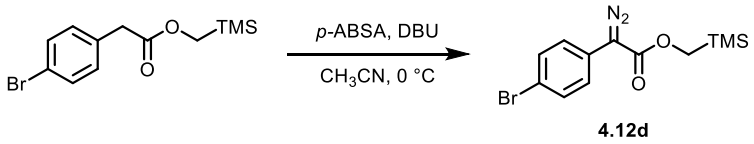

**4.12c**

**neopentyl 2-(4-bromophenyl)-2-diazoacetate (4.12c):** The ester from the previous step (6.4 g, 22.5 mmol, 1.0 equiv.), and *p*-ABSA (8.1 g, 33.7 mmol, 1.5 equiv.) were dissolved in acetonitrile (100 mL) and the solution cooled to 0 °C. DBU (6.7 mL, 45 mmol, 2.0 equiv.) was added dropwise and the solution stirred for 3 days, and quenched with saturated aqueous ammonium chloride (75 mL) and water (25 mL). The mixture

was extracted with $Et_2O$ (100 mL) and the organic layer was separated, washed with brine (50 mL) and dried over $MgSO_4$ and concentrated. The crude orange powder was dissolved in pentane and loaded onto a short silica gel column, eluting with 5% $Et_2O$ in pentane. The orange fractions were collected and concentrated to give the diazo as an orange solid (5.5 g, 79% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 7.53-7.48 (m, 2H), 7.40-7.36 (m, 2H), 3.97 (s, 2H), 0.98 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 165.0, 132.2, 125.5, 125.0, 119.4, 74.5, 31.7, 26.6 (the resonance resulting from the diazo carbon was not detected); IR (neat): 2962, 2867, 2083, 1694, 1161 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{13}H_{15}O_2N_2BrNa$ 333.0209, found 333.021;

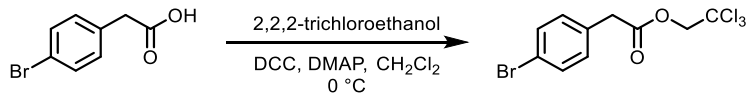



**(trimethylsilyl)methyl 2-(4-bromophenyl)acetate:** The carboxylic acid (3.0 g, 14.0 mmol, 1.0 equiv.), *N*,*N*-dimethyl-4-aminopyridine (DMAP) (171 mg, 1.4 mmol, 0.1 equiv.) and the alcohol (2.1 mL, 16.7 mmol, 1.2 equiv.) were dissolved in dichloromethane (15 mL). The solution was cooled to 0 °C and a solution of *N*,*N*-dicyclohexylcarbodiimide (DCC) (3.2 g, 15.4 mmol, 1.1 equiv.) in dichloromethane (5 mL) was poured into the reaction mixture slowly. The solution was stirred 2 hours and then the solids removed by filtration, washing with $Et_2O$ (25 mL). The filtrate was concentrated and purified by column chromatography (4% $Et_2O$ in pentane) to give the product as a colorless oil (3.7 g, 88% yield). This was used as such in the next reaction:




4.12d

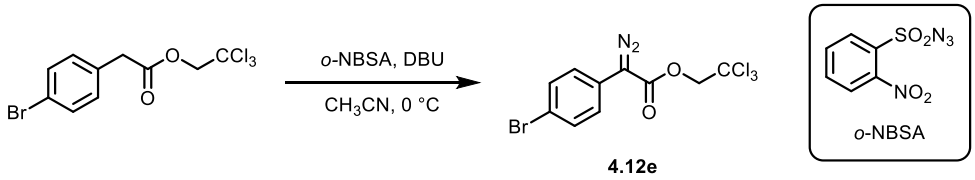
**(trimethylsilyl)methyl 2-(4-bromophenyl)-2-diazoacetate (4.12d):** The ester from the previous step (3.0 g, 10.0 mmol, 1.0 equiv.) and *p*-ABSA (3.6 g, 14.9 mmol, 1.5 equiv.) were dissolved in acetonitrile (40 mL) and the solution cooled to 0 °C. DBU (3.0 mL, 19.9 mmol, 2.0 equiv.) was added dropwise and the mixture stirred overnight, warming to room temperature over that time. The solution was quenched with saturated aqueous ammonium chloride (50 mL) and extracted with $Et_2O$ (50 mL). The organic layer was dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography (3% $Et_2O$ in pentane) to give the diazo as an orange solid (2.8 g, 88% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 7.51-7.48 (m, 2H), 7.39-7.36 (m, 2H), 3.94 (s, 2H), 0.12 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.9, 132.2, 125.4, 125.1, 119.4, 58.5, -2.9 (the resonance resulting from the diazo carbon was not detected); IR (neat): 2953, 2086, 1695, 1159 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{16}N_2O_2BrSi$ 327.0159, found 327.0163;




**2,2,2-trichloroethyl 2-(4-bromophenyl)acetate:** 4-bromophenylacetic acid (30.0 g, 140 mmol, 1.0 equiv.), DMAP (1.7 g, 14 mmol, 0.1 equiv.), and 2,2,2-trichloroethanol (25.1 g, 16 mL, 168 mmol, 1.2 equiv.) were dissolved in 300 mL $CH_2Cl_2$ and the solution cooled to 0 °C. A solution of DCC (31.7 g, 153 mmol, 1.1 equiv.) in $CH_2Cl_2$ (150 mL) was poured slowly into the cold reaction mixture. The reaction mixture was allowed to

stir overnight, at which point it had warmed to room temperature. The solids were removed by suction filtration, and washed with $Et_2O$ (100 mL). The filtrate was concentrated to give a yellow oil that solidified under high vacuum. The solid mass was broken up with a spatula and 150 mL hexanes was added to the flask. The mixture was heated until all but a small amount of white powder remained undissolved. The hot solution was filtered and cooled to room temperature before it was placed in a freezer (-25 °C) overnight. The crystals that had formed were collected by vacuum filtration, washing once with hexanes (100 mL). The product was dried by suction on the frit used for filtration to give a white crystalline solid (38.8 g, 80% yield). This was used without further purification in the diazo transfer reaction.

This diazo was prepared using *o*-nitrobenzenesulfonyl azide as the diazo transfer reagent. This reagent was prepared according to a literature protocol.[31]




**4.12e**

**2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (4.12e):** The ester from the previous step (10.0 g, 28.9 mmol, 1.0 equiv.), together with *o*-NBSA (9.9 g, 43.4 mmol, 1.5 equiv.), were dissolved in acetonitrile (100 mL) and the solution cooled to 0 °C. DBU (9.5 mL, 63.6 mmol, 2.2 equiv.) was added dropwise via syringe. The solution was stirred for 1 hour at 0 °C before it was quenched with saturated aqueous $NH_4Cl$ (100 mL). The mixture was extracted with $Et_2O$ (200 mL). The organic layer was washed with $H_2O$ (100 mL) and brine (100 mL), dried over $MgSO_4$ and filtered. To the filtrate was added 50 g of silica gel and the solvent removed *in vacuo*. The dry silica was

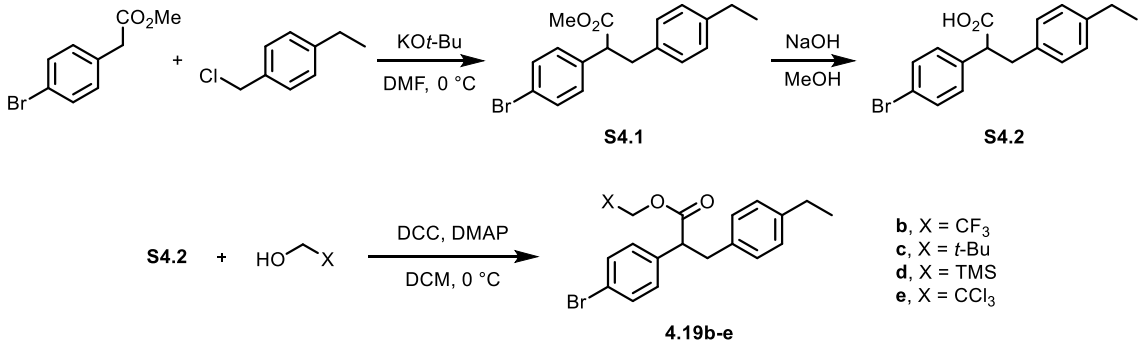
transferred to a column (containing 500 mL silica gel, packed with 2% $Et_2O$ in pentane) using the same solvent. The column was eluted with 2% $Et_2O$ in pentane, and the orange fractions were collected and combined. The solvent was removed on a rotovap below room temperature (keeping the flask out of the water bath), giving the product as an orange crystalline solid (9.3 g, 86% yield). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.57-7.51 (m, 2H), 7.42-7.36 (m, 2H), 4.92 (s, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 163.1, 132.4, 125.6, 124, 120.1, 95.1, 74.1 (t, $J$ = 16.4 Hz) (note: the resonance resulting from the diazo carbon was not observed); IR (film): 2953, 2089, 1709, 1490 cm$^{-1}$;

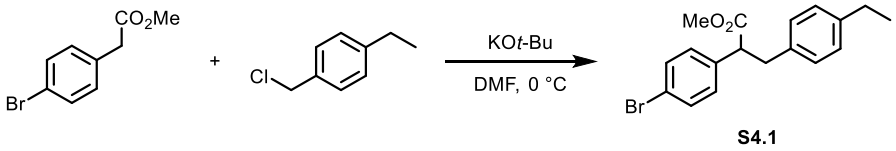
### 4.6.1.3 Experimental Data for C–H functionalization Compounds

***Characterization for primary functionalization compounds 4.19a-e in Table 4.1***

Since the compounds in Table 4.1 were formed as inseparable mixtures, authentic samples of the products from primary C–H functionalization were prepared by another method, and those samples were used for characterization. The method for preparation of authentic samples of **4.19b-e** is shown in Scheme 4.21 below.

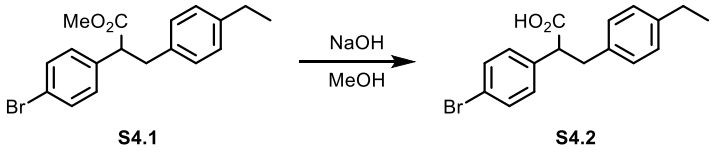
**Scheme 4.21** Preparation of **4.19b-e**






S4.1

**methyl 2-(4-bromophenyl)-3-(4-ethylphenyl)propanoate (S4.1):** 4-ethylbenzyl chloride (4.1g, 26.2 mmol, 1.2 equiv.) and methyl 4-bromophenylacetate (5.0g, 21.8 mmol, 1.0 equiv.) were dissolved in 50 mL DMF and cooled to 0 °C. Solid potassium *tert*-butoxide (2.9 g, 26.2 mmol, 1.2 equiv.) was added in one portion. The solution was stirred overnight, after which time it had warmed to room temperature. The reaction was quenched by the addition of $H_2O$ (50 mL) and was extracted with $Et_2O$ (75 mL). The organic layer was washed with $H_2O$ (50 mL) and dried over $MgSO_4$, and concentrated. The crude mixture was purified by column chromatography (1% →2% $Et_2O$ in pentane). The product was isolated as a colorless oil, but was not completely pure (4.4g, ~58% yield). This was used in the next step without further purification.

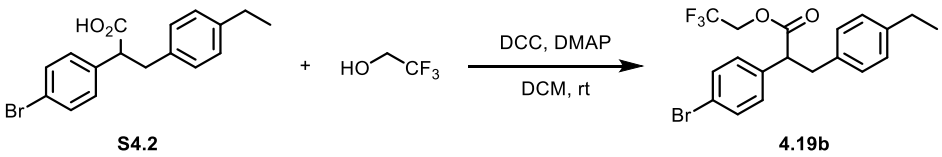



S4.1 S4.2

**2-(4-bromophenyl)-3-(4-ethylphenyl)propanoic acid (S4.2):** The ester **S4.1** (4.4g, 12.7 mmol, 1.0 equiv.) was dissolved in MeOH (200 mL) and a solution of NaOH (19 mL, 1 M in $H_2O$, 10 mmol, 1.5 equiv.) was added. The solution was stirred at room temperature overnight. The mixture was diluted with $H_2O$ (200 mL) and extracted with $Et_2O$ (100 mL). The aqueous phase was acidified to pH = 1.0 with concentrated HCl. The solution was then extracted with $Et_2O$ (2 x 100 mL). The organics were dried ($MgSO_4$) and concentrated. The crude material was purified by column chromatography

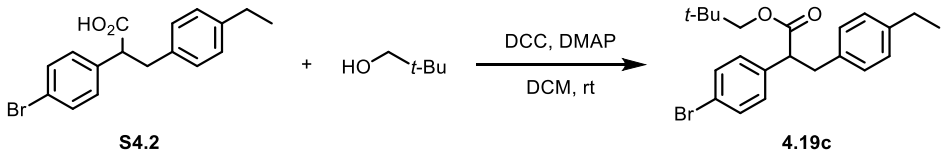
(4:1 hexanes:EtOAc) to give the product as an off-white solid (2.5 g, 60% yield). $^{1}$H NMR (600 MHz; $CDCl_3$) δ 7.44 (d, 2H, *J* = 8.4 Hz), 7.18 (d, 2H, *J* = 8.4 Hz), 7.06 (d, 2H, *J* = 8.0 Hz), 7.00 (d, 2H, *J* = 8.0 Hz), 3.81 (app t, 1H, *J* = 7.7 Hz), 3.36 (dd, 1H, *J* = 13.9, 8.0 Hz), 2.98 (dd, 1H, *J* = 13.9, 7.3 Hz), 2.60 (q, 2H, *J* = 7.6 Hz), 1.21 (t, 3H, *J* = 7.6 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 179.1, 142.6, 136.9, 135.3, 131.8, 129.9, 128.8, 128.0, 121.7, 52.9, 38.7, 28.5, 15.5; IR (neat): 3030, 2977, 2931, 2904, 1706 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{18}O_2Br$ 333.0485; found 333.0487;

The following procedure for DCC coupling is representative:

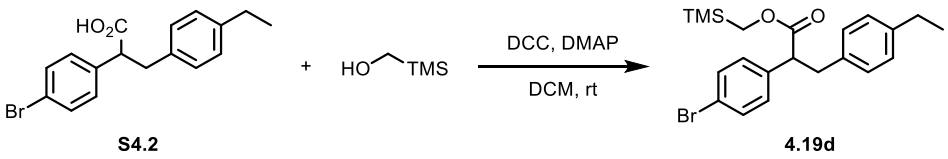



**2,2,2-trifluoroethyl 2-(4-bromophenyl)-3-(4-ethylphenyl)propanoate (4.19b):** The carboxylic acid **S4.2** (100 mg, 0.3 mmol, 1.0 equiv.), DMAP (4 mg, 0.03 mmol, 0.10 equiv.) and 2,2,2-trifluoroethanol (36 mg, 0.36 mmol, 1.2 equiv.) were added to a 4 mL glass screw-cap vial equipped with a micro stir bar and dissolved in 1 mL DCM. The solution was stirred until the solution became homogenous. Then a solution of DCC (68 mg, 0.33 mmol, 1.1 equiv.) in DCM (1 mL) was added in one portion by pipet. The solution was stirred at room temperature overnight. The mixture was filtered through a pad of celite in a pipet, and the filter cake washed with pentane. The filtrate was concentrated to give a crude oil that was purified by column chromatography (1% $Et_2O$ in pentane). The purest, first two fractions, containing the product were combined and concentrated to give a pure sample for characterization. $^{1}$H NMR (600 MHz; $CDCl_3$) δ 7.46 (d, 2H, *J* = 8.4 Hz), 7.20 (d, 2H, *J* = 8.4 Hz), 7.09 (d, 2H, *J* = 8.0 Hz), 7.03 (d, 2H, *J*

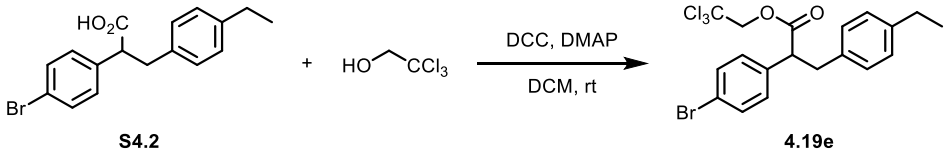
= 8.0 Hz), 4.45-4.33 (m, 2H), 3.93 (dd, 1H, *J* = 8.7, 7.0 Hz), 3.38 (dd, 1H, *J* = 13.9, 8.7 Hz), 3.03 (dd, 1H, *J* = 13.9, 7.0 Hz), 2.61 (q, 2H, *J* = 7.6 Hz), 1.22 (t, 3H, *J* = 7.6 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 171.5, 142.7, 136.5, 135.0, 131.9, 129.7, 128.8, 128.0, 122.8 (q, *J* = 277.2 Hz), 121.8, 60.6 (q, *J* = 36.7 Hz), 52.7, 39.1, 28.5, 15.6; IR (neat): 2966, 2931, 2873, 1754 cm$^{-1}$; HRMS (NSI) m/z: $[M+Na]^+$ calcd for $C_{19}H_{18}BrF_3O_2$ 437.0335; found 437.0334;




**neopentyl 2-(4-bromophenyl)-3-(4-ethylphenyl)propanoate (4.19c):** Prepared analogously to **4.19b**, with the acid (100 mg), DMAP (4 mg), and DCC (68 mg), as well as neopentyl alcohol (26 mg, 0.36 mmol, 1.2 equiv.). The product was purified by column chromatography (1% $Et_2O$ in pentane), taking the purest few fractions for characterization of the product **4.19c**. $^1$H NMR (600 MHz; $CDCl_3$) δ 7.46-7.42 (m, 2H), 7.25-7.21 (m, 2H), 7.08 (d, 2H, *J* = 8.3 Hz), 7.05 (d, 2H, *J* = 8.3 Hz), 3.85 (dd, 1H, *J* = 8.7, 7.0 Hz), 3.72 (s, 2H), 3.38 (dd, 1H, *J* = 13.8, 8.7 Hz), 3.01 (dd, 1H, *J* = 13.8, 7.0 Hz), 2.60 (q, 2H, *J* = 7.6 Hz), 1.21 (t, 3H, *J* = 7.6 Hz), 0.79 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 173.0, 142.4, 137.8, 135.7, 131.6, 129.8, 128.8, 127.9, 121.2, 74.1, 53.3, 39.1, 31.3, 28.4, 26.3, 15.6; IR (film): 2959, 2869, 1732, 1151 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{28}O_2Br$ 403.1267; found 403.1271;




**(trimethylsilyl)methyl 2-(4-bromophenyl)-3-(4-ethylphenyl)propanoate (4.19d):** Prepared analogously to **4.19b**, with the acid (100 mg), DMAP (4 mg), and DCC (68 mg), as well as (trimethylsilyl)methanol (38 mg, 0.36 mmol, 1.2 equiv.). The product was purified by column chromatography (1% $Et_2O$ in pentane), taking the purest few fractions for characterization of the product **4.19d**. $^1$H NMR (600 MHz; $CDCl_3$) δ 7.45-7.42 (m, 2H), 7.23-7.19 (m, 2H), 7.08 (d, 2H, *J* = 8.2 Hz), 7.04 (d, 2H, *J* = 8.2 Hz), 3.83 (dd, 1H, *J* = 8.8, 6.8 Hz), 3.73 (s, 2H), 3.36 (dd, 1H, *J* = 13.9, 8.8 Hz), 2.98 (dd, 1H, *J* = 13.9, 6.8 Hz), 2.60 (q, 2H, *J* = 7.6 Hz), 1.21 (t, 3H, *J* = 7.6 Hz), -0.07 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 173.6, 142.4, 138.0, 135.8, 131.6, 129.8, 128.8, 127.9, 121.2, 58.4, 53.2, 39.2, 28.5, 15.6, -3.2; IR (film): 2960, 2929, 1728, 1150 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{28}O_2SiBr$ 419.1037; found 419.1035;




**2,2,2-trichloroethyl 2-(4-bromophenyl)-3-(4-ethylphenyl)propanoate (4.19e):** Prepared analogously to **4.19b**, with the acid (100 mg), DMAP (4 mg), and DCC (68 mg), as well as 2,2,2-trichloroethanol (54 mg, 0.36 mmol, 1.2 equiv.). The product was purified by column chromatography (1% $Et_2O$ in pentane), taking the purest few fractions for characterization of the product **4.19e**. $^1$H NMR (600 MHz; $CDCl_3$) δ 7.46-7.43 (m, 2H), 7.25-7.22 (m, 2H), 7.07 (d, 2H, *J* = 8.3 Hz), 7.05 (d, 2H, *J* = 8.3 Hz), 4.67 (d, 1H, *J*

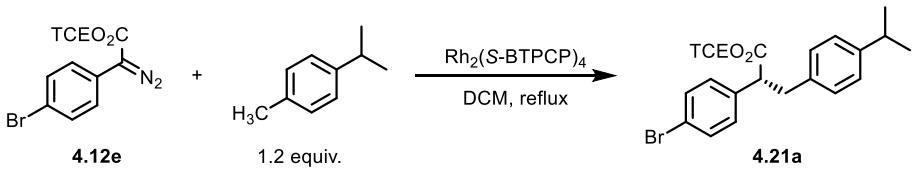
= 12.0 Hz), 4.62 (d, 1H, *J* = 12.0 Hz), 3.96 (dd, 1H, *J* = 8.9, 6.8 Hz), 3.40 (dd, 1H, *J* = 13.9, 8.9 Hz), 3.04 (dd, 1H, *J* = 13.9, 6.8 Hz), 2.58 (q, 2H, *J* = 7.6 Hz), 1.19 (t, 3H, *J* = 7.6 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 171.5, 142.8, 136.8, 135.3, 132.0, 130.1, 129.0, 128.2, 121.9, 94.8, 74.3, 53.1, 39.1, 28.6, 15.8; IR (neat): 2962, 2929, 1749, 1133 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{18}O_2BrCl_3Na$ 484.9448; found 484.9461;

### *Data for Compounds 4.21a-c*

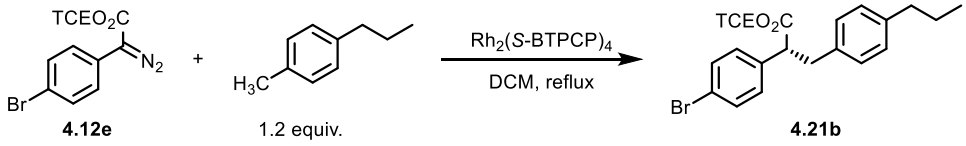
The substrate 4-isopropyltoluene was purchased from Sigma-Aldrich and used as received. Substrates 4-propyltoluene and 4-isobutyltoluene were prepared according to a literature procedure.[8]

**General Procedure**

An oven-dried, 10 mL round-bottomed flask, equipped with a magnetic stir bar and a reflux condenser was cooled to room temperature under argon. The flask was charged with the substrate (1.2 – 5.0 equiv.) and the catalyst (0.5 – 1 mol %), followed by 1 mL of dichloromethane. The solution was heated or cooled to the appropriate temperature (reflux, room temperature or 0 °C). The diazo compound was dissolved in 2.5 mL dichloromethane under argon, and added dropwise to the reaction mixture over 1.5 hours. The mixture was further stirred for 30-60 minutes before it was concentrated to give a crude, green residue. The crude mixture was purified by column chromatography to give the product or mixture of products.

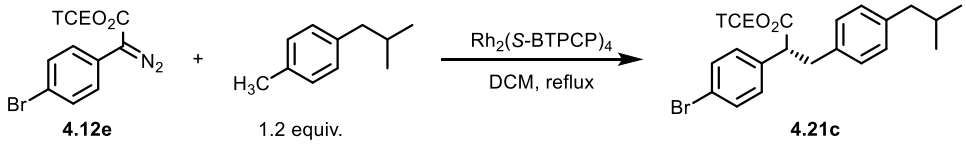



**2,2,2-trichloroethyl (*R*)-2-(4-bromophenyl)-3-(4-isopropylphenyl)propanoate (4.21a):** Using the general procedure above, the diazo (149 mg, 0.4 mmol), *p*-cymene (64 mg, 75 µL, 0.48 mmol, 1.2 equiv.) and $Rh_2$(*S*-BTPCP)$_4$ (7 mg, 0.004 mmol, 1 mol %), the product was isolated as a white solid (151 mg, 79% yield). mp 67-70 °C; $^1$H NMR (600 MHz; $CDCl_3$) δ 7.46 (d, 2H, *J* = 8.2 Hz), 7.26 (d, 2H, *J* = 8.2 Hz), 7.11 (d, 2H, *J* = 8.1 Hz), 7.08 (d, 2H, *J* = 8.1 Hz), 4.70 (d, 1H, *J* = 12 Hz), 4.69 (d, 1H, *J* = 12 Hz), 3.97 (dd, 1H, *J* = 9.1, 6.6 Hz), 3.41 (dd, 1H, *J* = 13.9, 9.1 Hz), 3.05 (dd, 1H, *J* = 13.9, 6.6 Hz), 2.86 (sep, 1H, *J* = 6.9 Hz), 1.22 (d, 6H, *J* = 6.9 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.6, 147.5, 136.9, 135.5, 132, 130.1, 129, 126.8, 121.9, 94.8, 74.3, 53.1, 39.2, 33.9, 24.2; IR (neat): 2958, 1741, 1373, 1138 cm$^{-1}$; HRMS (NSI) *m/z*: $[M-H]^-$ calcd for $C_{20}H_{19}O_2BrCl_3$ 474.964, found 474.9645; The ee was determined by chiral HPLC: SS Whelk column, 0.5 mL/min, 0 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 20.1 min, Minor: 18.5 min, 96% ee.




**2,2,2-trichloroethyl (*R*)-2-(4-bromophenyl)-3-(4-propylphenyl)propanoate (4.21b):** Using the general procedure above, the diazo (149 mg, 0.4 mmol, 1.0 equiv.), 4-*n*-propyltoluene (64 mg, 0.48 mmol, 1.2 equiv.) and $Rh_2$(*S*-BTPCP)$_4$ (7 mg, 0.004 mmol, 1 mol %), the product was purified by chromatography (1% $Et_2O$ in pentane) and isolated

as a white solid (158 mg, 83% yield). mp 44-47 °C; $^{1}$H NMR (600 MHz; $CDCl_3$) δ 7.46 (d, 2H, *J* = 8.4 Hz), 7.25 (d, 2H, *J* = 8.4 Hz), 7.06 (app s, 4H, ), 4.70 (d, 1H, *J* = 11.9 Hz), 4.63 (d, 1H, *J* = 11.9 Hz), 3.97 (dd, 1H, *J* = 8.9, 6.8 Hz), 3.42 (dd, 1H, *J* = 13.9, 8.9 Hz), 3.06 (dd, 1H, *J* = 13.9, 6.8 Hz), 2.57-2.50 (m, 2H), 1.66-1.57 (m, 2H), 0.93 (t, 3H, *J* = 7.3 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.6, 141.3, 136.8, 135.3, 132.0, 130.1, 129, 128.8, 121.9, 94.8, 74.3, 53.1, 39.2, 37.8, 24.8, 14; IR (neat): 2956, 2927, 2871, 1742 cm+; HRMS (NSI) *m/z*: $[M-H]^-$ calcd for $C_{20}H_{19}O_2BrCl_3$ 474.964, found 474.9633; The ee was determined by chiral HPLC: SS Whelk column, 1 mL/min, 0 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 57.7 min, Minor: 53.7 min, 97% ee.




**2,2,2-trichloroethyl (*R*)-2-(4-bromophenyl)-3-(4-isobutylphenyl)propanoate (4.21c):** Using the general procedure above, the diazo (149 mg, 0.4 mmol, 1.0 equiv.), 4-isobutyltoluene (71 mg, 0.48 mmol, 1.2 equiv.) and $Rh_2$(*S*-BTPCP)$_4$ (7 mg, 0.004 mmol, 1 mol %), the product was purified by chromatography (1% $Et_2O$ in pentane) and isolated as a white solid (174 mg, 88% yield). mp 59-62 °C; $^{1}$H NMR (600 MHz; $CDCl_3$) δ 7.46 (d, 2H, *J* = 8.4 Hz), 7.25 (d, 2H, *J* = 8.4 Hz), 7.05 (d, 2H, *J* = 8.1 Hz), 7.03 (d, 2H, *J* = 8.1 Hz), 4.70 (d, 1H, *J* = 12 Hz), 4.63 (d, 1H, *J* = 12 Hz), 3.97 (dd, 1H, *J* = 8.9, 6.8 Hz), 3.43 (dd, 1H, *J* = 13.9, 8.9 Hz), 3.06 (dd, 1H, *J* = 13.9, 6.8 Hz), 2.42 (d, 2H, *J* = 7.2 Hz), 1.87-1.77 (m, 1H), 0.89 (d, 6H, *J* = 6.6 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.6, 140.3, 136.8, 135.4, 132, 130.1, 129.4, 128.8, 121.9, 94.8, 74.3, 53.2, 45.2, 39.2, 30.4, 22.6; IR (neat): 2953, 2910, 2867, 1742, 1138 $cm^{-1}$; HRMS (NSI) *m/z*: $[M-H]^-$ calcd for

$C_{21}H_{21}O_2BrCl_3$ 488.9796, found 488.9802; The ee was determined by chiral HPLC: SS Whelk column, 0.2 mL/min, 0 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 87.9 min, Minor: 83.2 min, 97% ee.

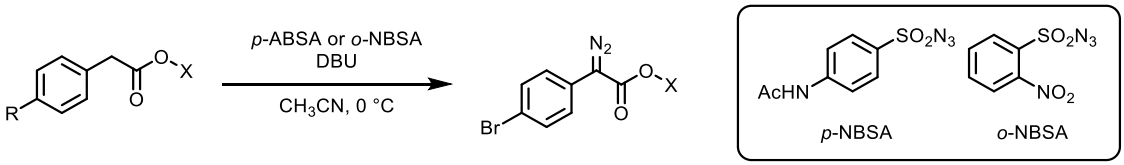
## 4.6.2 Modeling Site-Selective C–H Functionalization

4-ethyltoluene and 4-isopropyltoluene were purchased from Sigma-Aldrich and used as received. 4-isobutyltoluene was prepared according to a literature procedure.[8]

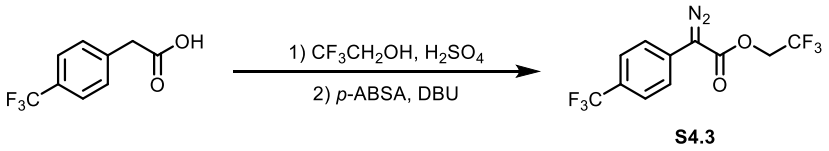
### 4.6.2.1 Preparation of Diazo Compounds

Diazo compounds were prepared by direct diazo transfer to the methylene compounds as per Scheme 4.22.

**Scheme 4.22** Preparation of diazo compounds

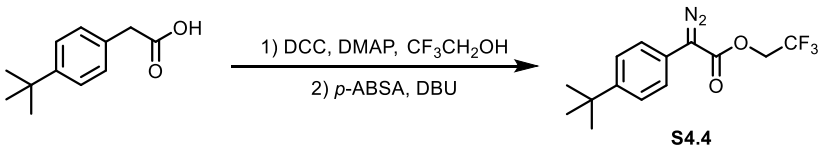



Methyl 4-*tert*-butylphenyldiazoacetate, methyl 4-bromophenyldiazoacetate, methyl 4-(trifluoromethyl)phenyldiazoacetate, methyl 4-chlorophenyldiazoacetate, and methyl 4-methoxyphenyldiazoacetate were prepared using *p*-ABSA, according to a literature procedure.[4] Preparation of 2,2,2-trifluoromethyl 4-bromophenyldiazoacetate and 2,2,2-trichloroethyl 4-bromophenyldiazoacetate is described in section 4.6.1.2. Other diazo compounds were prepared as described below.




**S4.3**

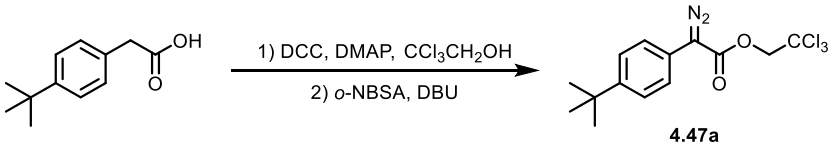
**2,2,2-trifluoroethyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate (S4.3):** 4-(trifluoromethyl)phenylacetic acid (8.0 g, 39.2 mmol, 1.0 equiv.) was dissolved in 75 mL of 2,2,2-trifluoroethanol. 10 drops of concentrated sulfuric acid was added and the mixture heated to reflux for 5 hours. It was allowed to cool to room temperature and quenched by addition of saturated $NaHCO_3$ (150 mL). The solution was extracted with $Et_2O$ (100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$, $H_2O$, and brine, and dried over $MgSO_4$ and concentrated. This gave a crude, waxy white solid, which was purified by column chromatography (5% $Et_2O$ in pentane). A portion of the purified material (2.2 g, 7.7 mmol, 1.0 equiv.) was dissolved in acetonitrile (50 mL) together with *p*-ABSA (2.8 g, 11.5 mmol, 1.5 equiv.) and the solution cooled to 0 °C. Then DBU (2.3 mL, 15.4 mmol, 2.0 equiv.) was added drop-wise. The solution was stirred for 6 hours and quenched with saturated aqueous $NH_4Cl$ (75 mL) and $H_2O$ (50 mL). The solution was extracted with $Et_2O$ (100 mL) and the organic layer separated, dried over $MgSO_4$, and concentrated. The crude material was purified by column chromatography (2% $Et_2O$ in pentane) to give the diazo as a yellow solid (1.3 g, 54% yield). 1H NMR (600 MHz; $CDCl_3$) δ 7.64 (d, 2H, $J$ = 8.5 Hz), 7.59 (d, 2H, $J$ = 8.5 Hz), 4.67 (d, 2H, $J$ = 8.3 Hz); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 162.5, 129.1, 128.2 (q, $J$ = 32.9 Hz), 126.0 (q, $J$ = 3.5 Hz), 124.0 (q, $J$ = 271.7 Hz), 123.5, 122.9 (q, $J$ = 277.4 Hz), 60.5 (q, $J$ = 37.1 Hz) (Note: the resonance resulting from the diazo carbon was not detected); IR (neat): 2978, 2097, 1716, 1075 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_7F_6N_2O_2$ 313.0406; found 313.0409;




**S4.4**

**2,2,2-trifluoroethyl 2-(4-(*tert*-butyl)phenyl)-2-diazoacetate (S4.4):** 4-*tert*-butylphenylacetic acid (7.0 g, 36.4 mmol, 1.0 equiv.) was dissolved in 75 mL of 2,2,2-trifluoroethanol and 10 drops of concentrated sulfuric acid were added. The mixture was heated to reflux for 5 hours and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ (75 mL) and $Et_2O$ (100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$, $H_2O$, and brine, and dried over $MgSO_4$. The solution was concentrated to give a colorless oil that was purified by column chromatography (5% $Et_2O$ in pentane). The ester product (5.8 g, 21.1 mmol, 1.0 equiv.) was dissolved in 100 mL acetonitrile with *p*-ABSA (31.7 mmol, 1.5 equiv.) and the solution cooled to 0 °C. Then DBU (6.3 mL, 42.2 mmol, 2.0 equiv.) was added drop-wise and the reaction stirred for 6 hours. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ (100 mL) and $H_2O$ (25 mL) and extracted with $Et_2O$ (150 mL). The organic layer was washed with brine and dried over $MgSO_4$ and concentrated. The crude material was purified by column chromatography (2% $Et_2O$ in pentane) to give the diazo as a red oil that solidified in the freezer (-25 °C) (585 mg, 9% yield). *Note: The yield of this diazo is low presumably because p-ABSA was used as the diazo transfer reagent. It is expected the yield would be significantly improved by the use of o-NBSA.* $^1$H NMR (600 MHz; $CDCl_3$) δ 7.44 (d, 2H, *J* = 8.5 Hz), 7.39 (d, 2H, *J* = 8.5 Hz), 4.65 (q, 2H, *J* = 8.4 Hz), 1.32 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 163.5, 149.8, 126.2, 124.2, 123.0 (q, *J* = 277.9 Hz), 121.1, 60.3 (q, *J* = 36.8 Hz), 34.6, 31.3 (the resonance resulting

from the diazo carbon was not detected); IR (film): 2966, 2906, 2872, 2091, 1716 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{15}O_2N_2F_3Na$ 323.0978; found 323.0979;

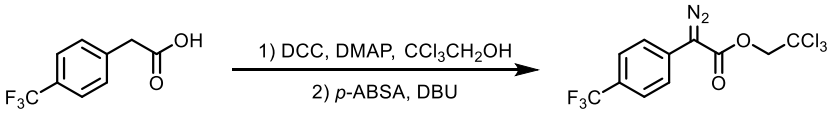



**4.47a**

**2,2,2-trichloroethyl 2-(4-(*tert*-butyl)phenyl)-2-diazoacetate (4.47a):** A solution of 4-*tert*-butylphenylacetic acid (5.0 g, 26.0 mmol, 1.0 equiv.), 2,2,2-trichloroethanol (4.6 g, 3.0 mL, 31.2 mmol, 1.2 equiv.) and DMAP (317 mg, 2.6 mmol, 0.1 equiv.), in 50 mL $CH_2Cl_2$ was cooled to 0 °C in an ice/water bath. Then DCC (5.9 g, 28.6 mmol, 1.1 equiv.), in 15 mL $CH_2Cl_2$ was poured into the cold reaction mixture. The solution was allowed to stir overnight, at which point it had reached ambient temperature. The precipitate was removed by vacuum filtration, washing once with $Et_2O$ (20 mL). The filtrate was concentrated to give a crude oil. This was dissolved in pentane and added to a column loaded with 100 mL silica gel, packed with 1% $Et_2O$ in pentane, and eluted with the same. The product was isolated as a crystalline white solid. (8.1 g, 96% yield). This was used immediately in the next step:

The ester (5.0 g, 15.5. mmol, 1.0 equiv.) and *o*-NBSA (5.3 g, 23.2 mmol, 1.5 equiv.) were dissolved in acetonitrile (100 mL) and the solution cooled to 0 °C. DBU (5.2 g, 5.1 mL, 34.1 mmol, 2.2 equiv.) was added dropwise. The solution was stirred 4 hours and quenched by addition of saturate aqueous $NH_4Cl$ (50 mL) and water (20 mL). The mixture was extracted with $Et_2O$ (200 mL). The mixture was washed with water (100 mL) and brine (100 mL), and dried over $MgSO_4$. The solution was concentrated to give a crude red oil. This was purified by a short column, using 2% and then 4% $Et_2O$ in

pentane. The product was isolated as an orange solid. $^{1}$H NMR (600 MHz; $CDCl_3$) δ 7.47-7.40 (m, 4H), 4.91 (s, 2H), 1.32 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$ with 2-3 mg $Cr(acac)_3$) δ 163.7, 149.7, 126.2, 124.2, 121.4, 95.2, 73.9, 34.6, 31.4 (the resonance resulting from the diazo carbon was not detected); IR (film): 2961, 2904, 2868, 2088, 1712 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H-N_2]^+$ calcd for $C_{14}H_{16}O_2Cl_3$ 321.0210; found 321.0206;

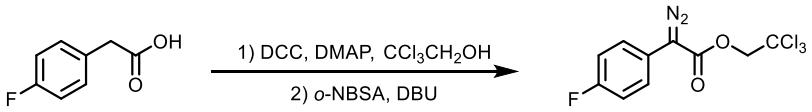



**4.47b**

**2,2,2-trichloroethyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate (4.47b):** A solution of 4-(trifluoromethyl)phenylacetic acid (10.0 g, 49 mmol, 1.0 equiv.), 2,2,2-trichloroethanol (8.8 g, 5.6 mL, 58.8 mmol, 1.2 equiv.) and DMAP (599 mg, 4.9 mmol, 0.1 equiv.) in $CH_2Cl_2$ (100 mL) was cooled to 0 °C in an ice/water bath. A solution of DCC (11.1 g, 53.9 mmol, 1.1 equiv.) in $CH_2Cl_2$ (25 mL) was poured into the cold reaction mixture. The solution was stirred overnight, at which point it had reached ambient temperature. The precipitate was filtered and washed with $Et_2O$. The filtrate was concentrated to give a crude oil, which was purified by column chromatography (2% $Et_2O$ in pentane), to give the product as a colorless oil (14.0 g, 85% yield). This was used immediately in the next step:

The ester from the previous step (5.0 g, 14.9 mmol, 1.0 equiv.) and *p*-ABSA (5.4 g, 22.4 mmol, 1.5 equiv.) were dissolved in acetonitrile (100 mL) and cooled to 0 °C. Then DBU (4.5 g, 4.4 mL, 29.8 mmol, 2.0 equiv.) was added dropwise. The solution was stirred 1.5 hours and quenched with saturated aqueous $NH_4Cl$ (75 mL) and water (20 mL)

and extracted with $Et_2O$ (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL) and dried over $MgSO_4$. The solution was concentrated to give a crude oil. This was purified by column chromatography (2% $Et_2O$ in pentane) to give the product as a yellow oil that solidified upon standing (2.0 g, 37% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 7.65 (d, 2H, *J* = 8.9 Hz), 7.63 (d, 2H, *J* = 8.9 Hz), 4.93 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$ with 2-3 mg $Cr(acac)_3$) δ 162.5, 129.2, 128 (q, *J* = 32.8 Hz), 125.9 (q, *J* = 3.5 Hz), 123.9 (q, *J* = 271.9), 123.5, 94.8, 73.9, 64.1; IR (neat): 2962, 2091, 1716, 1325 cm$^{-1}$; HRMS (ESI) *m*/*z*: $[2M+H-N_2]^+$ calcd for $C_{22}H_{13}O_4N_2Cl_6F_6$ 692.8905, found 692.8898;

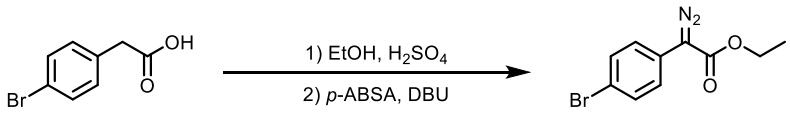



**4.47c**

**2,2,2-trichloroethyl 2-diazo-2-(4-fluorophenyl)acetate (4.47c):** A solution of 4-fluorophenylacetic acid (10.0 g, 64.9 mmol, 1.0 equiv.), 2,2,2-trichloroethanol (11.6 g, 7.5 mL, 77.9 mmol, 1.2 equiv.) and DMAP (793 mg, 6.5 mmol, 0.1 equiv.) in $CH_2Cl_2$ (150 mL) was cooled to 0 °C. A solution of DCC in $CH_2Cl_2$ (45 mL) was poured into the cold reaction mixture. The solution was stirred overnight, at which point it had reached ambient temperature. The precipitate was removed by filtration and washed with $Et_2O$. The filtrate was concentrated and purified by column chromatography (short silica plug, 5% $Et_2O$ in pentane). The product was isolated as a colorless oil (15.1 g, 82% yield). This was used immediately in the next step:

The ester from the previous step (5.0 g, 17.5 mmol, 1.0 equiv.) and *o*-NBSA (6.0 g, 26.3 mmol. 1.5 equiv.) were dissolved in acetonitrile (75 mL) and cooled to 0 °C. Then

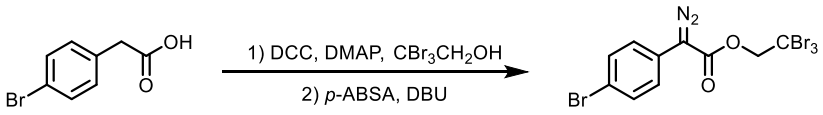
DBU (5.6 g, 5.5 mL, 38.5 mmol, 2.2 equiv.) was added dropwise. The solution was stirred for 2 hours and quenched with water (75 mL). The solution was extracted with pentane until the extracts were no longer yellow (required about 3 x 150 mL). These extracts were combined and poured directly onto a silica gel column and the pentane eluted with pressure until the solution reached the top of the silica. The column was then eluted with 1% $Et_2O$ in pentane. The yellow fractions were collected and concentrated (below room temperature) to give the product as a crystalline orange solid (5.0 g, 91% yield). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.50-7.43 (m, 2H), 7.15-7.08 (m, 2H), 4.90 (s, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$, with 2-3 mg of $Cr(acac)_3$) δ 163.4, 162.2 (d, $J$ = 247.1 Hz), 126.1, 120.4 (d, $J$ = 2.7 Hz), 116.3 (d, $J$ = 21.9 Hz), 95.1, 73.9 (The resonance resulting from the diazo carbon was not observed); IR (neat): 2954, 2093, 1690, 1507 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H-N_2]^+$ calcd for $C_{10}H_7O_2Cl_3F$ 282.9490; found 282.9487;




**S4.5**

**ethyl 2-(4-bromophenyl)-2-diazoacetate (S4.5):** The ethyl ester was prepared by stirring 4-bromophenylacetic acid with catalytic sulfuric acid in ethanol for 24 hours. The ester prepared in this manner (10.8 g, 44.4 mmol, 1.0 equiv.) and *p*-ABSA (16 g, 66.6 mmol, 1.5 equiv.) were dissolved in $CH_3CN$ (100 mL) and the solution cooled to room temperature. DBU (13.3 mL, 88.8 mmol, 2.0 equiv.) was added drop-wise. The reaction was stirred for 5 hours and quenched with aqueous $NH_4Cl$ (75 mL) and $H_2O$ (25 ml). The mixture was extracted with $Et_2O$ (150 mL). The organics were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by column

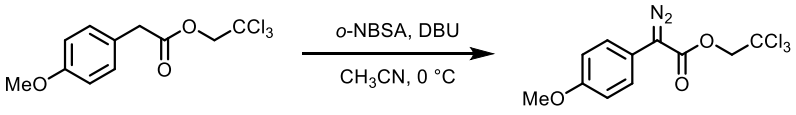
chromatography (5% $Et_2O$ in pentane) to give the diazo as an orange crystalline solid (11.2 g, 94% yield). The spectral data were consistent with those reported in the literature.[32]




**S4.6**

**2,2,2-tribromoethyl 2-(4-bromophenyl)-2-diazoacetate (S4.6):** 4-bromophenylacetic acid (10 g, 46.5 mmol, 1.0 equiv.), DMAP (567 mg, 4.65 mmol, 0.1 equiv.) and 2,2,2-tribromoethanol (15.8 g, 55.8 mmol, 1.2 equiv.) were dissolved in DCM (75 mL) and the solution cooled to 0 °C. A solution of DCC (10.5 g, 51.2 mmol, 1.1 equiv.) in DCM (25 mL) was poured into the reaction. The mixture was stirred overnight, after which time it had warmed to room temperature. The precipitate was removed by vacuum filtration, washing the solids with $Et_2O$. The filtrate was concentrated to give a crude white solid. This was dissolved in approximately 600 mL of boiling hexanes, and the remaining undissolved solid removed by filtration while the solution was hot. The hot filtrate was placed in an ice bath for 20 minutes, and then a freezer (-25 °C) for 2 hours. The crystals were collected by vacuum filtration, washing once with cold hexanes, and then dried under vacuum. (16.6 g, 74% yield). A portion of this ester product (3.6 g, 7.5 mmol, 1.0 equiv.), together with *o*-NBSA (2.6 g, 11.3 mmol, 1.5 equiv.) was suspended in acetonitrile (100 mL) and cooled to 0 °C. DBU (2.5 mL, 16.5 mmol, 2.2 equiv.) was added and the solution stirred for 1 hour. Reaction was quenched with saturated aqueous $NH_4Cl$ (100 ml) and extracted with $Et_2O$ (75 mL). The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. The crude mixture was purified by

column chromatography (1.5% $Et_2O$ in pentane), giving the diazo as an orange crystalline solid (1.9 g, 50% yield). $^1H$ NMR (600 MHz; $CDCl_3$) δ 7.54-7.51 (m, 2H), 7.41-7.38 (m, 2H), 5.09 (s, 2H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 162.8, 132.2, 125.5, 124.0, 119.9, 76.8, 35.8 (the resonance resulting from the diazo carbon was not detected); IR (neat): 2950, 2091, 1701, 1140 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H-N_2]^+$ calcd for $C_{10}H_7O_2Br_4$ 490.7123; found 490.7132;




**S4.7**

**2,2,2-trichloroethyl 2-diazo-2-(4-methoxyphenyl)acetate (S4.7):** Prepared by using *o*-NBSA and DBU similarly to **4.47c**. Characterization data: $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.38 (d, 2H, *J* = 8.7 Hz), 6.94 (d, 2H, *J* = 8.7 Hz), 4.88 (s, 2H), 3.08 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) 164.0, 158.6, 126.3, 116.2, 114.9, 95.3, 74.0, 55.6; IR (neat): 2953, 2935, 2090, 1690, 1234 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H-N_2]^+$ calcd for $C_{11}H_{10}O_3Cl_3$ 294.9690, found 294.9688;

### 4.6.2.2 General Procedures for C–H Functionalization Reactions and Measuring Site-Selectivity Ratios

For reactions with $Rh_2$(*S*-DOSP)$_4$, the solvent was 2,2-dimethylbutane. For reactions with $Rh_2$(*R*-BPCP)$_4$, the solvent was DCM.

A 10 mL, oven-dried round-bottomed flask, equipped with an egg shaped magnetic stir bar and a reflux condenser, was allowed to cool to room temperature under a stream of argon. The flask was charged with the catalyst (For DOSP – 1 mol %, 3.7 mg; For

BPCP – 0.5 mol %, 1.8 mg), the 4-substituted toluene substrate (0.6 mmol, 3.0 equiv.) and 1 mL of the appropriate solvent. This mixture was heated to reflux. Then the diazo (0.2 mmol, 1.0 equiv.) was dissolved in 2.5 mL of DCM and added slowly over 1.5 hours to the solution of catalyst and substrate at reflux. The reaction mixture was allowed to stir for 20-30 minutes at reflux before it was cooled to room temperature. The starting material was removed according to the following procedures:

For reactions conducted in 2,2-DMB with DOSP: once the reaction mixture had cooled to room temperature, it was directly transferred by pipet to a short (4-5 cm) silica gel column packed using hexanes. The column was flushed with hexanes (30-40 mL) to remove the excess substrate, and then the product collected by flushing the column with DCM (20 mL). The solvent was removed to give the crude material, free of the starting material.

For reactions conducted in DCM with BPCP: when the reaction mixture had cooled, the DCM was removed by rotary evaporation. The crude green oil was transferred using hexanes to a short (4-5 cm) silica gel column packed using hexanes. The column was flushed with hexanes (30-40 mL) to remove the excess substrate, and then the product was collected by flushing the column with DCM (20 mL). The solvent was removed to give the crude material, free from the excess starting material.

To measure the product ratios, the crude mixtures so obtained were analyzed by $^{1}H$ NMR using the following settings:

Instrument: 600 MHz INOVA

Number of scans: 32

Relaxation time: 3 or 10 seconds (essentially no difference in the measured ratio was observed)

The data was processed using MestReNova software, applying an auto-phase correction as well as a Whittaker Smoother baseline correction. The baseline was manually inspected. The ratios were measured by integration of the NMR peaks resulting from the indicated hydrogens in Figure 4.5.

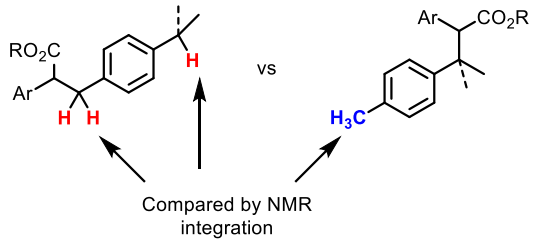
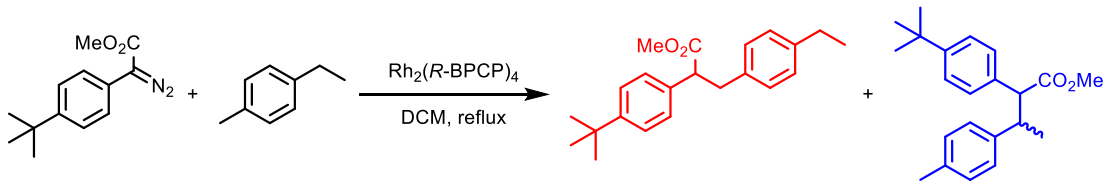
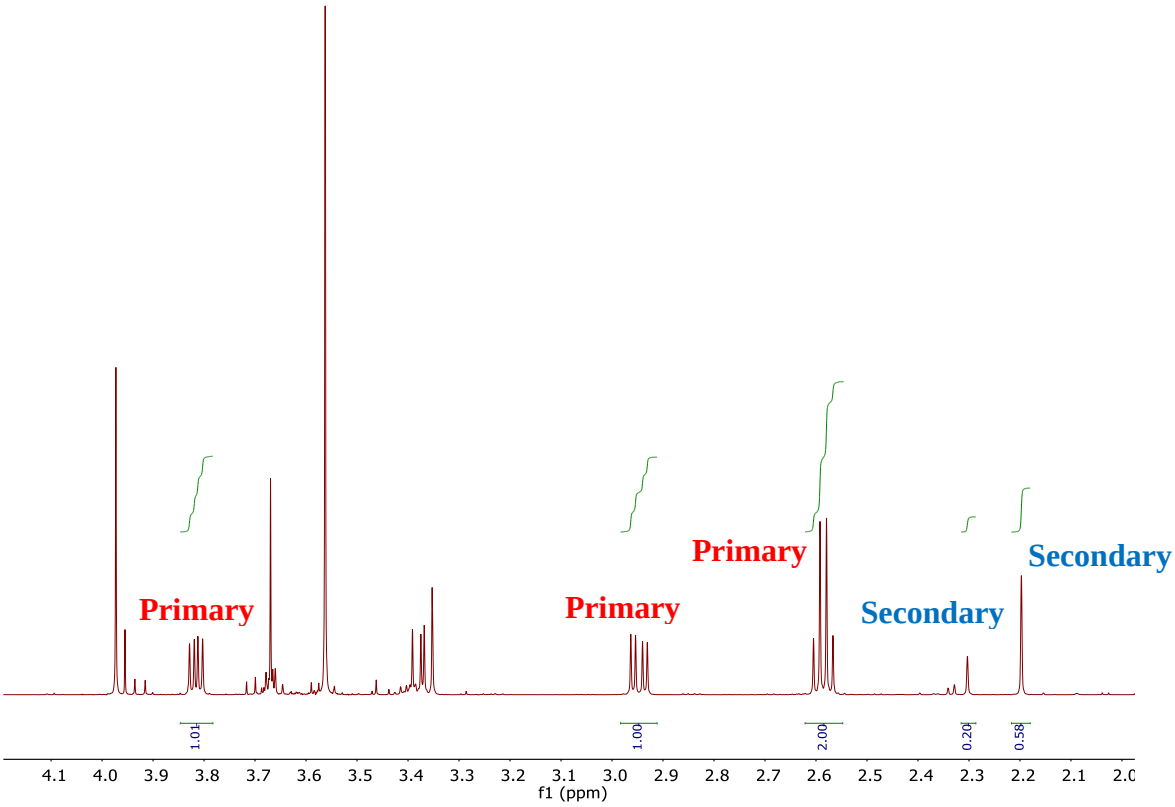


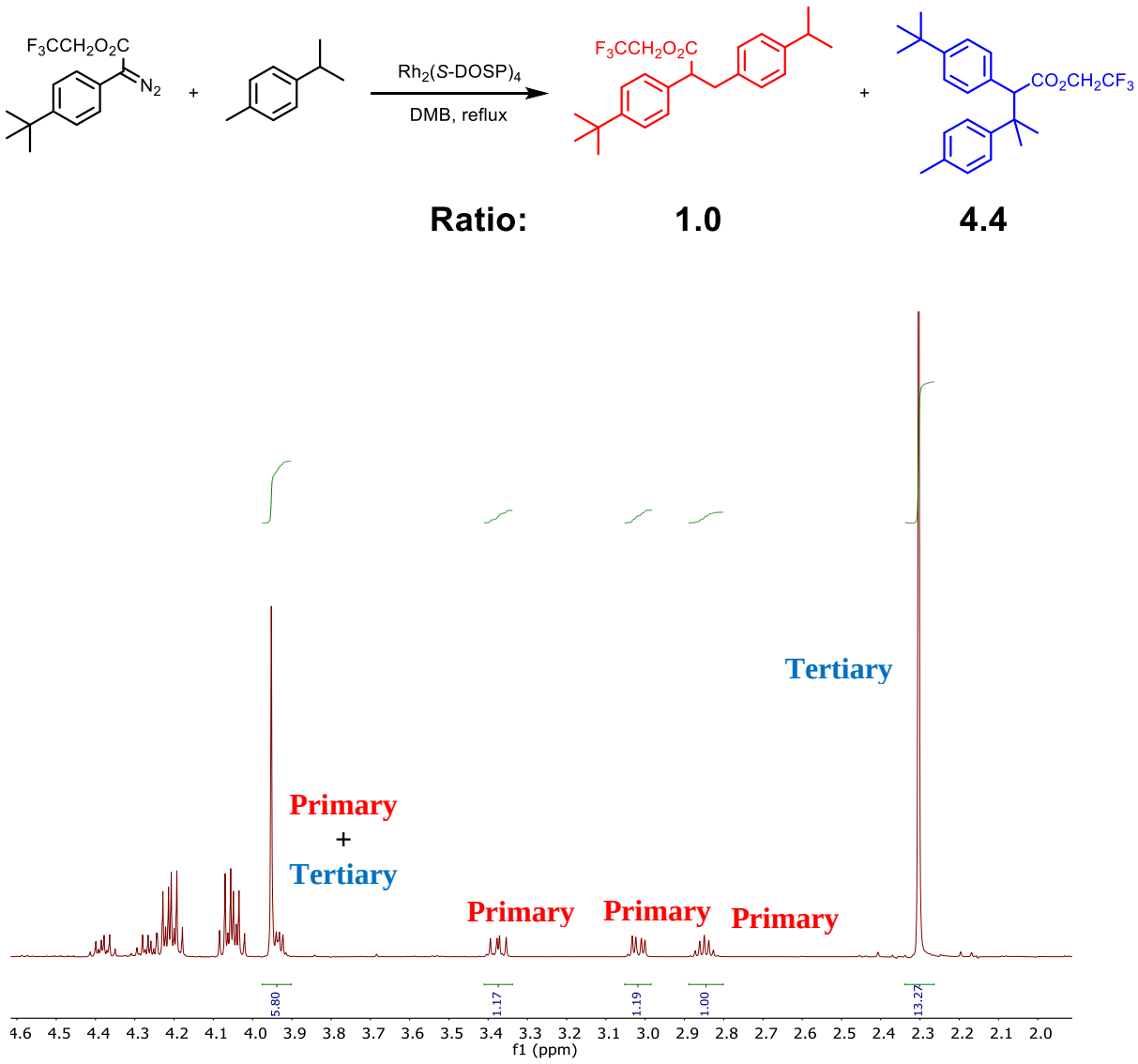

**Figure 4.5** Peaks used for NMR integration

A representative example of the key NMR peaks is shown below for both a reaction with 4-ethyltoluene and 4-isopropyltoluene.


MeO2C
N2
+
Rh2(R-BPCP)4
DCM, reflux
MeO2C
+
CO2Me

**Ratio: 3.8 1.0**


Primary
Primary
Primary
Secondary
Secondary
1.01
1.00
2.00
0.20
0.56
4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0
f1 (ppm)



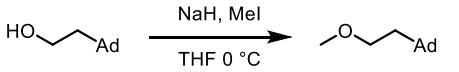

## 4.6.3 Functionalization of Methyl Ethers

### 4.6.3.1 Acquisition and Preparation of Substrates

4-ethyltoluene, butyl methyl ether (**4.43**), anhydrous *t*-butyl methyl ether (**4.41b**), methyl *t*-amyl ether (**4.41c**) and 4-fluoroanisole (**4.53**) were obtained from Sigma-Aldrich and used as received. Cyclopentyl methyl ether (**4.41a**) was obtained from TCI America

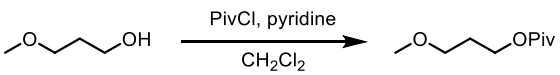
and stored over 4Å molecular sieves before use. All methyl ether substrates that were prepared were stored over 4Å molecular sieves before use.

### *Preparation of Methyl Ether Substrates*




**4.41d**
Ad = 1-adamantyl

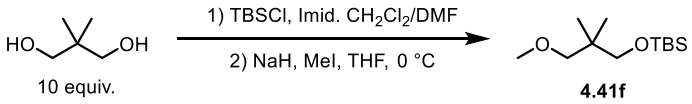
**1-(2-methoxyethyl)adamantane (4.41d):** To a 0 °C suspension of sodium hydride (60% in mineral oil, 800 mg, 20.0 mmol, 1.2 equiv.) in THF (50 mL) was added iodomethane (4.1 mL, 66.4 mmol, 4.0 equiv.), followed by dropwise addition of a solution of 1-adamantaneethanol (3.0 g, 16.6 mmol, 1.0 equiv.) in THF (10 mL). The mixture was stirred overnight, after which time the solution had warmed to room temperature. The reaction was carefully quenched by the addition of water (30 mL) and extracted with $Et_2O$ (50 mL). The organic layer was washed with saturated aqueous $NH_4Cl$ (25 mL) and brine (25 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified by column chromatography (5% $Et_2O$ in pentane) to give the product as a colorless oil (2.4 g, 75% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 3.42 (t, 2H, *J* = 7.5 Hz), 3.31 (s, 3H), 1.96-1.91 (m, 3H), 1.73-1.66 (m, 3H), 1.66-1.60 (m, 3H), 1.54-1.48 (m, 6H), 1.37 (t, 2H, *J* = 7.5 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 68.9, 58.7, 43.7, 42.9, 37.3, 31.9, 28.9; IR (neat): 2896, 2845, 2806, 1449 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{23}O$ 195.1743; found 195.1742;




**4.41e**

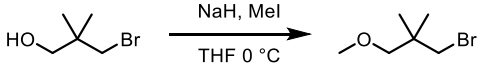
**3-methoxypropyl pivalate (4.41e):** To a solution of 3-methoxy-1-propanol (5.0 g, 55.5 mmol, 1.0 equiv.) in $CH_2Cl_2$ (150 mL) was added pyridine dropwise (18 mL, 222 mmol,

4.0 equiv.). Pivaloyl chloride (8.2 mL, 66.6 mmol, 1.2 equiv.) was added dropwise via syringe over 1 minute. The mixture was stirred overnight at room temperature. Water was added (100 mL). The organic layer was washed with water (100 mL), 0.5 M HCl (3x 75 mL), and brine (100 mL), and dried over $MgSO_4$. The solution was concentrated and purified by column chromatography (5% $Et_2O$ in pentane) to give a colorless oil (7.2 g, 74% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 4.15 (t, 2H, *J* = 6.4 Hz), 3.45 (t, 2H, *J* = 6.4 Hz), 3.34 (s, 3H), 1.90 (p, 2H, *J* = 6.4 Hz), 1.20 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 178.6, 69.3, 61.6, 58.8, 38.9, 29.1, 27.3; IR (neat): 2972, 2874, 1728, 1117 cm$^{-1}$; HRMS (NSI) *m/z:* $[M+H]^+$ calcd for $C_9H_{19}O_3$ 175.1329; found 175.1326;




***tert*-butyl(3-methoxy-2,2-dimethylpropoxy)dimethylsilane (4.41f):** 2,2-dimethyl-1,3-propanediol (41.7 g, 400 mmol, 10 equiv.) and *tert*-butyldimethylchlorosilane (6.0 g, 40 mmol, 1.0 equiv.) were dissolved in $CH_2Cl_2$/DMF (1:1 400 mL). Imidazole (2.7 g, 40 mmol, 1.0 equiv.) was added in one portion. The solution was stirred at room temperature overnight. The solution was quenched with water (150 mL) and saturated aqueous $NH_4Cl$ (100 mL). The organic layer was then washed with water (5x 100 mL) and brine (150 mL). The solution was dried over $MgSO_4$ and concentrated. The crude mixture was purified by passing through a silica gel plug, eluting with 10% EtOAc in hexanes. The mono-protected TBS alcohol was isolated as a colorless oil (7.8 g, 90% yield) and used immediately in the next step.

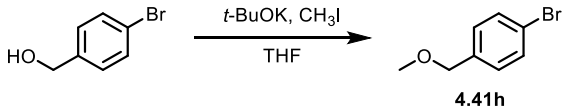
Sodium hydride (60% in mineral oil, 2.1 g, 53.6 mmol, 1.5 equiv.) was suspended in THF (75 mL) and the solution cooled to 0 °C. Iodomethane (6.7 mL, 107 mmol, 3.0 equiv.) was added via syringe. The product from the previous step (7.8 g, 35.7 mmol, 1.0 equiv.), as a solution in THF (10 mL), was added dropwise. The reaction was allowed to stir overnight, over which time it had warmed to room temperature. The reaction was quenched with water (60 mL) and extracted with $Et_2O$ (75 mL). The organic layer was washed with water (50 mL) and brine (50 mL), and dried over $MgSO_4$. The crude mixture was distilled using a Kugelrohr distillation apparatus (1 mmHg, 100 °C) to give the product as a colorless oil (6.7 g, 81% yield for second step). $^1$H NMR (400 MHz; $CDCl_3$) δ 3.33-3.29 (m, 5H), 3.11 (s, 2H), 0.89 (s, 9H), 0.84 (s, 6H), -0.02 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 79, 68.8, 59.5, 37.1, 26.1, 21.9, 18.5, -5.3; IR (neat): 2955, 2929, 2857, 1092 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{29}O_2Si$ 233.1931; found 233.1926;




**4.41g**

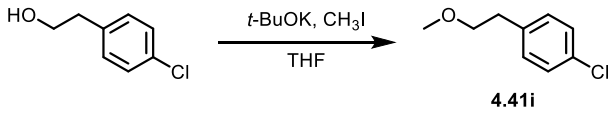
**1-bromo-3-methoxy-2,2-dimethylpropane (4.41g):** Sodium hydride (60% in mineral oil, 1.1g, 27.3 mmol, 1.2 equiv.) was suspended in THF (75 mL) and cooled to 0 °C. Iodomethane (5.7 mL, 91.2 mmol, 4.0 equiv.) was added via syringe. 3-bromo-2,2-dimethyl-1-propanol (3.8 g, 22.8 mmol, 1.0 equiv.), was added dropwise via syringe (which was rinsed with 10 mL THF). The mixture was stirred overnight, after which time it had warmed to room temperature. The reaction was quenched with saturated $NH_4Cl$ (50 mL) and extracted with $Et_2O$ (75 mL). The organic layer was washed with

water (50 mL) and brine (50 mL) and dried over $MgSO_4$. The filtrate was concentrated <u>carefully</u> on the rotovap using a vacuum only strong enough to remove the THF. *This was necessary to avoid evaporation of the volatile product*. The crude mixture was then fractionally distilled at ambient pressure, gradually increasing the temperature of the oil bath. The product distilled at 100-110 °C (oil bath ~180 °C) and was collected as a colorless oil (2.4 g, 59% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 3.37 (s, 2H), 3.35 (s, 3H), 3.19 (s, 2H), 1.02 (s, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 79.1, 59.5, 43.7, 36.3, 23.6; IR (neat): 2962, 2927, 2874, 2818 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_6H_{14}OBr$ 181.0223; found 181.0218;



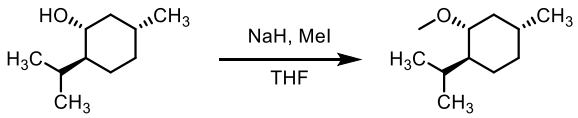

**4.41h**

**1-bromo-4-(methoxymethyl)benzene (4.41h):** Prepared using a method analogous to **4.41i** (see below) with 4-bromobenzyl alcohol (5.0 g, 26.7 mmol, 1.0 equiv.) in THF (50 mL), potassium *tert*-butoxide (4.5 g, 40.1 mmol, 1.5 equiv.), and iodomethane (5.0 mL, 80.1 mmol, 3.0 equiv.). The crude residue was distilled with a Kugelrohr distillation apparatus (0.8 mmHg, 80 °C air bath) to give the product as a colorless oil (4.7 g, 87% yield). The spectral data matched those reported previously.[33] $^1$H NMR (600 MHz; $CDCl_3$) δ 7.49-7.45 (m, 2H), 7.21 (d, 2H, $J$ = 8.4 Hz), 4.40 (s, 2H), 3.38 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 137.4, 131.7, 129.5, 121.7, 74.1, 58.4;




4.41i

**Methyl 4-chlorophenethyl ether (4.41i):** To a solution of 4-chlorophenethyl alcohol (5.0 g, 31.9 mmol, 1.0 equiv.) in THF (70 mL) was added solid potassium *tert*-butoxide (5.4 g, 47.9 mmol, 1.5 equiv.) in one portion. The mixture was stirred 15 minutes and iodomethane (6.0 mL, 95.7 mmol, 3.0 equiv.) added via syringe. The solution was stirred overnight. The reaction mixture was quenched with $H_2O$ (75 mL) and extracted with $Et_2O$ (75 mL). The organic layer was washed with $H_2O$ (2 x 50 mL) and brine (50 mL), and dried over $MgSO_4$. The solution was treated with decolorizing carbon and filtered. The solvent was removed and the crude residue distilled with a Kugelrohr distillation apparatus (0.5 mmHg, 95 °C air bath), to give the product as a colorless oil (4.6 g, 85% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 7.25 (d, 2H, *J* = 8.3 Hz), 7.15 (d, 2H, *J* = 8.3 Hz), 3.57 (t, 2H, *J* = 6.9 Hz), 3.34 (s, 3H), 2.84 (t, 2H, *J* = 6.9 Hz); +C NMR (100 MHz, $CDCl_3$) δ 137.7, 132.1, 130.4, 128.6, 73.4, 58.9, 35.7; IR (neat): 2924, 2869, 2825, 1491 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_9H_{12}OCl$ 171.0571; found 171.0568;



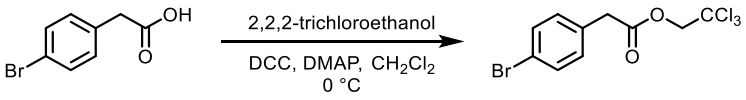

4.51

**(1*S*,2*R*,4*R*)-1-isopropyl-2-methoxy-4-methylcyclohexane (4.51):** Prepared in a manner analogous to compound **4.41d**. $[\alpha]_D^{20}$: -63.7 (c. 1.45, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 3.34 (s, 3H), 2.93 (app td, 1H, *J* = 10.6, 4.2 Hz), 2.22-2.09 (m, 2H), 1.68-1.57 (m, 2H), 1.40-1.30 (m, 1H), 1.19 (app ddt, 1H, *J* = 12.5, 10.3, 3.1 Hz), 1.02-0.76 (m, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 80.6, 56.1, 48.5, 39.9, 34.8, 31.7, 25.9, 23.7, 22.6,

21.1, 16.5; IR (neat): 2953, 2919, 2868, 2817, 1096 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{23}O$ 171.1743; found 171.1742;

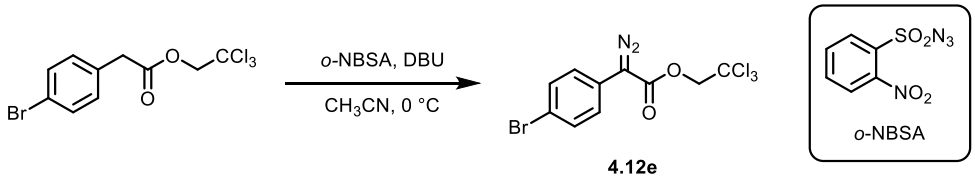
### 4.6.3.2 Preparation of Diazo Compounds

Yields for diazo compounds containing the 2,2,2-trichloroethyl ester were higher when prepared using *o*-nitrobenzenesulfonyl azide as the diazo transfer reagent (CAUTION! POTENTIALLY EXPLOSIVE! USE PROPER PRECAUTIONS FOR HANDLING THIS AZIDE.). This reagent was prepared according to a literature protocol.[31] Diazo compounds with methyl esters were prepared using the standard azide transfer reagent *p*-acetamidobenzenesulfonyl azide (*p*-ABSA).



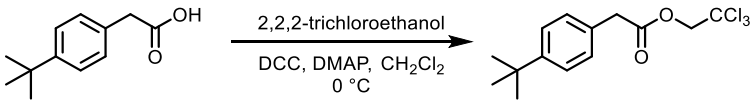

**2,2,2-trichloroethyl 2-(4-bromophenyl)acetate:** 4-bromophenylacetic acid (30.0 g, 140 mmol, 1.0 equiv.), DMAP (1.7 g, 14 mmol, 0.1 equiv.), and 2,2,2-trichloroethanol (25.1 g, 16 mL, 168 mmol, 1.2 equiv.) were dissolved in 300 mL $CH_2Cl_2$ and the solution cooled to 0 °C. A solution of DCC (31.7 g, 153 mmol, 1.1 equiv.) in $CH_2Cl_2$ (150 mL) was poured slowly into the cold reaction mixture. The reaction mixture was allowed to stir overnight, at which point it had warmed to room temperature. The solids were removed by suction filtration, and washed with $Et_2O$ (100 mL). The filtrate was concentrated to give a yellow oil that solidified under high vacuum. The solid mass was broken up with a spatula and 150 mL hexanes was added to the flask. The mixture was heated until all but a small amount of white powder remained undissolved. The hot

solution was filtered and cooled to room temperature before it was placed in a freezer (-25 °C) overnight. The crystals that had formed were collected by vacuum filtration, washing once with hexanes (100 mL). The product was dried by suction on the frit used for filtration to give a white crystalline solid (38.8 g, 80% yield). This was used without further purification in the diazo transfer reaction.

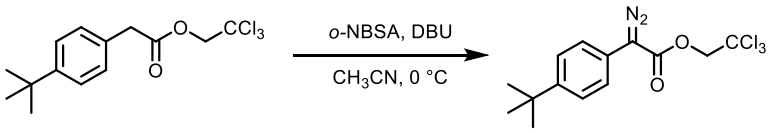



**2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (4.12e):** The ester from the previous step (10.0 g, 28.9 mmol, 1.0 equiv.), together with *o*-NBSA (9.9 g, 43.4 mmol, 1.5 equiv.), were dissolved in acetonitrile (100 mL) and the solution cooled to 0 °C. DBU (9.5 mL, 63.6 mmol, 2.2 equiv.) was added dropwise via syringe. The solution was stirred for 1 hour at 0 °C before it was quenched with saturated aqueous $NH_4Cl$ (100 mL). The mixture was extracted with $Et_2O$ (200 mL). The organic layer was washed with $H_2O$ (100 mL) and brine (100 mL), dried over $MgSO_4$ and filtered. To the filtrate was added 50 g of silica gel and the solvent removed *in vacuo*. The dry silica was transferred to a column (containing 500 mL silica gel, packed with 2% $Et_2O$ in pentane) using the same solvent. The column was eluted with 2% $Et_2O$ in pentane, and the orange fractions were collected and combined. The solvent was removed on a rotovap below room temperature (keeping the flask out of the water bath), giving the product as an orange crystalline solid (9.3 g, 86% yield). $^1H$ NMR (400 MHz; $CDCl_3$) δ 7.57-7.51 (m, 2H), 7.42-7.36 (m, 2H), 4.92 (s, 2H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 163.1, 132.4, 125.6,

124, 120.1, 95.1, 74.1 (t, $J$ = 16.4 Hz) (note: the resonance resulting from the diazo carbon was not observed); IR (film): 2953, 2089, 1709, 1490 $cm^{-1}$; HRMS (NSI) *m/z*: $[M]^+$ calcd for $C_{10}H_6O_2N_2BrCl_3$ 369.8673; found 369.868;



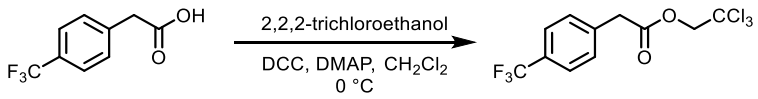

**2,2,2-trichloroethyl 2-(4-(*tert*-butyl)phenyl)acetate:** A solution of 4-*tert*-butylphenylacetic acid (5.0 g, 26.0 mmol, 1.0 equiv.), 2,2,2-trichloroethanol (4.6 g, 3.0 mL, 31.2 mmol, 1.2 equiv.) and DMAP (317 mg, 2.6 mmol, 0.1 equiv.), in 50 mL $CH_2Cl_2$ was cooled to 0 °C in an ice/water bath. Then DCC (5.9 g, 28.6 mmol, 1.1 equiv.), in 15 mL $CH_2Cl_2$ was poured into the cold reaction mixture. The solution was allowed to stir overnight, at which point it had reached ambient temperature. The precipitate was removed by vacuum filtration, washing once with $Et_2O$ (20 mL). The filtrate was concentrated to give a crude oil. This was dissolved in pentane and added to a column loaded with 100 mL silica gel, packed with 1% $Et_2O$ in pentane, and eluted with the same. The product was isolated as a crystalline white solid. (8.1 g, 96% yield). This was used immediately in the next step:




**4.47a**

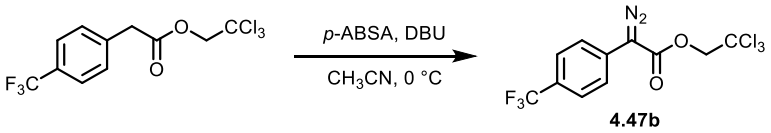
**2,2,2-trichloroethyl 2-(4-(*tert*-butyl)phenyl)-2-diazoacetate (4.47a):** The ester (5.0 g, 15.5. mmol, 1.0 equiv.) and o-NBSA (5.3 g, 23.2 mmol, 1.5 equiv.) were dissolved in acetonitrile (100 mL) and the solution cooled to 0 °C. DBU (5.2 g, 5.1 mL, 34.1 mmol, 2.2 equiv.) was added dropwise. The solution was stirred 4 hours and quenched by

addition of saturate aqueous $NH_4Cl$ (50 mL) and water (20 mL). The mixture was extracted with $Et_2O$ (200 mL). The mixture was washed with water (100 mL) and brine (100 mL), and dried over $MgSO_4$. The solution was concentrated to give a crude red oil. This was purified by a short column, using 2% and then 4% $Et_2O$ in pentane. The product was isolated as an orange solid. $^1H$ NMR (600 MHz; $CDCl_3$) δ 7.47-7.40 (m, 4H), 4.91 (s, 2H), 1.32 (s, 9H); $^{13}C$ NMR (150 MHz, $CDCl_3$ with 2-3 mg $Cr(acac)_3$) δ 163.7, 149.7, 126.2, 124.2, 121.4, 95.2, 73.9, 34.6, 31.4 (the resonance resulting from the diazo carbon was not detected); IR (film): 2961, 2904, 2868, 2088, 1712 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H-N_2]^+$ calcd for $C_{14}H_{16}O_2Cl_3$ 321.0210; found 321.0206;

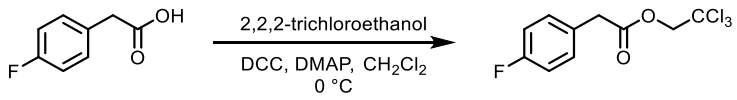



**2,2,2-trichloroethyl 2-(4-(trifluoromethyl)phenyl)acetate:** A solution of 4-(trifluoromethyl)phenylacetic acid (10.0 g, 49 mmol, 1.0 equiv.), 2,2,2-trichloroethanol (8.8 g, 5.6 mL, 58.8 mmol, 1.2 equiv.) and DMAP (599 mg, 4.9 mmol, 0.1 equiv.) in $CH_2Cl_2$ (100 mL) was cooled to 0 °C in an ice/water bath. A solution of DCC (11.1 g, 53.9 mmol, 1.1 equiv.) in $CH_2Cl_2$ (25 mL) was poured into the cold reaction mixture. The solution was stirred overnight, at which point it had reached ambient temperature. The precipitate was filtered and washed with $Et_2O$. The filtrate was concentrated to give a crude oil, which was purified by column chromatography (2% $Et_2O$ in pentane), to give the product as a colorless oil (14.0 g, 85% yield). This was used immediately in the next step:

(note: this diazo was prepared using *p*-ABSA, though it is expected the yield would be higher by using *o*-NBSA, as mentioned above)

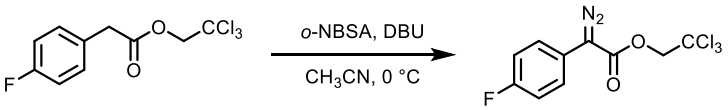



**2,2,2-trichloroethyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate (4.47b):** The ester from the previous step (5.0 g, 14.9 mmol, 1.0 equiv.) and *p*-acetamidobenzenesulfonyl azide [*p*-ABSA] (5.4 g, 22.4 mmol, 1.5 equiv.) were dissolved in acetonitrile (100 mL) and cooled to 0 °C. Then DBU (4.5 g, 4.4 mL, 29.8 mmol, 2.0 equiv.) was added dropwise. The solution was stirred 1.5 hours and quenched with saturated aqueous $NH_4Cl$ (75 mL) and water (20 mL) and extracted with $Et_2O$ (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL) and dried over $MgSO_4$. The solution was concentrated to give a crude oil. This was purified by column chromatography (2% $Et_2O$ in pentane) to give the product as a yellow oil that solidified upon standing (2.0 g, 37% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 7.65 (d, 2H, *J* = 8.9 Hz), 7.63 (d, 2H, *J* = 8.9 Hz), 4.93 (s, 2H); 13C NMR (100 MHz, $CDCl_3$ with 2-3 mg $Cr(acac)_3$) δ 162.5, 129.2, 128 (q, *J* = 32.8 Hz), 125.9 (q, *J* = 3.5 Hz), 123.9 (q, *J* = 271.9), 123.5, 94.8, 73.9, 64.1; IR (neat): 2962, 2091, 1716, 1325 cm$^{-1}$; HRMS (ESI) *m*/*z*: $[2M+H-N_2]^+$ calcd for $C_{22}H_{13}O_4N_2Cl_6F_6$ 692.8905, found 692.8898;




**2,2,2-trichloroethyl 2-(4-fluorophenyl)acetate:** A solution of 4-fluorophenylacetic acid (10.0 g, 64.9 mmol, 1.0 equiv.), 2,2,2-trichloroethanol (11.6 g, 7.5 mL, 77.9 mmol, 1.2 equiv.) and DMAP (793 mg, 6.5 mmol, 0.1 equiv.) in $CH_2Cl_2$ (150 mL) was cooled to 0

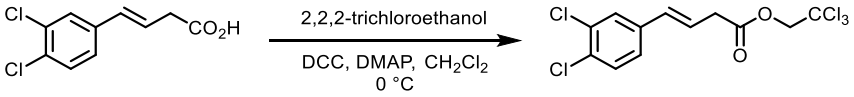
°C. A solution of DCC in $CH_2Cl_2$ (45 mL) was poured into the cold reaction mixture. The solution was stirred overnight, at which point it had reached ambient temperature. The precipitate was removed by filtration and washed with $Et_2O$. The filtrate was concentrated and purified by column chromatography (short silica plug, 5% $Et_2O$ in pentane). The product was isolated as a colorless oil (15.1 g, 82% yield). This was used immediately in the next step:




**4.47c**

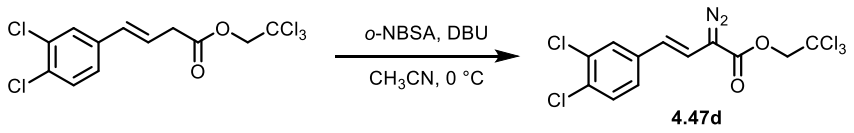
**2,2,2-trichloroethyl 2-diazo-2-(4-fluorophenyl)acetate (4.47c):** The ester from the previous step (5.0 g, 17.5 mmol, 1.0 equiv.) and *o*-NBSA (6.0 g, 26.3 mmol. 1.5 equiv.) were dissolved in acetonitrile (75 mL) and cooled to 0 °C. Then DBU (5.6 g, 5.5 mL, 38.5 mmol, 2.2 equiv.) was added dropwise. The solution was stirred for 2 hours and quenched with water (75 mL). The solution was extracted with pentane until the extracts were no longer yellow (required about 3 x 150 mL). These extracts were combined and poured directly onto a silica gel column and the pentane eluted with pressure until the solution reached the top of the silica. The column was then eluted with 1% $Et_2O$ in pentane. The yellow fractions were collected and concentrated (below room temperature) to give the product as a crystalline orange solid (5.0 g, 91% yield). $^1$H NMR (400 MHz; $CDCl_3$) δ 7.50-7.43 (m, 2H), 7.15-7.08 (m, 2H), 4.90 (s, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$, with 2-3 mg of $Cr(acac)_3$) δ 163.4, 162.2 (d, $J$ = 247.1 Hz), 126.1, 120.4 (d, $J$ = 2.7 Hz), 116.3 (d, $J$ = 21.9 Hz), 95.1, 73.9 (The resonance resulting from the diazo

carbon was not observed); IR (neat): 2954, 2093, 1690, 1507 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H-N_2]^+$ calcd for $C_{10}H_7O_2Cl_3F$ 282.9490; found 282.9487;



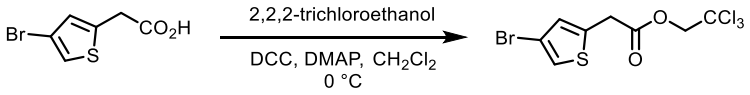

(*E*)-4-(3,4-dichlorophenyl)-3-butenoic acid was prepared according to a literature procedure (the first step in a three-step sequence for preparing a related diazo).[34]

**2,2,2-trichloroethyl (*E*)-4-(3,4-dichlorophenyl)but-3-enoate:** A solution of (*E*)-3,4-dichlorophenyl-3-butenoic acid (2.6 g, 11.3 mmol 1.0 equiv.), 2,2,2-trichloroethanol (2.0 g, 1.3 mL, 13.6 mmol, 1.2 equiv.) and DMAP (138 mg, 1.1 mmol, 0.1 equiv.) in $CH_2Cl_2$ (25 mL) was cooled to 0 °C. A solution of DCC in $CH_2Cl_2$ (8 mL) was poured into the cold reaction mixture. The solution was stirred overnight, at which point it had reached ambient temperature. The precipitate was removed by filtration and washed with $Et_2O$. The filtrate was concentrated and purified by column chromatography (2% $Et_2O$ in pentane). The product was isolated as a yellow oil that solidified on standing (3.9 g, 95% yield). This was used immediately in the next step:

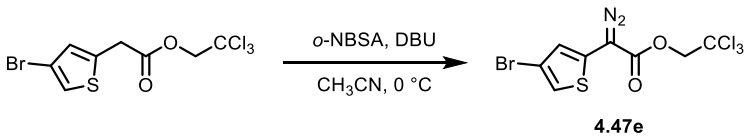



**2,2,2-trichloroethyl (*E*)-2-diazo-4-(3,4-dichlorophenyl)but-3-enoate (4.47d):** The ester from the previous step (3.9 g, 10.8 mmol, 1.0 equiv.) and *o*-NBSA (3.7 g, 16.2 mmol, 1.5 equiv.) were dissolved in acetonitrile (100 mL) and the solution cooled to 0 °C. DBU (3.6 g, 3.6 mL, 23.8 mmol, 2.2 equiv.) was added dropwise. The solution was stirred for 1 hour and quenched by addition of saturate aqueous $NH_4Cl$ (25 mL) and water (10 mL).

The mixture was extracted with $Et_2O$ (50 mL). The mixture was washed with water (100 mL) and brine (100 mL), and dried over $MgSO_4$. The solution was concentrated to give a crude red solid. This solid was transferred to a silica gel column using pentane (required ~ 500 mL) and eluted with 2% $Et_2O$ in pentane. The red/orange fractions were combined and concentrated (below room temperature) to give the product as a crystalline red solid (2.4 g, 57% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 7.43 (d, 1H, *J* = 1.9 Hz), 7.38 (d, 1H, *J* = 8.4 Hz), 7.18 (dd, 1H, *J* = 8.4, 1.9 Hz), 6.49 (d, 1H, *J* = 16.3 Hz), 6.20 (d, 1H, *J* = 16.3 Hz), 4.90 (s, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$, with 2-3 mg $Cr(acac)_3$) δ 163.0, 136.7, 133.0, 131.0, 130.7, 127.6, 125.0, 121.4, 112.9, 94.9, 74.2; IR (neat): 3058, 2954, 2083, 1708 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_8N_2O_2Cl_5$ 386.9023; found 386.9035;

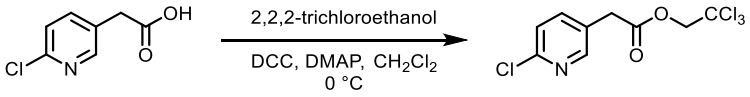



**2,2,2-trichloroethyl 2-(4-bromothiophene)acetate:** A solution of 4-bromothiophene-2-acetic acid (5.0 g, 22.6 mmol, 1.0 equiv.), 2,2,2-trichloroethanol (4.0 g, 2.6 mL, 27.1 mmol, 1.2 equiv.) and DMAP (281 mg, 2.3 mmol, 0.1 equiv.) in $CH_2Cl_2$ (50 mL) was cooled to 0 °C in an ice/water bath. Then DCC (5.1 g, 24.9 mmol, 1.1 equiv.) in $CH_2Cl_2$ (15 mL) was poured into the cold reaction mixture. The solution was stirred overnight, over which time it had warmed to room temperature. The precipitate was removed by vacuum filtration, and washed with $Et_2O$ (10 mL). The filtrate was concentrated to give a crude brown oil, and purified by column chromatography (3% $Et_2O$ in pentane), to give the product as a light yellow oil (7.8 g, 98% yield). This was used immediately in the next step:



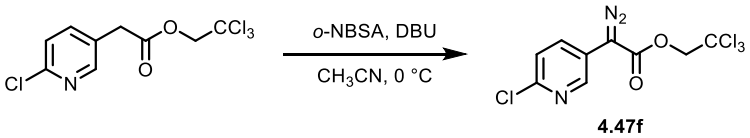

**4.47e**

**2,2,2-trichloroethyl 2-(4-bromothiophen-2-yl)-2-diazoacetate (4.47e):** The ester from the previous step (2.4 g, 6.8 mmol, 1.0 equiv.) and *o*-NBSA (2.3 g, 10.2 mmol. 1.5 equiv.) were dissolved in acetonitrile (25 mL) and cooled to 0 °C. Then DBU (2.3 g, 2.2 mL, 15.0 mmol, 2.2 equiv.) was added dropwise. The solution was stirred for 1 hour and quenched with saturated aqueous $NH_4Cl$ (15 mL) and water (5 mL). The solution was extracted with pentane (3 x 150 mL). These extracts were combined and concentrated until they had been reduced by about ½. This concentrated solution was loaded onto a silica gel column. The column was then eluted with 1% $Et_2O$ in pentane. The yellow fractions were collected and concentrated to give the product as a red/orange solid (1.8 g, 69% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 7.23 (d, 1H, $J$ = 1.4 Hz), 6.79 (d, 1H, $J$ = 1.4 Hz), 4.91 (s, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 126.8, 123.1, 110.0, 94.8, 74.4 (the resonances from the diazo and carbonyl carbons could not be detected, though their presence was confirmed by IR); IR (film): 3111, 2954, 2092, 1704, 1125 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_8H_5N_2O_2SCl_3Br$ 376.8315; found 376.8317;



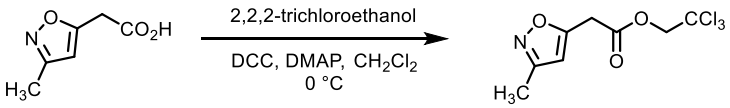

**2,2,2-trichloroethyl 2-(6-chloropyridin-3-yl)acetate:** A solution of 6-chloropyridine-3-acetic acid (5.0 g, 29.1 mmol 1.0 equiv.), 2,2,2-trichloroethanol (5.2 g, 3.3 mL, 34.9 mmol, 1.2 equiv.) and DMAP (355 mg, 32.0 mmol, 0.1 equiv.) in $CH_2Cl_2$ (75 mL) and

DMF (30 mL) was cooled to 0 °C. A solution of DCC in $CH_2Cl_2$ (25 mL) was poured into the cold reaction mixture. The solution was stirred overnight, at which point it had reached ambient temperature. The precipitate was removed by vacuum filtration and washed with $Et_2O$. The filtrate was washed with water (50 mL) and brine (50 mL), and dried over $MgSO_4$. The solution was concentrated and purified by column chromatography (4:1 hexanes:EtOAc). The product was isolated as a colorless oil (8.5 g, 97% yield). This was used immediately in the next step.

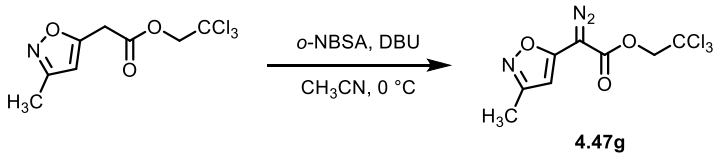



**4.47f**

**2,2,2-trichloroethyl 2-(6-chloropyridin-3-yl)-2-diazoacetate (4.47f):** The ester from the previous step (5.0 g, 16.5 mmol, 1.0 equiv.) and *o*-NBSA (5.7 g, 24.8 mmol, 1.5 equiv.) were dissolved in acetonitrile (75 mL) and the solution cooled to 0 °C. DBU (5.5 g, 5.4 mL, 36.3 mmol, 2.2 equiv.) was added dropwise. The solution was stirred for 2 hours and quenched by addition of saturate aqueous $NH_4Cl$ (50 mL) and water (15 mL). The mixture was extracted with $Et_2O$ (2 x 50 mL). The organics were washed with brine (75 mL) and dried over $MgSO_4$. The solution was concentrated and purified by column chromatography (10% $Et_2O$ in pentane) to give the product as an orange solid (4.2 g, 78% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 8.49 (d, 1H, $J$ = 2.6 Hz), 7.86 (dd, 1H, $J$ = 8.5, 2.6 Hz), 7.38 (d, 1H, $J$ = 8.5 Hz), 4.93 (s, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$, with 2-3 mg $Cr(acac)_3$) δ 162.6, 149.0, 144.6, 134.0, 124.5, 121.1, 94.8, 74.1 (the resonance resulting from the diazo carbon was not detected); IR (neat): 2962, 2106, 1695, 1468 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_9H_6N_3O_2Cl_4$ 327.9209; found 327.9205;



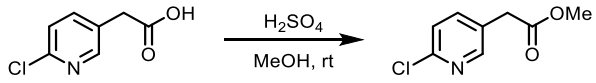

**2,2,2-trichloroethyl 2-(3-methylisoxazol-5-yl)acetate:** A solution of 3-methylisoxazole-5-acetic acid (5.1 g, 36.1 mmol 1.0 equiv.), 2,2,2-trichloroethanol (6.5 g, 4.1 mL, 43.3 mmol, 1.2 equiv.) and DMAP (439 mg, 3.6 mmol, 0.1 equiv.) in $CH_2Cl_2$ (75 mL) was cooled to 0 °C. A solution of DCC in $CH_2Cl_2$ (15 mL) was poured into the cold reaction mixture. The solution was stirred overnight, at which point it had reached ambient temperature. The precipitate was removed by vacuum filtration and washed with $Et_2O$. The filtrate was concentrated and purified by column chromatography (4:1 hexanes:EtOAc). The product was isolated as a colorless oil (9.5 g, 97% yield). This was used immediately in the next step:



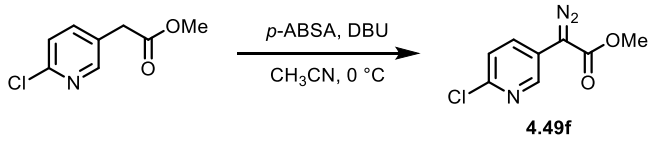

**4.47g**

**2,2,2-trichloroethyl 2-diazo-2-(3-methylisoxazol-5-yl)acetate (4.47g):** The ester from the previous step (4.0 g, 14.7 mmol, 1.0 equiv.) and *o*-NBSA (5.0 g, 22.1 mmol, 1.5 equiv.) were dissolved in acetonitrile (50 mL) and the solution cooled to 0 °C. DBU (4.9 g, 4.8 mL, 32.3 mmol, 2.2 equiv.) was added dropwise. The solution was stirred for 1 hour and quenched by addition of saturate aqueous $NH_4Cl$ (40 mL) and water (15 mL). The mixture was extracted with $Et_2O$ (60 mL). The organics were washed with water (50 mL) and brine (50 mL) and dried over $MgSO_4$. The solution was concentrated and purified by column chromatography (4:1 hexanes:EtOAc) to give the product as an

orange solid (3.3 g, 77% yield). $^{1}$H NMR (600 MHz; $CDCl_3$) δ 6.42 (s, 1H), 4.92 (s, 2H), 2.31 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 161.0, 154.9, 120.1, 94.6, 74.4, 11.5 (the resonance resulting from the diazo carbon could not be detected); IR (film): 2958, 2108, 1715, 1598 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_8H_7N_3O_3Cl_3$ 297.9548; found 297.9542;




**methyl 2-(6-chloropyridin-3-yl)acetate:** Prepared by stirring 6-chloropyridine-3-acetic acid in methanol with 6 drops of sulfuric acid overnight. Workup consisted of quenching with saturated aqueous sodium bicarbonate and extracting with $Et_2O$. This gave the methyl ester sufficiently pure for the diazo transfer:




**4.49f**

**methyl 2-(6-chloropyridin-3-yl)-2-diazoacetate (4.49f):** The methyl ester (4.0 g, 21.6 mmol, 1.0 equiv.) and *p*-ABSA (7.8 g, 32.3 mmol, 1.5 equiv.) were dissolved in acetonitrile (100 mL) and the solution cooled to 0 °C. DBU (6.6 g, 6.5 mL, 43.2 mmol, 2.0 equiv.) was added dropwise. The solution was stirred overnight and quenched by addition of saturated aqueous $NH_4Cl$ (75 mL) and water (25 mL). The mixture was extracted with $Et_2O$ (150 mL). The organics were washed with brine (75 mL) and dried over $MgSO_4$. The solution was concentrated and purified by column chromatography (4:1 hexanes:EtOAc) to give the product as an orange solid (4.1 g, 89% yield). $^{1}$H NMR

(600 MHz; $CDCl_3$) δ 8.45 (d, 1H, *J* = 2.6 Hz), 7.86 (dd, 1H, *J* = 8.5, 2.6 Hz), 7.34 (d, 1H, *J* = 8.5 Hz), 3.89 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 164.6, 148.4, 144.3, 133.7, 124.2, 121.8, 52.4 (the resonance resulting from the diazo carbon was not detected); IR (film): 2955, 2094, 1686 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_8H_7N_3O_2Cl$ 212.0221, found 212.0218;

### 4.6.3.3 General Procedures for C–H Functionalization Reactions

**General Procedure A (for reactions at 0 °C)**

An oven-dried, 10 mL round-bottomed flask was cooled to room temperature under argon before it was charged with the catalyst (0.5 mol %) and substrate (1.2 equiv.), followed by dry, degassed DCM (1 mL). The solution was cooled to 0 °C in an ice/water bath. The diazo compound (0.4 mmol) was dissolved in 2.5 mL DCM under argon and added dropwise to the reaction mixture over 3 hours. The flask used to dissolve the diazo, and the needle/syringe were rinsed with 0.5 mL of DCM, which was added to the reaction. The solution was stirred for 1 hour at 0 °C and was allowed to warm to room temperature. The solvent was removed *in vacuo* and the crude reside purified by column chromatography.

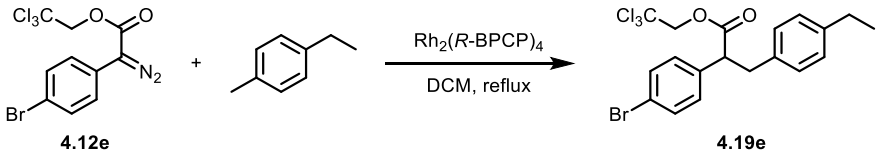
**General Procedure B (for reactions at reflux)**

An oven-dried, 10 mL round-bottomed flask, equipped with a magnetic stir bar and a reflux condenser was cooled to room temperature under argon. The flask was charged with the catalyst (0.5 mol %), substrate (1.2 equiv.), and 1 mL dichloromethane. The solution was heated to reflux. The diazo compound was dissolved in 2.5 mL dichloromethane under argon, and added dropwise to the reaction mixture over 1.5 hours.

The mixture was further stirred for 30-60 minutes before it was cooled to room temperature and concentrated to give a crude residue. The crude mixture was purified by column chromatography.

### 4.6.3.4 Experimental Data for C–H Functionalization Products

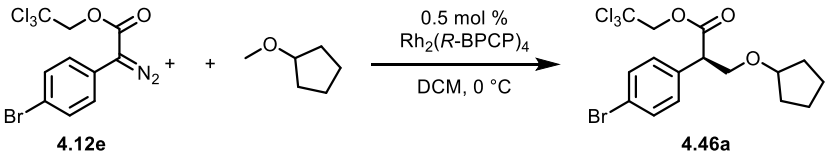
***Procedure for preparation of 4.19e***




**2,2,2-trichloroethyl (*S*)-2-(4-bromophenyl)-3-(4-ethylphenyl)propanoate (4.19e):** Prepared using the general procedure B above, with 4-ethyltoluene (58 mg, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.5 mol %) and the diazo **4.12e** (149 mg, 0.4 mmol, 1.0 equiv.), purifying the product by column chromatography (2% $Et_2O$ in pentane), which was isolated as a colorless oil (140 mg, 75% yield). $[\alpha]_D^{20}$: 40.7 (c. 1.3, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.46-7.43 (m, 2H), 7.25-7.22 (m, 2H), 7.07 (d, 2H, *J* = 8.3 Hz), 7.05 (d, 2H, *J* = 8.3 Hz), 4.67 (d, 1H, *J* = 12.0 Hz), 4.62 (d, 1H, *J* = 12.0 Hz), 3.96 (dd, 1H, *J* = 8.9, 6.8 Hz), 3.40 (dd, 1H, *J* = 13.9, 8.9 Hz), 3.04 (dd, 1H, *J* = 13.9, 6.8 Hz), 2.58 (q, 2H, *J* = 7.6 Hz), 1.19 (t, 3H, *J* = 7.6 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 171.5, 142.8, 136.8, 135.3, 132.0, 130.1, 129.0, 128.2, 121.9, 94.8, 74.3, 53.1, 39.1, 28.6, 15.8; IR (neat): 2962, 2929, 1749, 1133 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{18}O_2BrCl_3Na$ 484.9448; found 484.9461; The ee was determined by chiral HPLC: OD-H column, 0.5 mL/min, 0 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 29.1 min, Minor: 31.8 min, 99% ee.

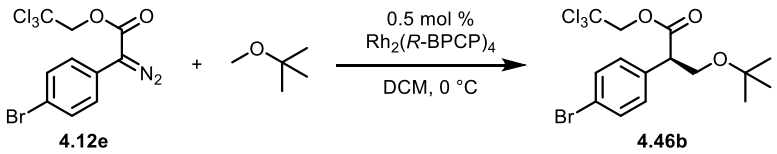
### *Methyl ether functionalization products*


**2,2,2-trichloroethyl (*R*)-2-(4-bromophenyl)-3-butoxypropanoate (4.44b):** Prepared using the general procedure A above with butyl methyl ether (57 µL, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (149 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (2% $Et_2O$ in pentane) to give the product as a colorless oil (135 mg, 78% yield). $[\alpha]_D^{20}$: 0.7922 (c. 1.09, $CHCl_3$, sample 84% ee); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.48-7.44 (m, 2H), 7.27-7.23 (m, 2H), 4.75 (s, 2H), 4.04-3.95 (m, 2H), 3.69 (dd, 1H, *J* = 8.1, 4.2 Hz), 3.51-3.41 (m, 2H), 1.52 (ddt, 2H, *J* = 9.0, 7.9, 6.4 Hz), 1.37-1.28 (m, 2H), 0.89 (t, 3H, *J* = 7.4 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.6, 134.2, 132.0, 130.2, 122.2, 94.9, 74.4, 71.9, 71.5, 61.7, 31.8, 18.4, 14.1; IR (film): 2957, 2932, 2867, 1753, 1489 cm$^{-1}$; HRMS (NSI) *m/z*: [M-H]+ calcd for $C_{15}H_{17}O_3BrCl_3$ 428.9432; found 428.9436; The ee was determined by chiral HPLC: OJ-H column, 0.5 mL/min, 0 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 23.1 min, Minor: 26.9 min, 88% ee.



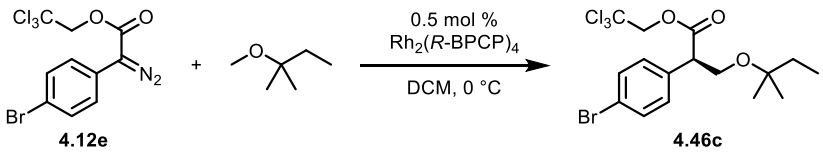

**2,2,2-trichloroethyl (*R*)-2-(4-bromophenyl)-3-(cyclopentyloxy)propanoate (4.46b):** Prepared using the general procedure A above with cyclopentyl methyl ether (56 µL, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (149

mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (2% $Et_2O$ in pentane) to give the product as a colorless oil (148 mg, 83% yield). $[\alpha]_D^{20}$: -1.47 (c. 1.07, $CHCl_3$); $^1H$ NMR (600 MHz; $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.26-7.23 (m, 2H), 4.77 (d, 1H, *J* = 12.0 Hz), 4.73 (d, 1H, *J* = 12.0 Hz), 3.99 (m, 3H), 3.67-3.61 (m, 1H), 1.71-1.56 (m, 6H), 1.54-1.45 (m, 2H); $^{13}C$ NMR (100 MHz, CDCl3) δ 170.7, 134.3, 132.0, 130.2, 122.2, 94.9, 82.2, 74.4, 70.0, 52.0, 32.4, 32.3, 23.7; IR (film): 2954, 2869, 1753, 1488 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}O_3BrCl_3$ 442.9578; found 442.9587; The ee was determined by chiral HPLC: AS-H column, 0.25 mL/min, 0 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 24.4 min, Minor: 20.1 min, 91% ee.



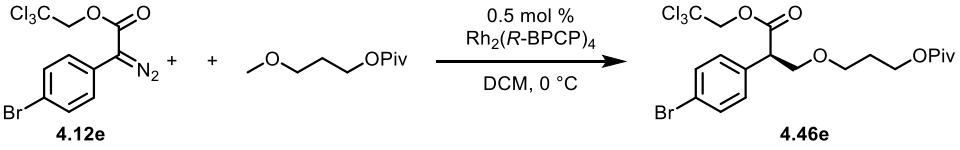

**2,2,2-trichloroethyl (*R*)-2-(4-bromophenyl)-3-(*tert*-butoxy)propanoate (4.46b):** Prepared using the general procedure A above with *t*-butyl methyl ether (57 µL, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (149 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (2% $Et_2O$ in pentane) to give the product as a colorless oil (139 mg, 80% yield). $[\alpha]_D^{20}$: 1.5 (c. 0.99, $CHCl_3$); $^1H$ NMR (600 MHz; $CDCl_3$) δ 7.48-7.44 (m, 2H), 7.28-7.24 (m, 2H), 4.79 (d, 1H, *J* = 12.0 Hz), 4.71 (d, 1H, *J* = 12.0 Hz), 3.96 (dd, 1H, *J* = 9.3, 8.3 Hz), 3.90 (dd, 1H, *J* = 9.3, 5.0 Hz), 3.59 (dd, 1H, *J* = 8.3, 5.0 Hz), 1.16 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 170.9, 134.5, 132.0, 130.3, 122.1, 95.0, 74.3, 73.3, 63.7, 52.4, 27.6; IR (film): 2973, 2872, 1754, 1488 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{19}O_3BrCl_3$ 430.9578; found

430.9582; The ee was determined by chiral HPLC: AS-H column, 0.25 mL/min, 0 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 20.2 min, Minor: 17.4 min, 94% ee.




**2,2,2-trichloroethyl (*R*)-2-(4-bromophenyl)-3-(*tert*-pentyloxy)propanoate (4.46c):** Prepared using the general procedure A above with *t*-amyl methyl ether (64 µL, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (149 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (1% $Et_2O$ in pentane) to give the product as a colorless oil (126 mg, 70% yield). $[\alpha]_D^{20}$: 1.56 (c. 1.22, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.27-7.25 (m, 2H), 4.78 (d, 1H, *J* = 12 Hz), 4.71 (d, 1H, *J* = 12 Hz), 3.95-3.88 (m, 2H), 3.56 (dd, 1H, *J* = 7.4, 4.2 Hz), 1.46 (q, 2H, *J* = 7.5 Hz), 1.10 (s, 3H), 1.10 (s, 3H), 0.81 (t, 3H, *J* = 7.5 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 170.9, 134.6, 131.9, 130.3, 122.1, 95, 75.7, 74.4, 63.4, 52.3, 33.2, 25, 24.9, 8.4; IR (film): 2971, 2877, 1754, 1139 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+NH_4]^+$ calcd for $C_{16}H_{24}O_3NCl_3Br$ 462.0000; found 462.0010; The ee was determined by chiral HPLC: AS-H column, 0.25 mL/min, 0 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 17.9 min, Minor: 16.4 min, 93% ee.


**2,2,2-trichloroethyl (*R*)-3-(2-(adamantan-1-yl)ethoxy)-2-(4-bromophenyl)propanoate (4.46d):** Prepared using the general procedure A above with 1-(2-methoxyethyl)adamantane (93 mg, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (149 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (1% to 2% $Et_2O$ in pentane) to give the product as a colorless oil (133 mg, 62% yield). $[\alpha]_D^{20}$: 7.22 (c. 0.93, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.48-7.44 (m, 2H), 7.26-7.23 (m, 2H), 4.76 (d, 1H, *J* = 12.0 Hz), 4.72 (d, 1H, *J* = 12.0 Hz), 4.02-3.95 (m, 2H), 3.71-3.64 (m, 1H), 3.54-3.46 (m, 2H), 1.91 (bs, 3H, ), 1.72-1.65 (m, 3H), 1.63-1.57 (m, 3H), 1.48-1.42 (m, 6H), 1.37-1.29 (m, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 170.6, 134.3, 132.1, 130.3, 122.2, 94.9, 74.5, 71.9, 67.7, 51.8, 43.6, 42.9, 37.3, 31.9, 28.9; IR (film): 2898, 2845, 1754, 1489, 1110 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{29}O_3Cl_3Br$ 537.0360; found 537.0369; The ee was determined by chiral HPLC: AS-H column, 0.5 mL/min, 0 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 15.9 min, Minor: 13.4 min, 89% ee.

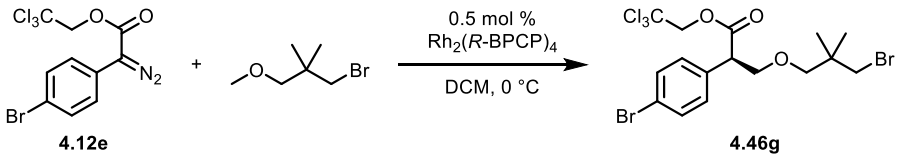



**(*R*)-3-(2-(4-bromophenyl)-3-oxo-3-(2,2,2-trichloroethoxy)propoxy)propyl pivalate (4.46e):** Prepared using the general procedure A above with 3-methoxypropyl pivalate (84 mg, 94 μL, .48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %),

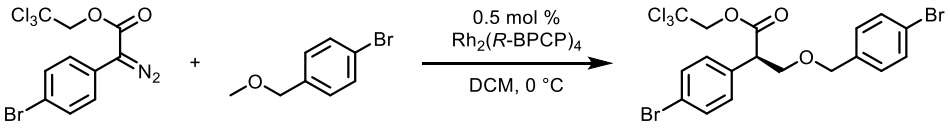
and the diazo (149 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (2% to 4% acetone in hexanes) to give the product as a colorless oil (171 mg, 83% yield). $[\alpha]_D^{20}$: 2.54 (c. 1.0, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.48-7.44 (m, 2H), 7.25-7.22 (m, 2H), 4.78-4.73 (m, 2H), 4.11-4.07 (m, 2H), 4.02 (dd, 1H, *J* = 9.0, 8.8 Hz), 3.97 (dd, 1H, *J* = 9.0, 5.0 Hz), 3.70 (dd, 1H, *J* = 8.8, 5.0 Hz), 3.53 (t, 2H, *J* = 6.2 Hz), 1.89-1.84 (m, 2H), 1.19 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.7, 170.5, 134, 132.1, 130.2, 122.3, 94.9, 74.4, 72, 68, 61.4, 51.6, 38.9, 29.1, 27.4; IR (neat): 2960, 2870, 1754, 1723 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{25}O_5BrCl_3$ 516.9946; found 516.9961; The ee was determined by chiral HPLC: AS-H column, 1 mL/min, 1 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 5.2 min, Minor: 5.7 min, 92% ee.


**2,2,2-trichloroethyl (*R*)-2-(4-bromophenyl)-3-(3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropoxy)propanoate (4.46f):** Prepared using the general procedure A above with *tert*-butyl(3-methoxy-2,2-dimethylpropoxy)dimethylsilane (112 mg, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (149 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (1% $Et_2O$ in pentane) to give the product as a colorless oil (135 mg, 58% yield). $[\alpha]_D^{20}$: 2.65 (c. 1.08, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.45-7.41 (m, 2H), 7.23-7.21 (m, 2H), 4.76 (d, 1H, *J* = 11.9 Hz), 4.71 (d, 1H, *J* = 11.9 Hz), 3.99-3.93 (m, 2H), 3.69-3.63 (m, 1H), 3.26 (d, 1H, *J* = 9.4 Hz), 3.24 (d, 1H, *J* = 9.4 Hz), 3.21 (d, 1H, *J* = 8.6 Hz), 3.18 (d, 1H, *J* = 8.6 Hz), .88 (s, 9H), .79 (s, 6H), 0.00 (s, 3H), 0.00 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 170.6, 134.4,

132.0, 130.3, 122.1, 94.9, 77.3, 74.5, 72.6, 68.8, 51.7, 37.3, 26.1, 21.9, 18.5, -5.3, -5.3; IR (neat): 2954, 2856, 1755, 1092 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{35}O_4SiCl_3Br$ 575.0548; found 575.0568; The ee was determined by chiral HPLC: SS Whelk column, 0.3 mL/min, 0.2 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 18.9 min, Minor: 17.7 min, 93% ee.




**2,2,2-trichloroethyl (*R*)-3-(3-bromo-2,2-dimethylpropoxy)-2-(4-bromophenyl)propanoate (4.46g):** Prepared using the general procedure A above with 1-bromo-3-methoxy-2,2-dimethylpropane (87 mg, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (149 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (1% $Et_2O$ in pentane) to give the product as a colorless oil (162 mg, 77% yield). $[\alpha]_D^{20}$: 1.06 (c. 1.30, $CHCl_3$); 1H NMR (600 MHz; $CDCl_3$) δ 7.48-745 (m, 2H), 7.27-7.23 (m, 2H), 4.78 (d, 1H, *J* = 11.9 Hz), 4.72 (d, 1H, *J* = 11.9 Hz), 4.05-3.98 (m, 2H), 3.72 (dd, 1H, *J* = 8.2, 4.5 Hz), 3.3 (s, 2H), 3.28 (s, 2H), 0.98 (s, 3H), 0.97 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 170.4, 134, 132.1, 130.3, 122.2, 94.9, 77.4, 74.5, 72.4, 51.6, 43.4, 36.4, 23.6, 23.6; IR (film): 2961, 2870, 1753, 1115 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{20}O_3Br_2Cl_3$ 522.8839; found 522.8831; The ee was determined by chiral HPLC: AS-H column, 0.5 mL/min, 0 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 15.7 min, Minor: 14.1 min, 97% ee.



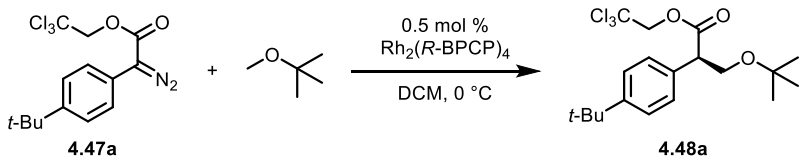

4.12e 4.46h

**2,2,2-trichloroethyl (*R*)-3-((4-bromobenzyl)oxy)-2-(4-bromophenyl)propanoate (4.46h):** Prepared using the general procedure A above with methyl 4-bromobenzyl ether (97 mg, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (149 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (2% - 4% $Et_2O$ in pentane) to give the product as a colorless oil (161 mg, 74% yield). $[\alpha]_D^{20}$: 8.66 (c. 0.82, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.48-7.43 (m, 4H), 7.24-7.20 (m, 2H), 7.16-7.12 (m, 2H), 4.78-4.72 (m, 2H), 4.51 (d, 1H, *J* = 12.2 Hz), 4.48 (d, 1H, *J* = 12.2 Hz), 4.06 (dd, 1H, ), 4.01 (dd, 1H, *J* = 9.0, 5.0 Hz), 3.72 (dd, 1H, *J* = 8.7, 5.0 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.4, 136.8, 133.8, 132.1, 131.7, 130.2, 129.4, 122.4, 121.9, 94.8, 74.4, 72.8, 71.3, 51.7; IR (film): 2864, 1751, 1487, 1010 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{16}O_3Br_2Cl_3$ 542.8526; found 542.8539; The ee was determined by chiral HPLC: OD-R column, 1 mL/min, 2.5 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 8.2 min, Minor: 7.1 min, 91% ee.


4.12e 4.46i

**2,2,2-trichloroethyl (*R*)-2-(4-bromophenyl)-3-(4-chlorophenethoxy)propanoate (4.46i):** Prepared using the general procedure A above with methyl 4-chlorophenethyl ether (82 mg, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %),

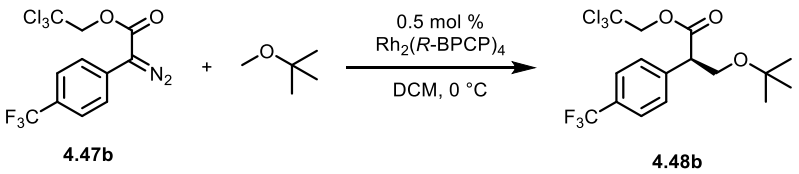
and the diazo (149 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (2% - 4% $Et_2O$ in pentane) to give the product as a colorless oil (152 mg, 74% yield). $[\alpha]_D^{20}$: 2.97 (c. 0.93, CHCl3); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.47-7.42 (m, 2H), 7.25-7.17 (m, 4H), 7.11-7.05 (m, 2H), 4.71-4.64 (m, 2H), 4.00 (dd, 1H, *J* = 8.8, 8.9 Hz), 3.95 (dd, 1H, *J* = 8.8, 5.3 Hz), 3.70 (dd, 1H, *J* = 8.9, 5.3 Hz), 3.68-3.62 (m, 2H), 2.80 (t, 2H, *J* = 6.6 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.4, 137.5, 134, 132.2, 132.1, 130.5, 130.2, 128.6, 122.3, 94.8, 74.4, 72.1, 72, 51.6, 35.7; IR (neat): 2865, 1751, 1489, 1011 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{18}O_3BrCl_4$ 512.9188; found 512.9194; The ee was determined by chiral HPLC: AS-H column, 0.5 mL/min, 0.5 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 22.1 min, Minor: 17.9 min, 88% ee.




4.47a 4.48a

**2,2,2-trichloroethyl (*R*)-3-(*tert*-butoxy)-2-(4-(*tert*-butyl)phenyl)propanoate (4.48a):** Prepared using the general procedure A above with *tert*-butyl methyl ether (42 mg, 57 μL, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (140 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (1% $Et_2O$ in pentane) to give the product as a colorless oil (106 mg, 67% yield). $[\alpha]_D^{20}$: -10.6 (c. 0.47, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.36-7.33 (m, 2H), 7.32-7.29 (m, 2H), 4.85 (d, 1H, *J* = 12 Hz), 4.65 (d, 1H, *J* = 12 Hz), 4.01 (dd, 1H, *J* = 10.3, 8.5 Hz), 3.93 (dd, 1H, *J* = 10.3, 4.5 Hz), 3.56 (dd, 1H, *J* = 8.5, 4.5 Hz), 1.30 (s, 9H), 1.18 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 171.6, 151, 132.3, 128.1, 125.8, 95.1, 74.3, 73.6, 64.2, 52.6, 34.7, 31.5, 27.6; IR (neat): 2962, 2925, 2869, 1756, 1363 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for

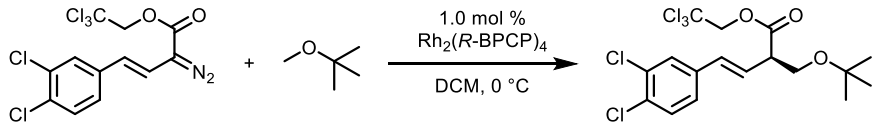
$C_{19}H_{28}O_3Cl_3$ 409.1099, found 409.1105; The ee was determined by chiral HPLC: AS-H column, 0.25 mL/min, 0 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 15.2 min, Minor: 14.2 min, 99% ee.




**2,2,2-trichloroethyl (*R*)-3-(*tert*-butoxy)-2-(4-(trifluoromethyl)phenyl)propanoate (4.48b):** Prepared using the general procedure A above with *tert*-butyl methyl ether (42 mg, 57 μL, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (145 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (1% $Et_2O$ in pentane) to give the product as a colorless oil (135 mg, 80% yield). $[\alpha]_D^{20}$: 1.5 (c. 1.35, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.60 (d, 2H, *J* = 8.2 Hz), 7.52 (d, 2H, *J* = 8.2 Hz), 4.81 (d, 1H, *J* = 12 Hz), 4.73 (d, 1H, *J* = 12 Hz), 4.05-3.96 (m, 2H), 3.70-3.60 (m, 1H), 1.17 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 165.6, 134.5, 125.3 (q, *J* = 32.6 Hz), 124.1, 120.8 (q, *J* = 3.5 Hz), 119.2 (q, *J* = 272 Hz), 89.9, 69.4, 68.8, 58.7, 47.7, 22.6; IR (neat): 2976, 1755, 1324, 1125 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}F_3O_3Cl_3$ 421.0346; found 421.0349; The ee was determined by chiral HPLC: AS-H column, 0.25 mL/min, 0 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 16.2 min, Minor: 15.1 min, 98% ee.


4.47c 4.48c

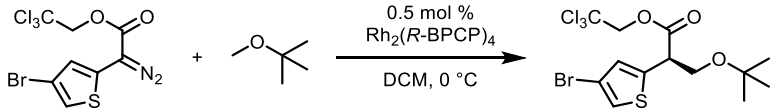
**2,2,2-trichloroethyl (*R*)-3-(*tert*-butoxy)-2-(4-fluorophenyl)propanoate (4.48c):** Prepared using the general procedure A above with *tert*-butyl methyl ether (42 mg, 57 μL, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (125 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (1% $Et_2O$ in pentane) to give the product as a colorless oil (111 mg, 74% yield). $[\alpha]_D^{20}$: 4.54 (c. 1.22, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.37-7.33 (m, 2H), 7.04-6.99 (m, 2H), 4.79 (d, 1H, *J* = 12.0 Hz), 4.72 (d, 1H, *J* = 12.0 Hz), 3.97 (dd, 1H, *J* = 9.5, 8.3 Hz), 3.92 (dd, 1H, *J* = 9.5, 4.8 Hz), 3.58 (dd, 1H, *J* = 8.3, 4.8 Hz), 1.17 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 171, 162.4 (d, *J* = 246 Hz), 131.0 (d, *J* = 3.2 Hz), 130.0 (d, *J* = 8.0 Hz), 115.5 (d, *J* = 21.4 Hz), 94.8, 74.1, 73.1, 63.7, 51.9, 27.4; IR (neat): 2974, 2873, 1754, 1138 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{19}FO_3Cl_3$ 371.0378; found 371.0384; The ee was determined by chiral HPLC: AS-H column, 0.25 mL/min, 0 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 11.2 min, Minor: 9.5 min, 82% ee.




4.47d 4.48d

**2,2,2-trichloroethyl (*R*,*E*)-2-(*tert*-butoxymethyl)-4-(3,4-dichlorophenyl)but-3-enoate (4.48d):** Prepared using the general procedure A above with *tert*-butyl methyl ether (42 mg, 57 μL, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (7.0 mg, 0.004 mmol, 1.0 mol %), and the diazo (155 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (1%

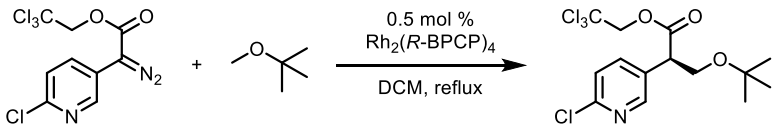
$Et_2O$ in pentane) to give the product as a colorless oil (73 mg, 41% yield). $[\alpha]_D^{20}$: -0.59 (c. 1.7, $CHCl_3$); $^1H$ NMR (600 MHz; $CDCl_3$) δ 7.44 (d, 1H, *J* = 2.1 Hz), 7.37 (d, 1H, *J* = 8.3 Hz), 7.19 (dd, 1H, *J* = 8.3, 2.1 Hz), 6.51 (d, 1H, *J* = 16 Hz), 6.23 (d, 1H, *J* = 16.0, 8.6 Hz), 4.81 (d, 1H, *J* = 12 Hz), 4.77 (d, 1H, *J* = 12 Hz), 3.77 (dd, 1H, *J* = 8.5, 8.3 Hz), 3.61 (dd, 1H, *J* = 8.5, 5.4 Hz), 3.58-3.53 (m, 1H), 1.18 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 170.9, 136.8, 132.9, 131.9, 131.7, 130.7, 128.3, 125.8, 125.8, 95, 74.3, 73.7, 63.1, 50.6, 27.6; IR (neat): 2973, 2872, 1753, 1132 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{20}O_3Cl_5$ 446.9850; found 446.9870; The ee was determined by chiral HPLC: AS-H column, 0.5 mL/min, 0 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 14.0 min, Minor: 12.6 min, 94% ee.




**4.47e** **4.48e**

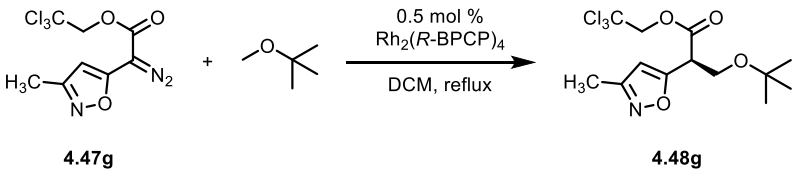
**2,2,2-trichloroethyl (*R*)-2-(4-bromothiophen-2-yl)-3-(*tert*-butoxy)propanoate (4.48e):** Prepared using the general procedure A above with *tert*-butyl methyl ether (42 mg, 57 μL, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (151 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (1% $Et_2O$ in pentane) to give the product as a colorless oil (99 mg, 57% yield). $[\alpha]_D^{20}$: -8.34 (c. 2.43, $CHCl_3$); $^1H$ NMR (600 MHz; $CDCl_3$) δ 7.15 (d, 1H, *J* = 1.5 Hz), 6.97 (dd, 1H, *J* = 1.5, 0.7 Hz), 4.81 (d, 1H, *J* = 11.9 Hz), 4.74 (d, 1H, *J* = 11.9 Hz), 4.17 (dd, 1H, *J* = 8.4, 5.1 Hz), 3.89 (dd, 1H, *J* = 8.5, 8.4 Hz), 3.71 (dd, 1H, *J* = 8.5, 5.1 Hz), 1.18 (s, 9H); 13C NMR (100 MHz, $CDCl_3$) δ 169.9, 138.4, 129.3, 122.9, 109.4, 94.8, 74.6, 74.0, 64.1, 48.1, 27.5; IR (neat): 2973, 2872, 1756, 1089 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for

$C_{13}H_{17}O_3BrCl_3S$ 436.9142; found 436.9151; The ee was determined by chiral HPLC: AS-H column, 0.25 mL/min, 0 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 18.3 min, Minor: 21.9 min, 96% ee.



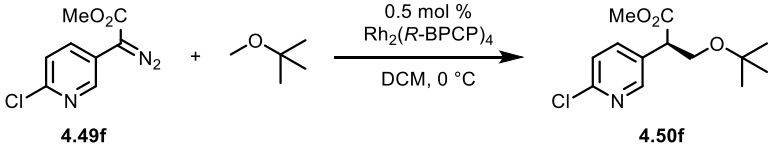

**4.47f** **4.48f**

**2,2,2-trichloroethyl (*R*)-3-(*tert*-butoxy)-2-(6-chloropyridin-3-yl)propanoate (4.48f):** Prepared using the general procedure B above with *tert*-butyl methyl ether (42 mg, 57 μL, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (132 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (10% $Et_2O$ in pentane) to give the product as a colorless oil (71 mg, 46% yield). $[\alpha]_D^{20}$: -4.8 (c. 2.03, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 8.40 (d, 1H, *J* = 2.5 Hz), 7.75 (dd, 1H, *J* = 8.3, 2.5 Hz), 7.31 (d, 1H, *J* = 8.3 Hz), 4.80-4.74 (m, 2H), 3.94 (dd, 1H, *J* = 7.3, 5.6 Hz), 3.89 (dd, 1H, *J* = 8.5, 7.3 Hz), 3.73 (dd, 1H, *J* = 8.5, 5.6 Hz), 1.15 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 170.1, 151.2, 150, 139.1, 130.7, 124.3, 94.8, 74.5, 74, 63.3, 49.6, 27.5; IR (neat): 2974, 2874, 1754, 1460, 1089 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{18}NO_3Cl_4$ 388.0035; found 388.0030; The ee was determined by chiral HPLC: AS-H column, 0.5 mL/min, 0.5 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 15.7 min, Minor: 14.9 min, 82% ee.




**4.47g** **4.48g**

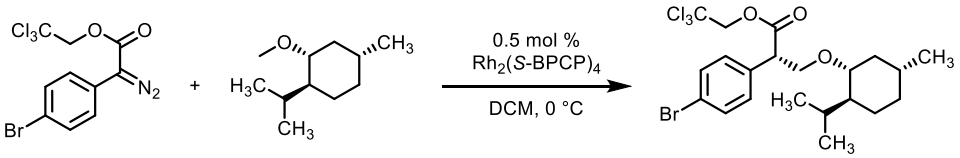
**2,2,2-trichloroethyl (*S*)-3-(*tert*-butoxy)-2-(3-methylisoxazol-5-yl)propanoate (4.48g):** Prepared using the general procedure B above with *tert*-butyl methyl ether (42 mg, 57 μL, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (119 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (1% $Et_2O$ in pentane) to give the product as a colorless oil (48 mg, 34% yield). [α]D: -1.8 (c. 0.8, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 6.17 (s, 1H), 4.82 (d, 1H, *J* = 11.9 Hz), 4.78 (d, 1H, *J* = 11.9 Hz), 4.19 (dd, 1H, *J* = 7.5, 5.4 Hz), 3.92 (dd, 1H, *J* = 8.6, 7.5 Hz), 3.87 (dd, 1H, *J* = 8.6, 5.4 Hz), 2.3 (s, 3H), 1.17 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.8, 166.2, 159.9, 103.9, 94.4, 74.5, 73.9, 61.3, 45.6, 27.3, 11.5; IR (neat): 2974, 1760, 1149, 1090 cm$^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{19}NO_4Cl_3$ 358.0374; found 358.0380; The ee was determined by chiral HPLC: AD-H column, 1 mL/min, 1 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 8.6 min, Minor: 11.1 min, 75% ee.




**4.49f** **4.50f**

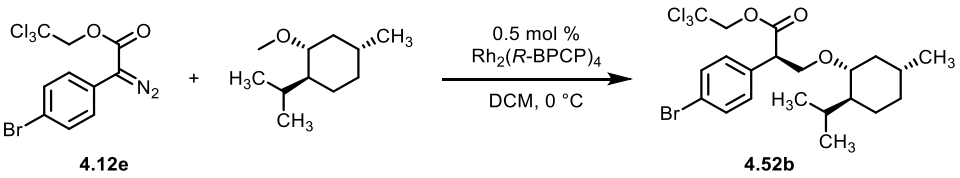
**methyl (*R*)-3-(*tert*-butoxy)-2-(6-chloropyridin-3-yl)propanoate (4.50f):** Prepared using the general procedure B above with *tert*-butyl methyl ether (42 mg, 57 μL, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.004 mmol, 0.5 mol %), and the diazo (85 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (10% $Et_2O$ in pentane) to give the product as a colorless oil (24 mg, 22% yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 8.32 (d,

1H, *J* = 2.5 Hz), 7.70 (dd, 1H, *J* = 8.3, 2.5 Hz), 7.30 (d, 1H, *J* = 8.3 Hz), 3.85 (dd, 1H, *J* = 8.4, 7.4 Hz), 3.79 (dd, 1H, *J* = 7.4, 6.0 Hz), 3.71 (s, 3H), 3.63 (dd, 1H, *J* = 8.4, 6.0 Hz), 1.13 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 172.2, 150.8, 149.9, 138.9, 131.6, 124.2, 73.8, 63.5, 52.5, 50.0, 27.5; IR (film): 2974, 2874, 1738, 1460 $cm^{-1}$; HRMS (APCI) m/z: $[M+H]^+$ calcd for $C_{13}H_{19}NO_3Cl$ 272.1048; found 272.1050;

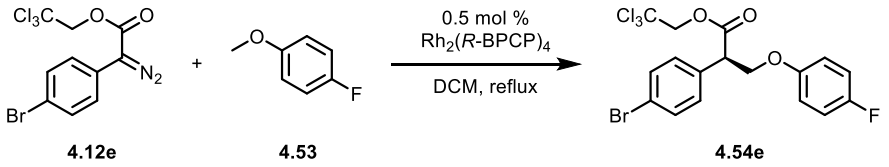



**2,2,2-trichloroethyl (*S*)-2-(4-bromophenyl)-3-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)propanoate (4.52a):** Prepared using the general procedure A above with (1*S*,2*R*,4*R*)-1-isopropyl-2-methoxy-4-methylcyclohexane (**4.51**) (82 mg, 0.48 mmol, 1.2 equiv.), $Rh_2$(*S*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (149 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (1% $Et_2O$ in pentane) to give a colorless oil. This contained a small amount of the starting material methyl ether, which was removed under vacuum (0.5 mm Hg) at 100 °C for one hour to give the pure product as a colorless oil (107 mg, 52% yield). $[\alpha]_D^{20}$: -22.6 (c. 1.18, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.26-7.23 (m, 2H), 4.75 (d, 1H, *J* = 11.9 Hz), 4.70 (d, 1H, *J* = 11.9 Hz), 3.95 (dd, 1H, *J* = 9.6, 5.0 Hz), 3.88 (dd, 1H, *J* = 9.6, 8.8 Hz), 3.84 (dd, 1H, *J* = 8.8, 5.0 Hz), 3.13 (app td, 1H, *J* = 10.6, 4.1 Hz), 2.13-2.03 (m, 2H), 1.67-1.57 (m, 2H), 1.38-1.29 (m, 1H), 1.19 (ddt, 1H, *J* = 13.4, 10.3, 3.2 Hz), 1.00-0.78 (m, 9H), 0.75 (d, 3H, *J* = 6.9 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 170.9, 134.1, 132.0, 130.2, 122.2, 94.9, 80.3, 74.5, 69.8, 52.1, 48.4, 40.3, 34.7, 31.6, 25.7, 23.5, 22.5, 21.1,

16.4; IR (neat): 2952, 2920, 2867, 1754 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{29}O_3Cl_3Br$ 513.0378; found 513.0360;

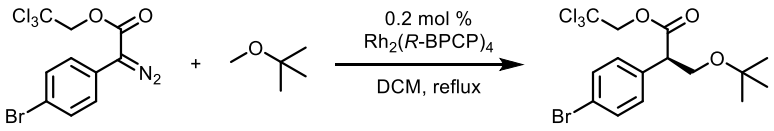



**2,2,2-trichloroethyl (*R*)-2-(4-bromophenyl)-3-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)propanoate (4.52b):** Prepared using the general procedure A above with (1*S*,2*R*,4*R*)-1-isopropyl-2-methoxy-4-methylcyclohexane (**4.51**) (82 mg, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (149 mg, 0.4 mmol, 1.0 equiv.), purifying by column chromatography (1% $Et_2O$ in pentane) to give a colorless oil. This contained a small amount of the starting material methyl ether, which was removed under vacuum (0.5 mm Hg) at 100 °C for one hour to give the pure product as a colorless oil (128 mg, 62% yield). $[\alpha]_D^{20}$: -21.4 (c. 4.0, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.27-7.23 (m, 2H), 4.75 (d, 1H, *J* = 12.0 Hz), 4.72 (d, 1H, *J* = 12.0 Hz), 4.22 (dd, 1H, *J* = 9.1, 8.3 Hz), 3.94 (dd, 1H, *J* = 8.3, 6.2 Hz), 3.57 (dd, 1H, *J* = 9.1, 6.2 Hz), 3.02 (app td, 1H, *J* = 10.6, 4.1 Hz), 2.12-2.07 (m, 1H), 2.01-1.93 (m, 1H), 1.65-1.55 (m, 2H), 1.37-1.27 (m, 1H), 1.19-1.13 (m, 1H), 0.95-0.78 (m, 9H), 0.63 (d, 3H, *J* = 7.0 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 170.6, 134.6, 131.9, 130.3, 122.1, 94.9, 80.2, 74.4, 69.7, 52.0, 48.3, 40.3, 34.7, 31.7, 25.7, 23.5, 22.5, 21.1, 16.4; IR (film): 2953, 2920, 2867, 1754 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{29}O_3Cl_3Br$ 513.0360, found 513.0369;



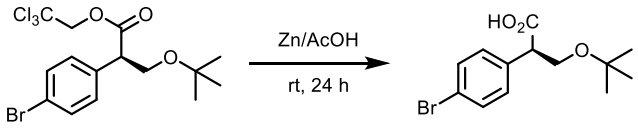

**2,2,2-trichloroethyl (*R*)-2-(4-bromophenyl)-3-(4-fluorophenoxy)propanoate (4.54e):** Prepared using the general procedure B above (using a 3 hour addition time), with *p*-fluoroanisole (61 mg, 54 μL, 0.48 mmol, 1.2 equiv.), $Rh_2$(*R*-BPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), and the diazo (149 mg, 0.4 mmol, 1.0 equiv.). The reaction was cooled to room temperature, and concentrated. The yield was determined by $^1$H NMR: 0.4 mmol of trichloroethylene was added to the crude reaction mixture. By NMR, the yield was 65%. A sample for characterization was obtained by column chromatography (0.5% to 1% $Et_2O$ in pentane): $[\alpha]_D^{20}$: 6.21 (c. 1.95, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.31-7.27 (m, 2H), 6.99-6.93 (m, 2H), 6.84-6.79 (m, 2H), 4.80 (d, 1H, *J* = 12.0 Hz), 4.77 (d, 1H, *J* = 12.0 Hz), 4.56-4.51 (m, 1H), 4.21-4.16 (m, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 170.0, 157.8 (d, *J* = 239 Hz), 154.5 (d, *J* = 1.7 Hz), 133.3, 132.3, 130.2, 122.7, 116.1 (two doublets, *J* unknown), 94.8, 74.5, 69.6, 51.2; IR (film): 2954, 1752, 1505 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{14}FO_3Cl_3Br$ 468.9170; found 468.9178; The ee was determined by chiral HPLC: AS-H column, 1 mL/min, 1 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 9.3 min, Minor: 8.1 min, 97% ee.

### *Procedure for gram-scale preparation of 7b*




An oven-dried round-bottomed flask was cooled to room temperature under argon and charged with $Rh_2$(*R*-BPCP)$_4$ (10.6 mg, 0.2 mol %), *tert*-butyl methyl ether (0.43 mL, 320 mg, 3.6 mmol), and DCM (4 mL). The solution was heated to reflux. The diazo **1b** (1.1g, 3.0 mmol, 1.0 equiv.), in 6 mL DCM, was added dropwise over 1.5 hours. After the addition was complete, the needle/syringe was rinsed into the reaction vessel with 1 mL DCM, to ensure all of the diazo had been transferred. The solution was allowed to stir for 30 minutes at reflux, and was then cooled to room temperature. The solvent was removed by rotary evaporation, and the crude mixture purified by filtering through a short plug of silica gel, eluting with 5% $Et_2O$ in penane. The product was isolated as a colorless oil (1.24g, 95% yield). HPLC analysis indicated the product was formed in 90% ee.

### *Deprotection of trichloroethyl ester*




**(*R*)-2-(4-bromophenyl)-3-(*tert*-butoxy)propanoic acid (4.55):** The ester **4.46b** (150 mg, 0.35 mmol, 1.0 equiv.) was dissolved in 2 mL of glacial acetic acid, and zinc powder (113 mg, 1.7 mmol, 5.0 equiv.) was added. The solution was allowed to stir at room

temperature for 24 h. The starting material had been fully consumed as indicated by TLC analysis. The solution was diluted with $H_2O$ (10 mL) and extracted with EtOAc (2 x 15 mL). The organic extracts were washed with $H_2O$ and brine, dried over $MgSO_4$ and concentrated to give the product as a white solid (95 mg, 90% yield). $[\alpha]_D^{20}$: 7.0 (c. 1.46, $CHCl_3$); $^1H$ NMR (600 MHz; $CDCl_3$) δ 7.46-7.43 (m, 2H), 7.23-7.20 (m, 2H), 3.88 (dd, 1H, *J* = 8.9, 8.7 Hz), 3.77 (dd, 1H, *J* = 8.9, 5.3 Hz), 3.57 (dd, 1H, *J* = 8.7, 5.3 Hz), 1.16 (s, 9H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 177.6, 134.9, 132.0, 130.3, 122.0, 74.2, 63.6, 52.2, 27.5; IR (neat): 2969, 2870, 2589, 1705 $cm^{-1}$; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{18}O_3Br$ 301.0434; found 301.0440; The ee was determined by chiral HPLC: AS-H column, 1 mL/min, 2 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 9.6 min, Minor: 9.2 min, 90% ee.

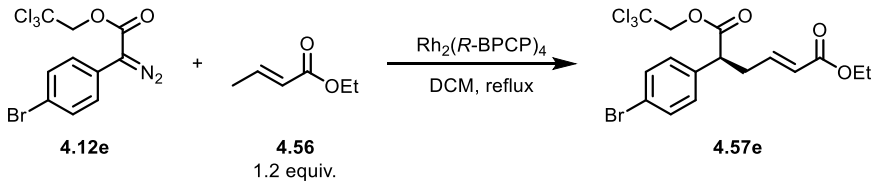
## 4.6.4 Functionalization of Electron-Deficient Substrates

Relative concentrations of 1.0, 2.0 and 4.0 in Table 4.8 refer to the following amounts of diazo and solvents:

Relative concentration = 1.0: 0.4 mmol diazo in 2.5 mL of DCM, and catalyst/substrate in 1.0 mL DCM

Relative concentration = 2.0: 0.4 mmol diazo in 1.2 mL of DCM, and catalyst/substrate in 0.5 mL DCM

Relative concentration = 4.0: 0.8 mmol diazo in 1.2 mL of DCM, and catalyst/substrate in 0.5 mL DCM




**1-ethyl 6-(2,2,2-trichloroethyl) (*S*,*E*)-5-(4-bromophenyl)hex-2-enedioate (4.57e):** An oven-dried, 10 mL round-bottomed flask, equipped with a reflux condenser and magnetic stir bar, was cooled to room temperature under argon. It was charged with the catalyst $Rh_2$(*R*-BPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), 0.5 mL DCM, and ethyl crotonate (**4.56**) (119 μL, 1.6 mmol, 2.0 equiv.). The solution was heated to reflux. The diazo compound **4.12e** (298 mg, 0.8 mmol, 1.0 equiv.) was dissolved in 1.2 mL of DCM and was taken into a syringe with a long needle (30 cm). The needle was positioned in the flask such that the tip of the needle was below the level of the refluxing solvent in the reflux condenser. The diazo solution was then added drop-wise over 3 hours. When the addition was complete, the needle was rinsed into the reaction with 0.3 mL of DCM to ensure all the diazo had been added. The solution was allowed to stir for 30 minutes at reflux, and then was cooled to room temperature. The solvent was removed under reduced pressure. Then 0.8 mmol of trichloroethylene was added and the crude mixture analyzed by $^1$H NMR, which was used to calculate the NMR yield (86%). The crude mixture was then purified by column chromatography (5% → 10% $Et_2O$ in pentane). The product was isolated as a colorless oil (270 mg, 74% isolated yield). $^1$H NMR (600 MHz; $CDCl_3$) δ 7.51-7.45 (m, 2H), 7.25-7.19 (m, 2H), 6.83 (app dt, 1H, *J* = 15.6, 7.1 Hz), 5.88 (app dt, 1H, *J* = 15.6, 1.5 Hz), 4.75 (d, 1H, *J* = 12.0 Hz), 4.70 (d, 1H, *J* = 12.0 Hz), 4.16 (q, 2H, *J* = 7.1 Hz), 3.83 (dd, 1H, *J* = 8.2, 7.1 Hz), 3.03 (dddd, 1H, *J* = 15.5, 8.5, 7.1, 1.5 Hz), 2.71 (app dtd, 1H, *J* = 15.3, 7.1, 1.5 Hz), 1.26 (t, 3H, *J* = 7.1 Hz); $^{13}$C

NMR (150 MHz, $CDCl_3$) δ 170.9, 166.1, 143.9, 135.9, 132.2, 129.9, 124.4, 122.3, 94.7, 74.4, 60.6, 49.9, 35.4, 14.4; IR (neat): 2981, 1750, 1716, 1139 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{16}O_4Cl_3BrNa$ 478.9190; found 478.9199; The ee was determined by chiral HPLC: OD-H column, 1 mL/min, 1 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 16.3 min, Minor: 14 min, 95% ee.

## 4.6.5 Crystal Structure Data for 4.55

**Table 1 Crystal data and structure refinement for 4.55.**

| | |
|---|---|
| Identification code | **4.55** |
| Empirical formula | $C_{13}H_{16.5}BrO_3$ |
| Formula weight | 300.67 |
| Temperature/K | 110(2) |
| Crystal system | orthorhombic |
| Space group | $P2_12_12_1$ |
| a/Å | 5.460(2) |
| b/Å | 19.858(7) |
| c/Å | 25.535(10) |
| α/° | 90 |
| β/° | 90 |
| γ/° | 90 |
| Volume/$Å^3$ | 2768.6(18) |
| Z | 8 |
| $\rho_{calc}g/cm^3$ | 1.443 |
| $\mu/mm^{-1}$ | 2.964 |
| F(000) | 1228.0 |
| Crystal size/$mm^3$ | 1.443 × 0.054 × 0.033 |
| Radiation | MoKα (λ = 0.71073) |
| 2Θ range for data collection/° | 3.792 to 47.066 |
| Index ranges | $-6 \le h \le 5$, $-18 \le k \le 22$, $-28 \le l \le 21$ |
| Reflections collected | 10242 |
| Independent reflections | 4028 [$R_{int}$ = 0.2262, $R_{sigma}$ = 0.2834] |
| Data/restraints/parameters | 4028/257/283 |
| Goodness-of-fit on $F^2$ | 1.003 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0886, $wR_2$ = 0.1995 |
| Final R indexes [all data] | $R_1$ = 0.1946, $wR_2$ = 0.2831 |
| Largest diff. peak/hole / e $Å^{-3}$ | 1.93/-1.81 |
| Flack parameter | 0.03(2) |

**Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 4.55. $U_{eq}$ is defined as 1/3 of of the trace of the orthogonalised $U_{IJ}$ tensor.**

| Atom | *x* | *y* | *z* | U(eq) |
|---|---|---|---|---|
| Br1 | 4445(4) | 4156.1(14) | 351.9(8) | 36.2(7) |
| O1 | 5460(30) | 93(8) | 1091(5) | 27(3) |
| O3 | 9360(20) | 1239(8) | 1793(4) | 28(4) |
| O2 | 5370(20) | 1225(9) | 2011(5) | 35(4) |
| C13 | 6990(40) | 1241(12) | 1680(7) | 22(2) |
| C3 | 7510(40) | 2289(12) | 601(7) | 24(3) |
| C12 | 1860(40) | -519(13) | 752(8) | 34(4) |
| C5 | 3790(40) | 2307(11) | 1093(7) | 23(3) |
| C1 | 5060(40) | 3256(12) | 586(7) | 23(3) |
| C2 | 7160(40) | 2913(12) | 429(8) | 24(3) |
| C8 | 4500(40) | 738(11) | 980(7) | 26(4) |
| C9 | 3740(40) | -480(12) | 1193(8) | 29(3) |
| C11 | 2500(40) | -352(13) | 1730(8) | 31(4) |
| C7 | 6440(40) | 1239(12) | 1106(7) | 22(2) |
| C10 | 5370(40) | -1079(12) | 1216(8) | 32(4) |
| C6 | 3390(40) | 2934(12) | 928(7) | 23(3) |
| C4 | 5920(40) | 1930(12) | 938(7) | 23(3) |
| Br1' | 8503(5) | -2495.2(15) | 2362.0(9) | 48.3(9) |
| O2' | 10360(20) | 938(7) | 2783(4) | 22(3) |
| O3' | 14310(20) | 712(8) | 2941(4) | 28(3) |
| O1' | 10460(30) | 1038(8) | 4068(5) | 29(2) |
| C6' | 7820(40) | -1151(11) | 2691(8) | 22(4) |
| C7' | 11370(40) | 151(11) | 3475(7) | 24(2) |
| C4' | 10660(40) | -510(12) | 3230(8) | 29(3) |
| C13' | 11890(40) | 652(12) | 3031(7) | 24(2) |
| C8' | 9460(40) | 453(11) | 3837(7) | 24(3) |
| C9' | 8710(40) | 1492(12) | 4300(8) | 30(2) |
| C3' | 12100(40) | -1093(12) | 3265(8) | 30(4) |
| C5' | 8420(40) | -570(12) | 2943(7) | 23(4) |
| C1' | 9280(40) | -1711(12) | 2725(8) | 29(3) |
| C12' | 7010(40) | 1138(12) | 4696(8) | 31(3) |
| C10' | 10380(40) | 1995(12) | 4605(8) | 33(3) |
| C2' | 11500(40) | -1650(13) | 3019(8) | 31(5) |

| | | | | |
|---|---|---|---|---|
| C11' | 7280(40) | 1885(13) | 3898(8) | 31(3) |

**Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for 4.55. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.**

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| Br1 | 41.6(12) | 44.5(17) | 22.7(10) | 2.4(11) | -0.6(10) | 7.5(13) |
| O1 | 23(4) | 33(4) | 25(5) | 0(3) | -3(4) | -1(3) |
| O3 | 17(4) | 51(12) | 15(6) | 8(6) | 1(4) | -3(4) |
| O2 | 15(5) | 72(13) | 18(6) | 6(6) | 0(4) | 1(6) |
| C13 | 18(4) | 30(5) | 19(5) | 1(4) | 2(4) | 0(3) |
| C3 | 23(3) | 26(3) | 23(3) | 1(2) | 0(2) | 0(2) |
| C12 | 29(7) | 41(11) | 32(7) | -3(6) | -5(6) | -2(6) |
| C5 | 23(3) | 25(4) | 22(3) | 0(2) | -1(2) | 0(2) |
| C1 | 22(3) | 29(3) | 18(4) | 0(3) | -3(3) | 0(3) |
| C2 | 23(3) | 26(3) | 23(3) | 1(2) | 0(2) | 0(2) |
| C8 | 24(4) | 29(4) | 27(4) | 0(2) | 0(3) | -1(2) |
| C9 | 25(5) | 35(5) | 28(5) | -1(4) | 0(4) | -2(4) |
| C11 | 28(8) | 38(11) | 28(6) | 1(5) | 1(5) | 0(7) |
| C7 | 18(4) | 30(5) | 19(5) | 1(4) | 2(4) | 0(3) |
| C10 | 27(7) | 38(6) | 31(8) | -1(5) | 1(6) | -1(5) |
| C6 | 23(3) | 25(4) | 22(3) | 0(2) | -1(2) | 0(2) |
| C4 | 22(3) | 29(3) | 18(4) | 0(3) | -3(3) | 0(3) |
| Br1' | 64.6(17) | 48(2) | 32.6(12) | -10.4(13) | 4.7(12) | -3.8(16) |
| O2' | 19(3) | 24(5) | 23(4) | 4(4) | -1(3) | -2(3) |
| O3' | 21(3) | 49(8) | 14(5) | 6(6) | -2(3) | 2(3) |
| O1' | 25(3) | 33(3) | 30(4) | -6(3) | 3(3) | -1(3) |
| C6' | 21(7) | 25(6) | 20(6) | 0(5) | 3(5) | -1(5) |
| C7' | 22(3) | 29(3) | 21(3) | 1(2) | -1(2) | 3(2) |
| C4' | 29(3) | 31(3) | 27(3) | -1(2) | 0(2) | 1(2) |
| C13' | 22(3) | 29(3) | 21(3) | 1(2) | -1(2) | 3(2) |
| C8' | 23(3) | 27(3) | 23(4) | 0(2) | 0(2) | 2(2) |
| C9' | 28(3) | 32(3) | 31(3) | -4(2) | 4(2) | 0(2) |
| C3' | 30(6) | 32(5) | 27(7) | 2(4) | 2(5) | 1(4) |
| C5' | 24(5) | 24(6) | 22(6) | 0(4) | 4(4) | 0(4) |
| C1' | 29(3) | 31(3) | 27(3) | -1(2) | 0(2) | 1(2) |
| C12' | 28(5) | 36(6) | 31(5) | -4(4) | 3(4) | 0(4) |
| C10' | 29(5) | 36(5) | 34(5) | -8(4) | 5(4) | -1(4) |
| C2' | 28(7) | 33(7) | 33(7) | -3(5) | 1(6) | 6(6) |
| C11' | 29(5) | 34(5) | 30(4) | -5(4) | 5(4) | 2(4) |

**Table 4 Bond Lengths for 4.55.**

| Atom | Atom | Length/Å | Atom | Atom | Length/Å |
|---|---|---|---|---|---|
| Br1 | C1 | 1.92(2) | Br1' | C1' | 1.86(2) |
| O1 | C8 | 1.41(3) | O2' | C13' | 1.19(2) |
| O1 | C9 | 1.50(3) | O3' | C13' | 1.35(2) |
| O3 | C13 | 1.32(2) | O1' | C8' | 1.41(3) |
| O2 | C13 | 1.22(2) | O1' | C9' | 1.44(3) |
| C13 | C7 | 1.50(3) | C6' | C5' | 1.36(3) |
| C3 | C2 | 1.33(3) | C6' | C1' | 1.37(3) |
| C3 | C4 | 1.42(3) | C7' | C4' | 1.51(3) |
| C12 | C9 | 1.53(3) | C7' | C13' | 1.54(3) |
| C5 | C6 | 1.33(3) | C7' | C8' | 1.52(3) |
| C5 | C4 | 1.44(3) | C4' | C3' | 1.40(3) |
| C1 | C2 | 1.39(3) | C4' | C5' | 1.43(3) |
| C1 | C6 | 1.42(3) | C9' | C12' | 1.54(3) |
| C8 | C7 | 1.49(3) | C9' | C10' | 1.56(3) |
| C9 | C11 | 1.55(3) | C9' | C11' | 1.51(3) |
| C9 | C10 | 1.49(3) | C3' | C2' | 1.31(3) |
| C7 | C4 | 1.47(3) | C1' | C2' | 1.43(3) |

**Table 5 Bond Angles for 4.55.**

| Atom | Atom | Atom | Angle/° | Atom | Atom | Atom | Angle/° |
|---|---|---|---|---|---|---|---|
| C8 | O1 | C9 | 119.4(17) | C8' | O1' | C9' | 115.6(16) |
| O3 | C13 | C7 | 114.3(16) | C5' | C6' | C1' | 121(2) |
| O2 | C13 | O3 | 123.8(17) | C4' | C7' | C13' | 107.8(16) |
| O2 | C13 | C7 | 121.9(18) | C4' | C7' | C8' | 114.9(18) |
| C2 | C3 | C4 | 126(2) | C8' | C7' | C13' | 108.8(18) |
| C6 | C5 | C4 | 122(2) | C3' | C4' | C7' | 123.2(19) |
| C2 | C1 | Br1 | 120.8(16) | C3' | C4' | C5' | 116(2) |
| C2 | C1 | C6 | 119(2) | C5' | C4' | C7' | 120(2) |
| C6 | C1 | Br1 | 120.0(16) | O2' | C13' | O3' | 123.6(19) |
| C3 | C2 | C1 | 119(2) | O2' | C13' | C7' | 125.0(18) |
| O1 | C8 | C7 | 107.3(18) | O3' | C13' | C7' | 111.4(17) |
| O1 | C9 | C12 | 109.4(17) | O1' | C8' | C7' | 108.3(18) |
| O1 | C9 | C11 | 107.7(17) | O1' | C9' | C12' | 112.5(19) |
| C12 | C9 | C11 | 111.5(17) | O1' | C9' | C10' | 102.8(17) |
| C10 | C9 | O1 | 103.9(17) | O1' | C9' | C11' | 112.9(16) |
| C10 | C9 | C12 | 113.1(19) | C12' | C9' | C10' | 108.4(17) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| C10 | C9 | C11 | 111.0(18) | C11' | C9' | C12' | 111.6(18) |
| C8 | C7 | C13 | 111.0(17) | C11' | C9' | C10' | 108(2) |
| C4 | C7 | C13 | 108.8(18) | C2' | C3' | C4' | 122(2) |
| C4 | C7 | C8 | 115.2(18) | C6' | C5' | C4' | 121(2) |
| C5 | C6 | C1 | 121(2) | C6' | C1' | Br1' | 121.1(16) |
| C3 | C4 | C5 | 113.6(19) | C6' | C1' | C2' | 117(2) |
| C3 | C4 | C7 | 122.1(19) | C2' | C1' | Br1' | 121.6(18) |
| C5 | C4 | C7 | 124.3(19) | C3' | C2' | C1' | 122(2) |

**Table 6 Hydrogen Bonds for 4.55.**

| D | H | A | d(D-H)/Å | d(H-A)/Å | d(D-A)/Å | D-H-A/° |
|---|---|---|---|---|---|---|
| O3 | H3 | O2' | 0.9592(14) | 1.6952(15) | 2.652(9) | 175(10) |

**Table 7 Torsion Angles for 4.55.**

| A | B | C | D | Angle/° | A | B | C | D | Angle/° |
|---|---|---|---|---|---|---|---|---|---|
| Br1 | C1 | C2 | C3 | 180.0(16) | Br1' | C1' | C2' | C3' | 178.1(18) |
| Br1 | C1 | C6 | C5 | 179.9(15) | C6' | C1' | C2' | C3' | 3(3) |
| O1 | C8 | C7 | C13 | -65(2) | C7' | C4' | C3' | C2' | -176(2) |
| O1 | C8 | C7 | C4 | 170.7(15) | C7' | C4' | C5' | C6' | 175.8(19) |
| O3 | C13 | C7 | C8 | 134(2) | C4' | C7' | C13' | O2' | 78(3) |
| O3 | C13 | C7 | C4 | -98(2) | C4' | C7' | C13' | O3' | -100(2) |
| O2 | C13 | C7 | C8 | -44(3) | C4' | C7' | C8' | O1' | 175.4(16) |
| O2 | C13 | C7 | C4 | 84(3) | C4' | C3' | C2' | C1' | -4(3) |
| C13 | C7 | C4 | C3 | 112(2) | C13' | C7' | C4' | C3' | 113(2) |
| C13 | C7 | C4 | C5 | -68(2) | C13' | C7' | C4' | C5' | -67(2) |
| C2 | C3 | C4 | C5 | 0(3) | C13' | C7' | C8' | O1' | -64(2) |
| C2 | C3 | C4 | C7 | 179(2) | C8' | O1' | C9' | C12' | 53(2) |
| C2 | C1 | C6 | C5 | -1(3) | C8' | O1' | C9' | C10' | 169.6(16) |
| C8 | O1 | C9 | C12 | 51(2) | C8' | O1' | C9' | C11' | -74(2) |
| C8 | O1 | C9 | C11 | -70(2) | C8' | C7' | C4' | C3' | -126(2) |
| C8 | O1 | C9 | C10 | 172.2(15) | C8' | C7' | C4' | C5' | 54(3) |
| C8 | C7 | C4 | C3 | -123(2) | C8' | C7' | C13' | O2' | -47(3) |
| C8 | C7 | C4 | C5 | 57(2) | C8' | C7' | C13' | O3' | 135.2(19) |
| C9 | O1 | C8 | C7 | 157.7(15) | C9' | O1' | C8' | C7' | 162.7(16) |
| C6 | C5 | C4 | C3 | 0(3) | C3' | C4' | C5' | C6' | -4(3) |
| C6 | C5 | C4 | C7 | -179.5(19) | C5' | C6' | C1' | Br1' | -177.9(15) |
| C6 | C1 | C2 | C3 | 1(3) | C5' | C6' | C1' | C2' | -3(3) |
| C4 | C3 | C2 | C1 | 0(3) | C5' | C4' | C3' | C2' | 4(3) |

C4 C5 C6 C1 0(3) C1' C6' C5' C4' 3(3)

**Table 8 Hydrogen Atom Coordinates (Å×10$^4$) and Isotropic Displacement Parameters (Å$^2$×10$^3$) for 4.55.**

| Atom | *x* | *y* | *z* | U(eq) |
|---|---|---|---|---|
| H3 | 9700(200) | 1110(50) | 2148(11) | 42 |
| H3A | 8925 | 2070 | 491 | 29 |
| H12D | 672 | -166 | 794 | 51 |
| H12E | 1044 | -948 | 763 | 51 |
| H12F | 2667 | -468 | 420 | 51 |
| H5 | 2652 | 2108 | 1316 | 28 |
| H2 | 8289 | 3116 | 208 | 29 |
| H8 | 2940 | 832 | 853 | 32 |
| H11D | 3731 | -243 | 1986 | 47 |
| H11E | 1640 | -750 | 1838 | 47 |
| H11F | 1372 | 16 | 1700 | 47 |
| H7 | 7931 | 1095 | 924 | 27 |
| H10D | 6339 | -1101 | 902 | 48 |
| H10E | 4399 | -1479 | 1247 | 48 |
| H10F | 6438 | -1042 | 1514 | 48 |
| H6 | 1991 | 3162 | 1037 | 28 |
| H3' | 14700(300) | 970(30) | 2628(16) | 42 |
| H6' | 6395 | -1168 | 2492 | 27 |
| H7' | 12881 | 84 | 3675 | 29 |
| H8'A | 7995 | 566 | 3641 | 29 |
| H8'B | 9016 | 131 | 4107 | 29 |
| H3'A | 13511 | -1085 | 3468 | 35 |
| H5' | 7354 | -206 | 2929 | 28 |
| H12A | 5740 | 903 | 4511 | 47 |
| H12B | 6289 | 1467 | 4924 | 47 |
| H12C | 7941 | 822 | 4900 | 47 |
| H10A | 11521 | 1748 | 4817 | 49 |
| H10B | 9384 | 2275 | 4825 | 49 |
| H10C | 11261 | 2271 | 4360 | 49 |
| H2' | 12559 | -2017 | 3035 | 38 |
| H11A | 8381 | 2070 | 3642 | 47 |
| H11B | 6412 | 2245 | 4068 | 47 |
| H11C | 6129 | 1592 | 3728 | 47 |

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# Chapter 5 – Asymmetric Cyclopropanation with Novel Diazo Esters

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**Contents**

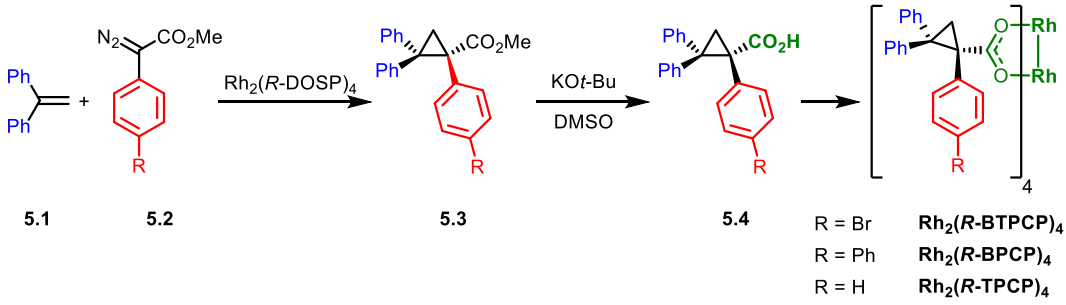
## 5.1 Introduction

A brief introduction to rhodium catalyzed cyclopropanation with donor/acceptor carbenes was given in Chapter 1. Here, a more extensive background of the details relevant to the work in this chapter will be provided. The premier catalyst for cyclopropanation of olefins with donor/acceptor carbenes has been $Rh_2(DOSP)_4$.[1] The catalyst's chief advantages have been its solubility in hydrocarbon solvents, and generality with regards to donor groups (many kinds of aryl and vinyl groups work well). However, it has some serious limitations as well. Perhaps most notably, while the catalyst typically gives good levels of asymmetric induction in hydrocarbon solvents, it typically does so *only* in hydrocarbon solvents. This is a problem with substrates that lack solubility in these solvents. Second, there is limited scope with regard to the acceptor group of the carbene, typically only methyl esters give reliably high levels of enantioselectivity. Bulkier esters (such as *i*-Pr and *t*-Bu) or other acceptor groups such as (ketones, cyano groups, etc.) result in drastic drops in enantioselectivity.[1]

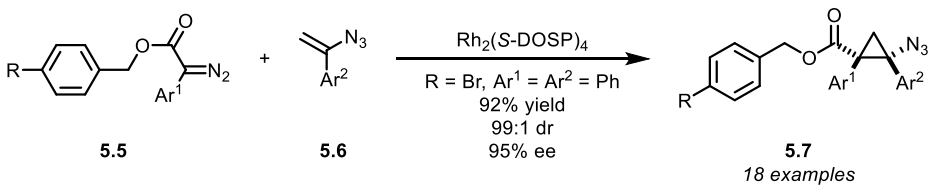
It was discovered that, with $Rh_2(PTAD)_4$, this limitation on acceptor groups could be overcome for certain acceptor groups such as phosphonate,[2] trifluoromethyl,[3] cyano,[4] and keto[5] groups. $Rh_2(PTAD)_4$ also expanded the scope of substitution patterns on the aryl donor group to some degree (such as for *ortho* substituted aryl groups).[6] The first limitation of $Rh_2(DOSP)_4$ was overcome by the development of a new class of catalysts: the triarylcyclopropane carboxylate catalysts, the first member of which was $Rh_2(BTPCP)_4$.[7] With this catalyst, cyclopropanation reactions could be conducted with high levels of asymmetric induction in both dichloromethane as well as hydrocarbon solvents. Additionally, bulky esters were tolerated with this catalyst.

With the introduction of the triarylcyclopropane carboxylate catalysts, a general, easy entry into cyclopropylcarboxylic acids **5.4** was necessary. The catalysts have been prepared by asymmetric cyclopropanation of 1,1-diphenylethylene (**5.1**) with methyl aryldiazoacetates **5.2**. Hydrolysis of the methyl ester gives the carboxylic acid ligand. Unfortunately, however, methyl esters are not always easily cleaved, especially when surrounded by considerable bulk.

**Scheme 5.1** Preparation of triarylcyclopropane carboxylate catalysts



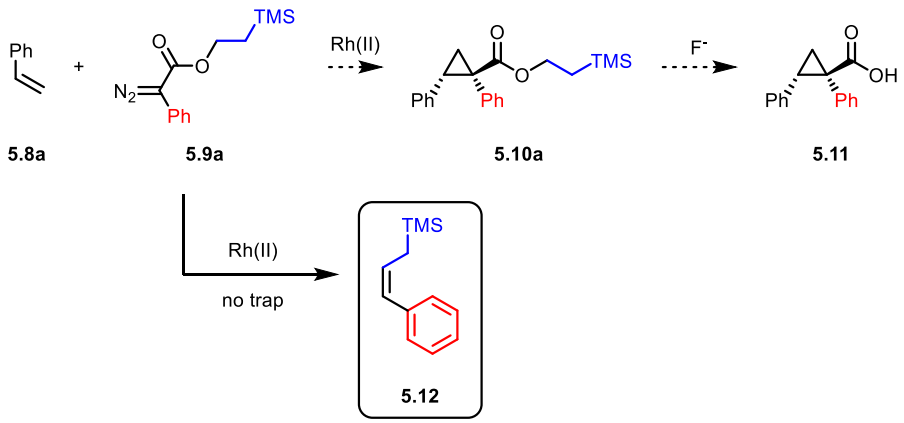

It was of interest to explore new esters that could be easily and selectively removed to reveal the carboxylic acid, both in the context of ligand synthesis (Scheme 5.1) or more generally in the preparation of cyclopropylcarboxylic acids. Ester size has been noted as being a limitation of $Rh_2(DOSP)_4$, and indeed there are very few examples of highly enantioselective cyclopropanation reactions of aryldiazoacetates with $Rh_2(DOSP)_4$ using esters larger than methyl. The most notable example involves the preparation of azido-substituted cyclopropanes using benzyl aryldiazoacetates (Eq. 5.1).[8] The cyclopropanes were generally isolated with levels of enantioselectivity in excess of 90% ee.




(Eq. 5.1)

It was of interest to us to use the 2-(trimethylsilyl)ethyl ester to prepare cyclopropanes. It was envisioned that the resulting 2-(trimethylsilyl)ethyl cyclopropyl ester **5.10a** could be easily deprotected to form the carboxylic acid **5.11**. Early on in this study, it was discovered that diazo ester **5.9a** was capable of forming allylsilane **5.12** in the absence of styrene; that reaction is the subject of Chapter 3 of this thesis. Nevertheless, it was found that these diazo esters were capable of highly enantioselective cyclopropanations in the presence of a variety of styrenes, without competition from this potential side reaction. The cyclopropanation reactions of these diazo esters is the subject of the first part of this chapter.

**Scheme 5.2** Potential problem associated with the use of 2-(trimethylsilyl)ethyl aryldiazos




With the development of the 2,2,2-trichloroethyl aryldiazoacetates for C–H functionalization reactions (Chapter 4 of this thesis), it was discovered that the triarylcyclopropane carboxylate catalysts (most notably $Rh_2(BPCP)_4$) paired excellently with these esters to give the products with high levels of asymmetric induction. As with the 2-(trimethylsilyl)ethyl aryldiazoacetates, the TCE esters can be easily cleaved under mild conditions (Zn/AcOH), as shown in Chapter 4. Additionally, observations during

the C–H functionalization studies suggested that the TCE esters were more likely to be crystalline than the corresponding methyl esters, and might be amenable to enantioenrichement by easy crystallization. The second part of this chapter investigates the cyclopropanation chemistry of these diazo compounds.

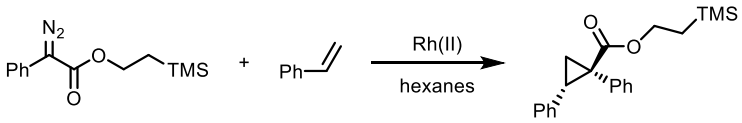
## 5.2 Results and Discussion

### 5.2.1 Cyclopropanation with 2-(trimethylsilyl)ethyl diazoacetates

*Note: this work was conducted together with Carolyn M. Cohen, an undergraduate student whom I mentored during her time in the group. All reactions were conducted by Carolyn unless otherwise stated.*

The reaction of TMSE phenyldiazoacetate **5.9a** with styrene (**5.8a**) was investigated with several catalysts (Table 5.1). It was surprising to find that the best results were obtained with $Rh_2$(*S*-DOSP)$_4$, since the TMSE ester is considerably bulkier than a methyl ester. Almost equally surprising was the poor level of enantioselectivity obtained with $Rh_2$(*S*-BTPCP)$_4$, since this catalyst has been shown to be unaffected by ester size in cyclopropanation reactions.[7]

**Table 5.1** Optimization of catalysts for TMSE phenyldiazoacetate cyclopropanation



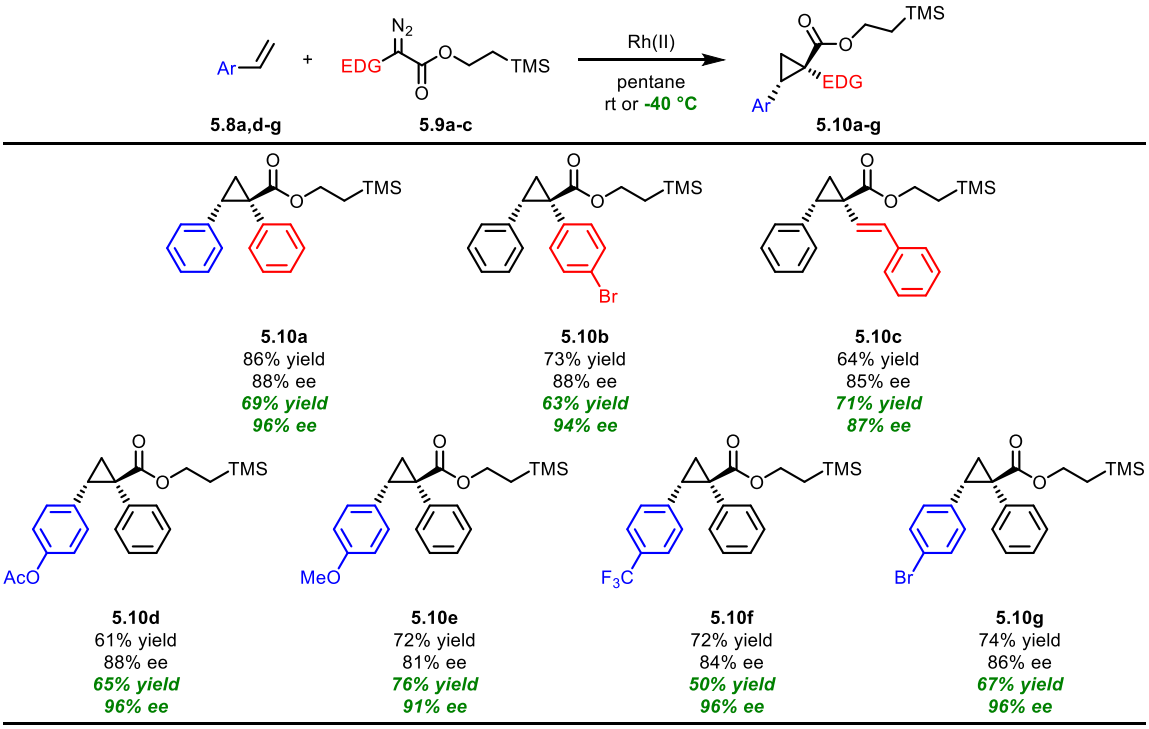

**5.9a** **5.8a** **5.10a**

| entry | catalyst | yield (%) | ee (%) |
|---|---|---|---|
| **1** | **$Rh_2$(*S*-DOSP)$_4$** | **87** | **87** |
| 2 | $Rh_2$(*S*-PTAD)$_4$ | 46[a] | -35 |
| 3 | $Rh_2$(*S*-BTPCP) | 67[a] | 43 |
| 4 | $Rh_2$(*S*-NTTL)$_4$ | 35[a] | -51 |

[a]Yields using unoptimized conditions

A variety of styrenes and TMSE diazos were examined in cyclopropanation with $Rh_2$(*S*-DOSP)$_4$ (Scheme 5.3) (note: **5.9c** was characterized only by NMR). Yields and levels of enantioselectivity were fairly consistent for all cyclopropanes prepared. The ee values ranged from 81-88 %. Both electron-rich and electron-deficient styrene derivatives worked well, as well as an interesting *p*-acetoxy styrene substrate.

**Scheme 5.3** Cyclopropanation of TMSE diazos at room temperature and -40 °C[a]



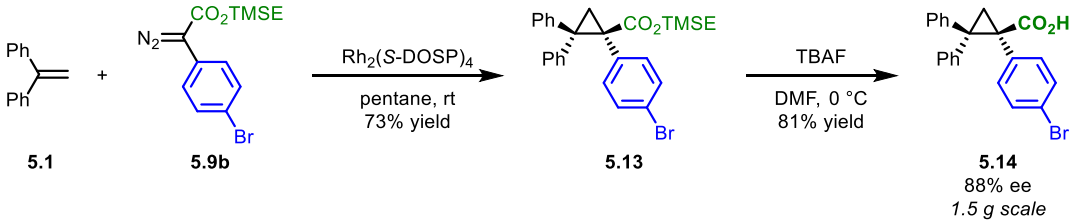

[a]Yield and ee values in bold/green are for the reaction conducted at -40 °C.

Though the levels of enantioselectivity were fairly good, it is known that at lower temperatures the selectivity can be improved. Thus, the reactions were repeated at -40 °C to compare to room temperature. Unsurprisingly, the levels of enantioselectivity were routinely about 10% higher, with the exception of **5.10c**, which improved from 85 to 87% ee. It is not immediately clear why the enantioselectivity did not improve with this diazo upon lowering the temperature. The absolute stereochemistry of these products was

tentatively assigned based on the model for $Rh_2(DOSP)_4$ catalyzed cyclopropanation reactions.[9]

The reaction was then extended to the synthesis of the ligand for $Rh_2(S\text{-BTPCP})_4$. Cyclopropanation of 1,1-diphenylethylene (**5.1**) with diazo **5.9b** gave the triarylcyclopropane **5.13** in 73% yield. The enantiomeric excess of this compound could not be easily determined by chiral HPLC, as conditions could not be found to separate the enantiomers. Therefore, **5.13** was directly converted to the carboxylic acid **5.14** by deprotection with TBAF. This reaction was conducted on a 1.5 g scale, and the isolated yield of **5.14** was 81%. The enantiomeric excess of this compound could be determined, and it was found to be 88% ee.

**Scheme 5.4** Preparation of $Rh_2(S\text{-BTPCP})_4$ ligand



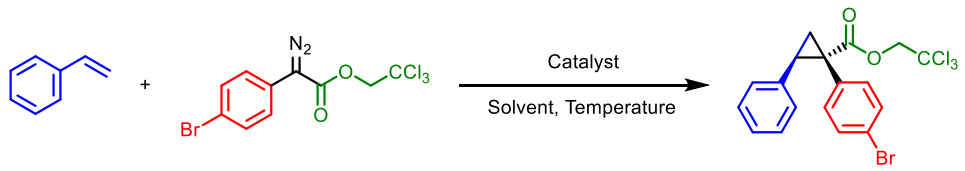

Thus, a brief study of cyclopropanation reactions with TMSE aryldiazoacetates has demonstrated that, with $Rh_2(DOSP)_4$ as the catalyst, cyclopropanes with good levels of enantiomeric excess could be formed from a variety of styrene derivatives. The extension of the reaction to the preparation of the BTPCP ligand is a demonstration that these diazos could be useful if easy, high yielding formation of the cyclopropyl carboxylic acid is desired.

## 5.2.2 Cyclopropanation with 2,2,2-trichloroethyl aryldiazoacetates

*Note: this work was conducted together with Jane Chang, an undergraduate student whom I mentored during her time in the group. All reactions were conducted by Jane unless otherwise stated.*

As with the TMSE aryldiazoacetates, it was of interest to determine the scope of cyclopropanation reactions with the TCE aryldiazoacetates. Thus, with diazo compound **5.15** the cyclopropanation of styrene was investigated with a variety of catalysts. Again, surprisingly, with $Rh_2$(*S*-DOSP)$_4$, the cyclopropane **5.16** was formed with 83% ee, despite the use of the bulky ester (entry 1). $Rh_2$(*S*-PTAD)$_4$ peformed moderately well, giving the product in 62% ee. Not surprisingly, the triarylcyclopropanecarboxylate catalysts $Rh_2$(*R*-BPCP)$_4$ and $Rh_2$(*S*-BTPCP)$_4$ gave routinely higher levels of enantioselectivity with diazo **5.15**. In pentane, $Rh_2$(*S*-BTPCP)$_4$ was superior, giving **5.16** in 90% ee, compared to 70% ee with $Rh_2$(*R*-BPCP)$_4$ (entries 3 and 4). Since these catalysts are known to perform well in chlorinated solvents, the reaction was investigated in dichloromethane (entries 5 and 6). In this solvent, the differences in enantioselectivity essentially disappeared, with ee values of 96 and 95%. The reaction was also conducted in 1,2-dichloroethane, and the level of enantioselectivity was slightly lower, though it could be improved by conducting the reaction at 0 °C (entry 9). Ultimately, it was decided that it was preferable to conduct the reaction at room temperature, so $Rh_2$(*R*-BPCP)$_4$ and DCM were chosen as the optimal set of conditions for this reaction.

**Table 5.2** Optimization of cyclopropanation with TCE aryldiazoacetate **5.15**

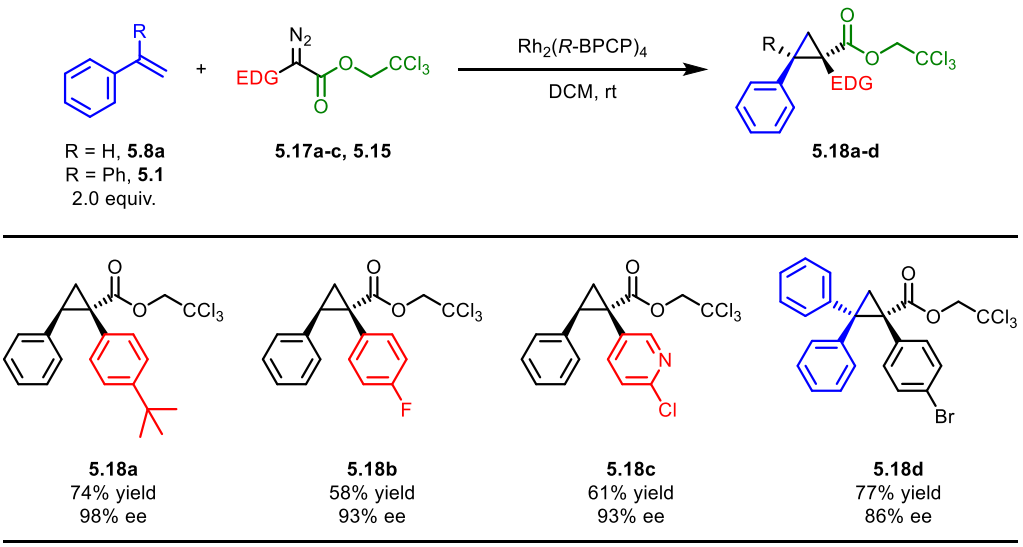



**5.8a** 2.0 equiv. **5.15** **5.16**

| entry | catalyst | catalyst loading (mol %) | solvent | temp (°C) | yield (%) | ee (%) |
|---|---|---|---|---|---|---|
| 1 | $Rh_2$(*S*-DOSP)$_4$ | 1.0 | pentane | rt | 88 | -83 |
| 2 | $Rh_2$(*S*-PTAD)$_4$ | 1.0 | pentane | rt | 64 | 62 |
| 3 | $Rh_2$(*S*-BTPCP)$_4$ | 0.5 | pentane | rt | 81 | -90 |
| 4 | $Rh_2$(*R*-BPCP)$_4$ | 0.5 | pentane | rt | 80 | 70 |
| **5** | **$Rh_2$(*R*-BPCP)$_4$** | **0.5** | **DCM** | **rt** | **69** | **96** |
| 6 | $Rh_2$(*S*-BTPCP)$_4$ | 0.5 | DCM | rt | 73 | -95 |
| 7 | $Rh_2$(*R*-BPCP)$_4$ | 0.5 | DCE | rt | 71 | 92 |
| 8 | $Rh_2$(*S*-BTPCP)$_4$ | 0.5 | DCE | rt | 68 | -90 |
| 9 | $Rh_2$(*R*-BPCP)$_4$ | 0.5 | DCE | 0 | 70 | 95 |

Under these conditions, a few diazo compounds were used in the reaction (Scheme 5.5). Thus, a series of cyclopropanes **5.18** were prepared in consistently good yields and excellent levels of enantioselectivity. Notably, a pyridyl diazo was also compatible with this chemistry. Interestingly, the lowest enantioselectivity was found in the preparation of **5.18d**, which was isolated in 86% ee. This is in contrast to the results that are typically seen with $Rh_2$(DOSP)$_4$, with which enantioselectivity is generally higher when using 1,1-diphenylethylene compared to styrene.[6,7,10,11] The absolute stereochemistry of these compounds is tentatively assigned based on the predictive model for $Rh_2$(BTPCP)$_4$ catalyzed cyclopropanation reactions, which has been shown here to give the same sense of asymmetric induction as $Rh_2$(BPCP)$_4$ (Table 5.2).

**Scheme 5.5** Cyclopropanation with a variety of TCE aryldiazoacetates




These results demonstrate that TCE aryldiazoacetates can make excellent partners in cyclopropanation reactions in combination with $Rh_2$(*R*-BPCP)$_4$. One advantage of the trichloroethyl ester is its ability to be cleaved under mild conditions (as with the TMSE ester). This has been demonstrated with the products of methyl ether C–H functionalization in Chapter 4, in which the ester was deprotected under mild conditions without racemization of a potentially acidic C–H bond chiral center. Thus it can be envisioned using this easy deprotection to prepare the ligands for the triarylcyclopropanecarboxylate catalysts.

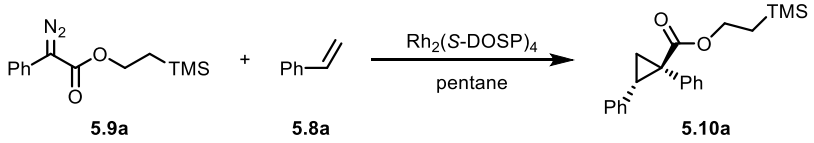
## 5.3 Conclusion

In conclusion, the preparation of cyclopropanes with TMSE and TCE esters has been achieved by using $Rh_2$(*S*-DOSP)$_4$ and $Rh_2$(*R*-BPCP)$_4$, respectively. In both cases, high levels of enantioselectivity are possible, and a range of diazo compounds and styrene derivatives undergo the reaction. Currently, efforts to further explore the scope of cyclopropanation with TCE aryldiazoacetates are underway.

Both of the methods were used to prepare the ligand for the catalyst $Rh_2(BTPCP)_4$, demonstrating one potential application for these methods. While these ligands have already been prepared conveniently from the corresponding methyl esters,[7,11] removal of the methyl ester requires strong base, and the use of DMSO as solvent. If a new catalyst should be of interest whose ligand is not compatible with those conditions, the mild nature of the alternatives presented here will be a complement to the existing method.

## 5.4 Experimental Section

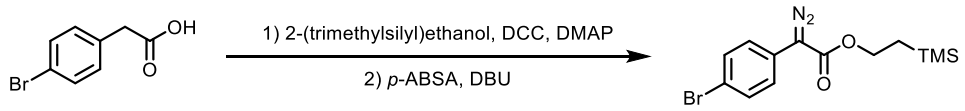
Prepataion and characterization of diazo **5.9a** is given in Chapter 3.




**5.9a** **5.8a** **5.10a**

**2-(trimethylsilyl)ethyl (1*R*,2*S*)-1,2-diphenylcyclopropane-1-carboxylate (5.10a):** In a 25-mL round bottom flask equipped with a magnetic stir bar, $Rh_2$(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %) and styrene (0.29 mL, 2.5 mmol, 5.0 equiv.) were dissolved in pentane (3 mL). To this was added a solution of diazo **5.9a** (131 mg, 0.5 mmol, 1.0 equiv.) in pentane (3 mL) dropwise over 1 hour. The volatiles were removed by rotary evaporation, and the crude residue was purified by column chromatography (4% $Et_2O$ in pentane), giving the product as a clear oil (145 mg, 86% yield). $[\alpha]^{20}_D$: -22.5° (c = 1.08, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.14-7.07 (m, 3H), 7.09-6.98 (m, 5H), 6.82-6.73 (m, 2H), 4.27-4.10 (m, 2H), 3.11 (dd, *J* = 9.3, 7.3 Hz, 1H), 2.13 (dd, *J* = 9.3, 4.9 Hz, 1H), 1.87 (dd, *J* = 7.3, 4.9 Hz, 1H), 1.00-0.84 (m, 2H), -0.03 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 174.2, 136.8, 135.1, 132.2, 128.3, 127.9, 127.8, 127.1, 126.5, 63.9, 37.9, 33.2, 20.5, 17.4, -1.3; IR (neat): 2952, 1709, 1249, 694 cm$^{-1}$; HRMS (NSI) *m/z*:

$[M+Na]^+$ calcd for $C_{21}H_{26}O_2NaSi$ 361.1594, found 361.1606; The ee was determined by chiral HPLC: SS-Whelk column, 1 mL/min 0% *i*PrOH in hexanes, $\lambda$ = 230 nm. $t_R$: Major: 35.1 min, Minor: 27.2 min, 88% ee

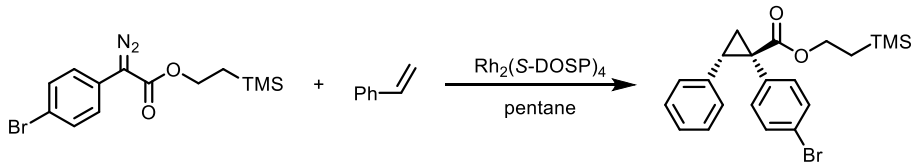



**5.9b**

**2-(trimethylsilyl)ethyl 2-(4-bromophenyl)-2-diazoacetate (5.9b):** A solution of 4-bromophenylacetic acid (25.0 g, 116 mmol, 1.0 equiv.), DMAP (1.4 g, 11.6 mmol, 0.1 equiv.), and 2-(trimethylsilyl)ethanol (16.4 g, 139 mmol, 1.2 equiv.) in DCM (200 mL) was cooled to 0 °C. Then a solution of DCC (26.0 g, 128 mmol, 1.1 equiv.) in DCM (50 mL) was quickly poured into the cold reaction mixture. The solution was stirred overnight, after which time it had warmed to room temperature. The precipitate was removed by filtration, washing several times with $Et_2O$ (3 x 50 mL). The filtrate was concentrated and the crude material purified by column chromatography (4% EtOAc in hexanes) to give the ester intermediate as a colorless oil (33.1 g, 90% yield).

A portion of this material (15.0 g, 47.6 mmol, 1.0 equiv.) was dissolved with *p*-ABSA (17.1 g, 71.4 mmol, 1.5 equiv.) in acetonitrile (150 mL), and the solution cooled to 0 °C. Then DBU (14.5 g, 95.2 mmol, 2.0 equiv.) was added drop-wise by syringe. The mixture was stirred overnight, after which time it had warmed to room temperature. It was diluted with $Et_2O$ (100 mL) and washed with saturated aqueous $NH_4Cl$ (150 mL). The aqueous layer was extracted with $Et_2O$ (70 mL). The organic layers were combined and dried over $MgSO_4$ and then concentrated to give a crude orange powder. This material was dissolved in a minimal amount of hexanes (required approximately 200 mL) and a

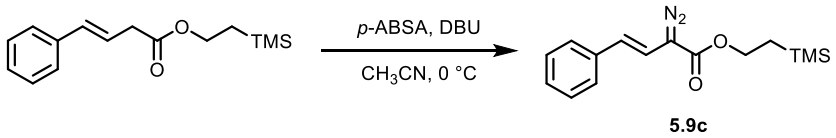
white/brown colored solid remained. This material was removed by filtration. The filtrate could be concentrated to give the diazo (14.6 g, 90% yield, pure by $^1$H NMR). The material so obtained was then easily purified further by passing through a plug of silica gel to remove "baseline" impurities. $^1$H NMR (600 MHz; $CDCl_3$) δ 7.48-7.45 (m, 2H), 7.36-7.33 (m, 2H), 4.38-4.34 (m, 2H), 1.09-1.04 (m, 2H), 0.06 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 165.0, 132.1, 125.4, 125.0, 119.3, 63.6, 17.8, -1.3 (the resonance resulting from the diazo carbon was not detected); IR (film): 2953, 2898, 2082, 1698 $cm^{-1}$; HRMS (NSI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{17}O_2N_2BrSiNa$ 363.0135; found 363.0135;




**5.9b** **5.8a** **5.10b**

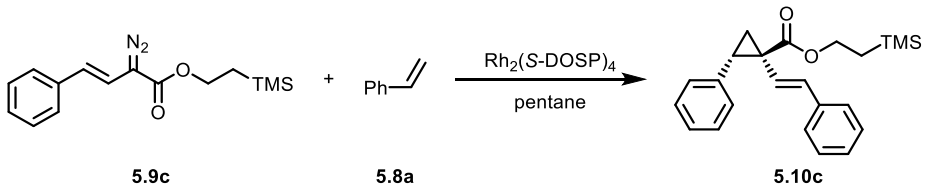
**2-(trimethylsilyl)ethyl (1*R*,2*S*)-1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate (5.10b):** In a 25-mL round bottom flask equipped with a magnetic stir bar, $Rh_2$(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %) and styrene (0.29 mL, 2.5 mmol, 5.0 equiv.) were dissolved in pentane (3 mL). To this was added a solution of diazo **5.9b** (171 mg, 0.5 mmol, 1.0 equiv.) in pentane (3 mL) dropwise over 1 hour. The volatiles were removed by rotary evaporation, and the crude residue was purified by column chromatography (3% $Et_2O$ in pentane), giving the product as a pale yellow oil (152 mg, 73% yield). $[\alpha]^{20}_D$: 2.10° (c = 1.01, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.26-7.22 (m, 2H), 7.10-7.07 (m, 3H), 6.90-6.87 (m, 2H), 6.80-6.75 (m, 2H), 4.23-4.11 (m, 2H), 3.09 (dd, *J* = 9.3, 7.3 Hz, 1H), 2.12 (dd, *J* = 9.3, 5.0 Hz, 1H), 1.81 (dd, *J* = 7.3, 5.0 Hz, 1H), 0.93-0.84 (m, 2H), -0.03 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 173.4, 136.0, 134.1,

133.6, 130.8, 128.0, 127.9, 126.5, 121.1, 63.8, 37, 32.9, 20.1, 17.2, -1.5; IR (neat): 2952, 1710, 1248, 834 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{21}H_{25}O_2BrNaSi$ 439.06994, found 439.0700; The ee was determined by chiral HPLC: SS-Whelk column, 1 mL/min. 0% *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 21.8 min, Minor: 14.1 min, 88% ee.



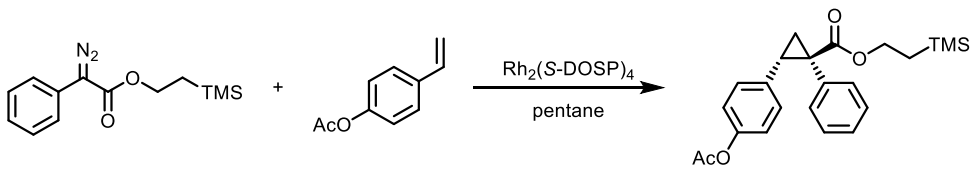

**5.9c**

**(*E*)-2-(trimethylsilyl)ethyl 2-diazo-4-phenylbut-3-enoate (5.9c):** The ester (1.0 g, 3.8 mmol, 1.0 equiv.) was dissolved in 50 mL $CH_3CN$. To this was added *p*-ABSA (1.4 g, 5.7 mmol, 1.5 equiv.), and the mixture was cooled to 0 °C. DBU (1.1 mL, 7.6 mmol, 2.0 equiv.) was added, and the mixture was stirred for 3 hours. The reaction was quenched with saturated aqueous $NH_4Cl$ and extracted with ether, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography (3% $Et_2O$ in pentane), giving the product as a red solid. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 4H), 7.24-7.16 (m, 1H), 6.49 (d, *J* = 16.3 Hz, 1H), 6.19 (d, *J* = 16.3 Hz, 1H), 4.40-4.32 (m, 2H), 1.10-1.01 (m, 2H), 0.10 - -0.02 (m, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 165.3, 136.8, 128.7, 127.0, 125.8, 122.8, 111.5, 63.7, 17.6, -1.5 (the resonance resulting from the diazo carbon was not detected);



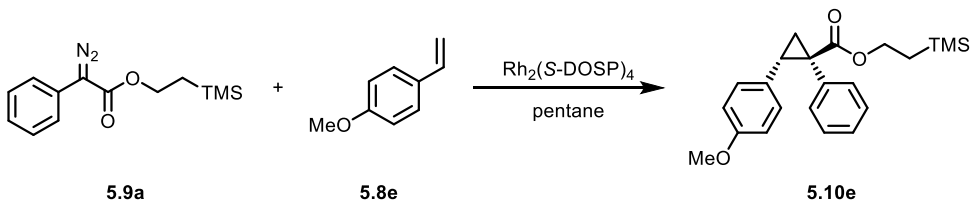

**5.9c** **5.8a** **5.10c**

**2-(trimethylsilyl)ethyl (1*S*,2*S*)-2-phenyl-1-((*E*)-styryl)cyclopropane-1-carboxylate (5.10c):** In a 25-mL round bottom flask equipped with a magnetic stir bar, $Rh_2$(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %) and styrene (0.29 mL, 2.5 mmol, 5.0 equiv.) were dissolved in pentane (3 mL). To this was added a solution of diazo **5.9c** (144 mg, 0.5 mmol, 1.0 equiv.) in pentane (3 mL) dropwise over 1 hour. The volatiles were removed by rotary evaporation, and the crude residue was purified by column chromatography (4% $Et_2O$ in pentane), giving the product as a clear oil (116 mg, 64% yield). $[\alpha]^{20}_D$: -76.9° (c = 1.01, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.27-7.09 (m, 10H), 6.33 (d, *J* = 16.0 Hz, 1H), 6.14 (d, *J* = 16.0 Hz, 1H), 4.34-4.18 (m, 2H), 2.99 (dd, *J* = 9.1, 7.3 Hz, 1H), 2.01 (dd, *J* = 9.1, 5.0 Hz, 1H), 1.80 (dd, *J* = 7.3, 5.0 Hz, 1H), 1.08 – 1.00 (m, 2H), 0.05 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 173.8, 137.2, 135.7, 132.9, 129.1, 128.4, 128.0, 127.3, 126.7, 126.3, 124.3, 63.6, 34.9, 33.5, 18.5, 17.4, -1.4; IR (neat): 2952, 1712, 1244, 834, 692 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{28}O_2NaSi$ 387.17508, found 387.17684; The ee was determined by chiral HPLC: SS-Whelk column, 1 mL/min, 0% *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 64.8 min, Minor: 45.7 min, 85% ee.



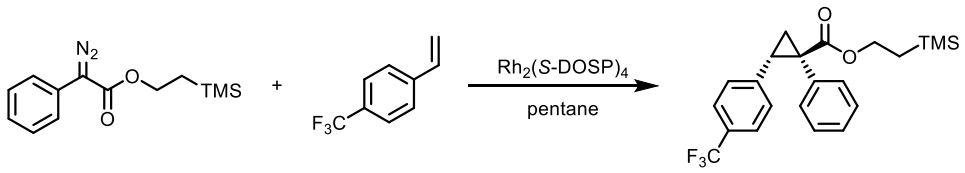

**5.9a** **5.8d** **5.10d**

**2-(trimethylsilyl)ethyl (1*R*,2*S*)-2-(4-acetoxyphenyl)-1-phenylcyclopropane-1-carboxylate (5.10d):** In a 25-mL round bottom flask equipped with a magnetic stir bar, $Rh_2$(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %) and 4-acetoxystyrene (0.38 mL, 2.5 mmol, 5.0 equiv.) were dissolved in pentane (3 mL). To this was added a solution of diazo **5.9a** (131 mg, 0.5 mmol, 1.0 equiv.) in pentane (3 mL) dropwise over 1 hour. The volatiles were removed by rotary evaporation, and the crude residue was purified by column chromatography (10% $Et_2O$ in pentane), giving the product as a clear oil (121 mg, 61% yield). $[\alpha]^{20}_D$: -21.5° (c = 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.13-7.08 (m, 3H), 7.02-6.98 (m, 2H), 6.80-6.70 (m, 4H), 4.21-4.09 (m, 2H), 3.08 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.20 (s, 3H), 2.12 (dd, *J* = 9.3, 4.9 Hz, 1H), 1.81 (dd, *J* = 7.2, 4.9 Hz, 1H), 0.93-0.84 (m, 2H), -0.06 (d, *J* = 1.3 Hz, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 173.8, 169.3, 149.0, 134.6, 134.2, 131.9, 128.8, 127.7, 127.0, 120.7, 63.7, 37.6, 32.2, 21.1, 20.5, 17.2, -1.6; IR (neat): 2953, 1764, 1708, 1193 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{28}O_4NaSi$ 419.1649, found 419.1642; The ee was determined by chiral HPLC: SS-Whelk column, 4% *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 31.9 min, Minor: 47.3 min, 87% ee;



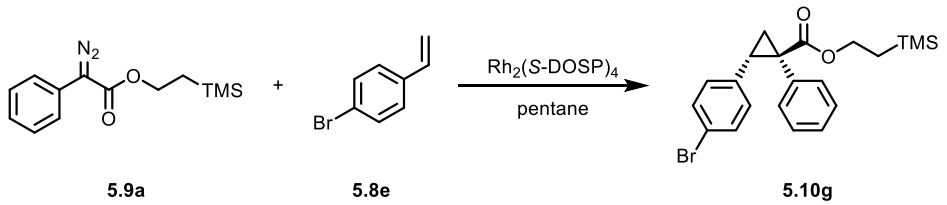

5.9a 5.8e 5.10e

**2-(trimethylsilyl)ethyl (1*R*,2*S*)-2-(4-methoxyphenyl)-1-phenylcyclopropane-1-carboxylate (5.10e):** In a 25-mL round bottom flask equipped with a magnetic stir bar, $Rh_2$(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %) and 4-methoxystyrene (0.33 mL, 2.5 mmol, 5.0 equiv.) were dissolved in pentane (3 mL). To this was added a solution of diazo **5.9a** (131 mg, 0.5 mmol, 1.0 equiv.) in pentane (3 mL) dropwise over 1 hour. The volatiles were removed by rotary evaporation, and the crude residue was purified by column chromatography (3% $Et_2O$ in pentane), giving the product as a clear oil (133 mg, 72% yield). $[\alpha]^{20}_D$: -17.9° (c = 1.03, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.13-7.08 (m, 3H), 7.03-6.98 (m, 2H), 6.70-6.64 (m, 2H), 6.61-6.56 (m, 2H), 4.22-4.09 (m, 2H), 3.68 (s, 3H), 3.03 (dd, *J* = 9.4, 7.3 Hz, 1H), 2.08 (dd, *J* = 9.4, 4.8 Hz, 1H), 1.76 (dd, *J* = 7.3, 4.8 Hz, 1H), 0.93-0.84 (m, 2H), -0.03 (d, *J* = 0.7 Hz, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 174.0, 158.0, 135.0, 132.0, 129.0, 128.5, 127.6, 126.8, 113.1, 63.5, 55.1, 37.3, 32.4, 20.3, 17.2, -1.5; IR (neat): 2952, 1708, 1515, 1246, 829 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{28}O_3NaSi$ 391.1700, found 391.1708; The ee was determined by chiral HPLC: SS-Whelk column, 1 mL/min, 1% *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 13.6 min, Minor: 11.6 min, 81% ee;




**5.9a** **5.8e** **5.10f**

**2-(trimethylsilyl)ethyl (1*R*,2*S*)-1-phenyl-2-(4-(trifluoromethyl)phenyl)cyclopropane-1-carboxylate (5.10f):** In a 25-mL round bottom flask equipped with a magnetic stir bar, $Rh_2$(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %) and 4-(trifluoromethyl)styrene (0.37 mL, 2.5 mmol, 5.0 equiv.) were dissolved in pentane (3 mL). To this was added a solution of diazo **5.9a** (131 mg, 0.5 mmol, 1.0 equiv.) in pentane (3 mL) dropwise over 1 hour. The volatiles were removed by rotary evaporation, and the crude residue was purified by column chromatography (4% $Et_2O$ in pentane), giving the product as a clear oil (146 mg, 72% yield). $[\alpha]^{20}_D$: -17.8° (c = 1.07, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 18.5 Hz, 2H), 7.18-7.08 (m, 3H), 7.05-6.96 (m, 2H), 6.84 (d, *J* = 8.1 Hz, 2H), 4.26-4.10 (m, 2H), 3.13 (dd, *J* = 9.2, 7.1 Hz, 1H), 2.17 (dd, *J* = 9.2, 5.0 Hz, 1H), 1.87 (dd, *J* = 7.2, 5.0 Hz, 1H), 0.96-0.84 (m, 2H), -0.04 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 173.5, 141.0, 134.2, 131.8, 128.2, 127.8, 127.2, 124.5, 63.9, 38.2, 32.2, 20.7, 17.2, -1.6; IR (neat): 2954, 1711, 1324, 834 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{25}O_2F_3NaSi$ 429.1468, found 429.1476; The ee was determined by chiral HPLC: SS-Whelk column, 1 mL/min, 0% *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 26.0 min, Minor: 18.2 min, 84% ee;



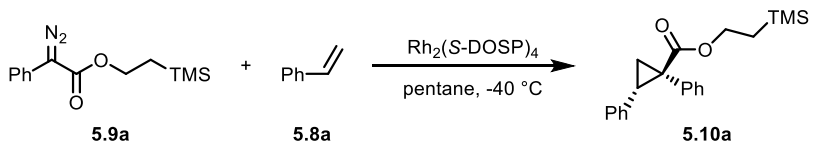

5.9a 5.8e 5.10g

**2-(trimethylsilyl)ethyl (1*R*,2*S*)-2-(4-bromophenyl)-1-phenylcyclopropane-1-carboxylate (5.10g):** In a 25-mL round bottom flask equipped with a magnetic stir bar, $Rh_2$(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %) and 4-bromostyrene (0.33 mL, 2.5 mmol, 5.0 equiv.) were dissolved in pentane (3 mL). To this was added a solution of diazo **5.9a** (131 mg, 0.5 mmol, 1.0 equiv.) in pentane (3 mL) dropwise over 1 hour. The volatiles were removed by rotary evaporation, and the crude residue was purified by column chromatography (3% $Et_2O$ in pentane), giving the product as a clear oil (154 mg, 74% yield). $[\alpha]^{20}_D$: -14.7° (c = 1.02, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.19-7.09 (m, 5H), 7.05-6.96 (m, 2H), 6.62 (d, *J* = 8.7 Hz, 2H), 4.25-4.07 (m, 2H), 3.02 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.12 (dd, *J* = 9.3, 5.0 Hz, 1H), 1.80 (dd, *J* = 7.2, 5.0 Hz, 1H), 0.95-0.84 (m, 2H), -0.07 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 173.7, 135.8, 134.4, 131.9, 130.7, 129.6, 127.8, 127.1, 120.1, 63.8, 37.8, 32.2, 20.5, 17.2, -1.6; IR (neat): 2952, 1709, 1248, 697 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+H-C_2H_4]^+$ calcd for $C_{19}H_{22}O_2BrSi$ 389.0567, found 389.0565; The ee was determined by chiral HPLC: SS-Whelk column, 1 mL/min, 0% *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 40.3 min, Minor: 29.4 min, 86% ee;

**Procedure for low-temperature cyclopropanation studies:**

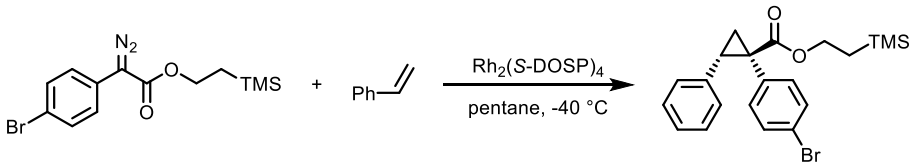
The same procedure was followed as for the preceding cyclopropanation reactions, with cooling of the catalyst and styrene mixture to -40 °C in a bath of dry ice and

acetonitrile. The diazo solution was then added at -40 °C, and following addition the mixture was allowed to warm slowly to room temperature.




**5.9a** **5.8a** **5.10a**

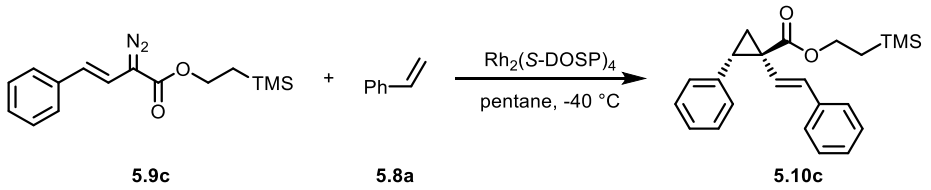
**2-(trimethylsilyl)ethyl (1*R*,2*S*)-1,2-diphenylcyclopropane-1-carboxylate (5.10a):** The above procedure for low-temperature cyclopropanation was followed, with $Rh_2$(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %), styrene (0.29 mL, 2.5 mmol, 5.0 equiv.), and diazo **5.9a** (131 mg, 0.5 mmol, 1.0 equiv.). The crude residue was purified by column chromatography (4% $Et_2O$ in pentane), giving the product as a clear oil (116 mg, 69% yield). The ee was determined by chiral HPLC: SS-Whelk column, 1 mL/min, 0% *i*PrOH in hexanes, $\lambda$ = 230 nm. $t_R$: Major: 37.8 min, Minor: 29.8 min, 96% ee;




**5.9b** **5.8a** **5.10b**

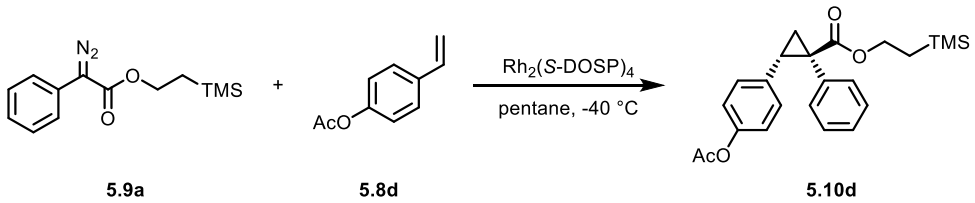
**2-(trimethylsilyl)ethyl (1*R*,2*S*)-1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate (5.10b):** The above procedure for low-temperature cyclopropanation was followed, with $Rh_2$(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %), styrene (0.29 mL, 2.5 mmol, 5.0 equiv.), and diazo **5.9b** (171 mg, 0.5 mmol, 1.0 equiv.). The crude residue was purified by column chromatography (4% $Et_2O$ in pentane), giving the product as a pale yellow oil (131 mg, 63% yield). The ee was determined by chiral HPLC (SS-Whelk, 0%

isopropanol in hexanes, 1 mL/min, UV 230 nm) $t_R$: Major: 49.6 min, Minor: 34.8 min, 95% ee;




**5.9c** **5.8a** **5.10c**

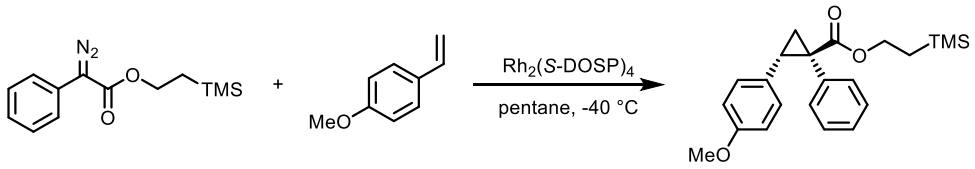
**2-(trimethylsilyl)ethyl (1*S*,2*S*)-2-phenyl-1-((*E*)-styryl)cyclopropane-1-carboxylate (5.10c):** The above procedure for low-temperature cyclopropanation was followed, with $Rh_2$(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %), styrene (0.29 mL, 2.5 mmol, 5.0 equiv.), and diazo **5.9c** (144 mg, 0.5 mmol, 1.0 equiv.). The crude residue was purified by column chromatography (4% $Et_2O$ in pentane), giving the product as a clear oil (129 mg, 71% yield). The ee was determined by chiral HPLC: SS-Whelk column, 1 mL/min, 0% *i*PrOH in hexanes, $\lambda$ = 230 nm. $t_R$: Major: 63.0 min, Minor: 44.3 min, 87% ee




**5.9a** **5.8d** **5.10d**

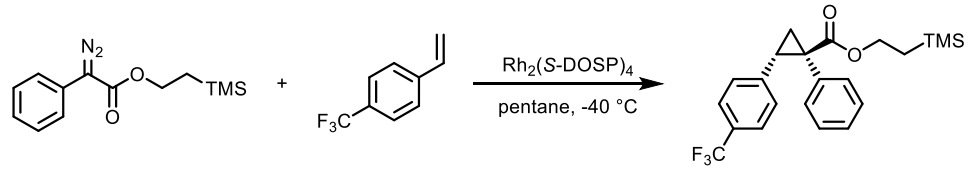
**2-(trimethylsilyl)ethyl (1*R*,2*S*)-2-(4-acetoxyphenyl)-1-phenylcyclopropane-1-carboxylate (5.10d):** The above procedure for low-temperature cyclopropanation was followed, with $Rh_2$(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %), 4-acetoxystyrene (0.38 mL, 2.5 mmol, 5.0 equiv.), and diazo **5.9a** (131 mg, 0.5 mmol, 1.0 equiv.). The crude residue was purified by column chromatography (7-20% $Et_2O$ in pentane), giving the product as a clear oil (128 mg, 65% yield). The ee was determined by chiral HPLC: SS-

Whelk column, 1 mL/min, 4% *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 35.8 min, Minor: 53.2 min, 96% ee




**5.9a** **5.8e** **5.10e**

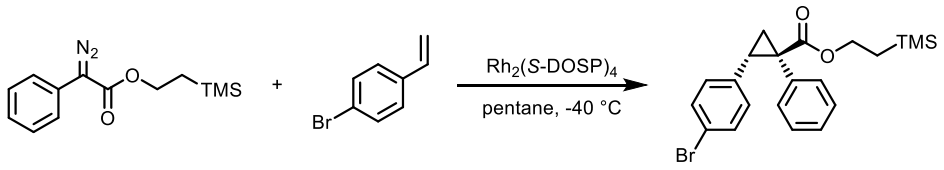
**2-(trimethylsilyl)ethyl (1*R*,2*S*)-2-(4-methoxyphenyl)-1-phenylcyclopropane-1-carboxylate (5.10e):** The above procedure for low-temperature cyclopropanation was followed, with $Rh_2$(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %), 4-methoxystyrene (0.33 mL, 2.5 mmol, 5.0 equiv.), and diazo **5.9a** (131 mg, 0.5 mmol, 1.0 equiv.). The crude residue was purified by column chromatography (4% $Et_2O$ in pentane), giving the product as a clear oil (140 mg, 76% yield). The ee was determined by chiral HPLC: SS-Whelk column, 1 mL/min, 1% *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 15.8 min, Minor: 13.5 min, 91% ee




**5.9a** **5.8e** **5.10f**

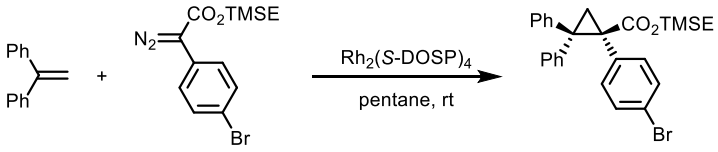
**2-(trimethylsilyl)ethyl (1*R*,2*S*)-1-phenyl-2-(4-(trifluoromethyl)phenyl)cyclopropane-1-carboxylate (5.10f):** The above procedure for low-temperature cyclopropanation was followed, with $Rh_2$(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %), 4-(trifluoromethyl)styrene (0.37 mL, 2.5 mmol, 5.0 equiv.), and diazo **5.9a** (131 mg, 0.5 mmol, 1.0 equiv.). The crude residue was purified by column chromatography (3%

$Et_2O$ in pentane), giving the product as a clear oil (102 mg, 50% yield). The ee was determined by chiral HPLC: SS-Whelk column, 1 mL/min, 0% *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 26.1 min, Minor: 18.5 min, 96% ee;




**5.9a** **5.8e** **5.10g**

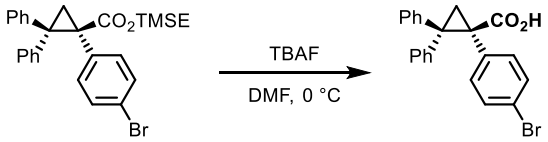
**2-(trimethylsilyl)ethyl (1*R*,2*S*)-2-(4-bromophenyl)-1-phenylcyclopropane-1-carboxylate (5.10g):** The above procedure for low-temperature cyclopropanation was followed, with $Rh_2$(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %), 4-bromostyrene (0.33 mL, 2.5 mmol, 5.0 equiv.), and diazo **5.9a** (131 mg, 0.5 mmol, 1.0 equiv.). The crude residue was purified by column chromatography (3% $Et_2O$ in pentane), giving the product as a clear oil (139 mg, 67% yield). The ee was determined by chiral HPLC: SS-Whelk column, 1 mL/min, 0% *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 40.3 min, Minor: 30.3 min, 96% ee;




**5.1** **5.9b** **5.13**

**2-(trimethylsilyl)ethyl (*S*)-1-(4-bromophenyl)-2,2-diphenylcyclopropane-1-carboxylate (5.13):** In a 25-mL round bottom flask equipped with a magnetic stir bar, $Rh_2$(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %) and 1,1-diphenylethylene (0.18 mL, 1.0 mmol, 2.0 equiv.) were dissolved in pentane (3 mL). To this was added a solution of

diazo **5.9b** (171 mg, 0.5 mmol, 1.0 equiv.) in pentane (3 mL) dropwise over 1 hour. The volatiles were removed by rotary evaporation, and the crude residue was purified by column chromatography (3% $Et_2O$ in pentane), giving the product as a clear oil (170 mg, 73% yield). $[\alpha]^{20}_D$: 62.7° (c = 1.55, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.52-7.47 (m, 2H), 7.34-7.19 (m, 7H), 7.05-6.91 (m, 5H), 3.87 (ddd, *J* = 11.8, 10.8, 5.8 Hz, 1H), 3.69 (ddd, *J* = 11.9, 10.8, 5.4 Hz, 1H), 2.67 (d, *J* = 5.6 Hz, 1H), 2.36 (d, *J* = 5.6 Hz, 1H), 0.61 (ddd, *J* = 13.6, 11.9, 5.8 Hz, 1H), 0.48 (ddd, *J* = 13.6, 11.8, 5.4 Hz, 1H), -0.09 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.7, 141.9, 139.4, 135.1, 133.5, 130.6, 130.0, 128.7, 128.3, 127.8, 127.0, 126.3, 121.1, 63.5, 44.5, 42.5, 22.5, 16.8, -1.6; IR (neat): 2951, 1715, 833, 694 $cm^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{27}H_{29}O_2BrNaSi$ 515.1012, found 515.1021;

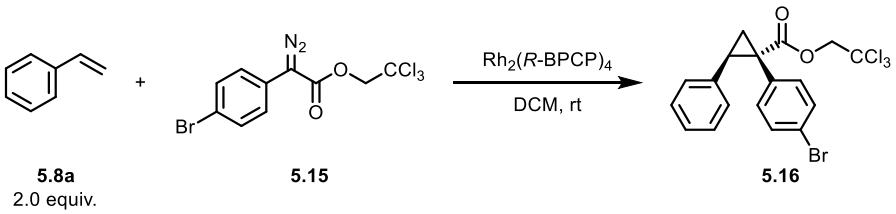



**5.13** **5.14**

**(*S*)-1-(4-bromophenyl)-2,2-diphenylcyclopropanecarboxylic acid (5.14):** Tetrabutylammonium fluoride hydrate (TBAF) (112 mg, 0.4 mmol, 2.0 equiv.) was added to a solution of cyclopropane **5.13** (0.1 g, 0.2 mmol, 1.0 equiv.) in 2 mL dimethylformamide (DMF) at 0 ºC, and the reaction was stirred overnight. The reaction was quenched with $dH_2O$ (2 mL) and 6M HCl (1 mL) and stirred for 20 minutes. The reaction was extracted 3x with EtOAc, and the combined extracts were washed 3x with $dH_2O$, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (25% EtOAc in hexanes), giving the carboxylic acid product as a white solid (48 mg, 61% yield). The spectral data were consistent with that found in the

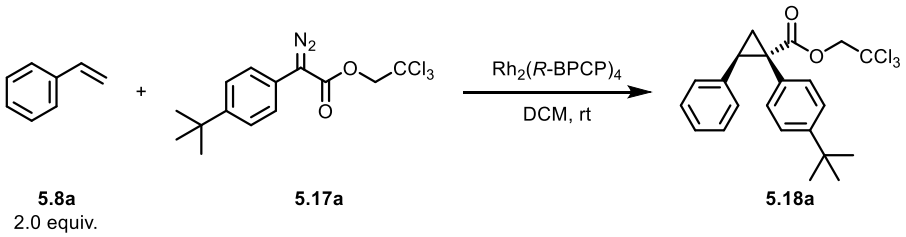
literature.[14] The ee was determined by chiral HPLC: AD-H column, 1 mL/min 5% *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 14.7 min, Minor: 22.3 min, 88% ee;

The preparation and experimental data for the TCE diazo compounds in this section can be found in chapter 4.

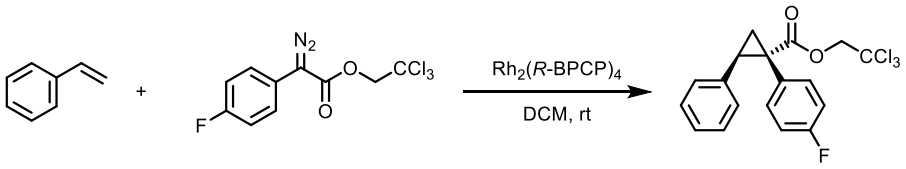



**5.8a** 2.0 equiv. **5.15** **5.16**

**2,2,2-trichloroethyl (1*S*,2*R*)-1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate (5.16):** The diazo (186 mg, 0.5 mmol, 1.0 equiv.) in 4 mL DCM was added dropwise over 30 minutes to a solution of $Rh_2$(*R*-BPCP)$_4$ (4.4 mg, 0.5 mol %) and styrene (0.12 mL, 1.0 mmol, 2.0 equiv.) in 2 mL DCM at room temperature. The solvent was removed, and the crude residue was purified by column chromatography (2% $Et_2O$ in pentane) to give the product as a white solid (156 mg, 69% yield). $[\alpha]^{20}_D$: 2.3 (c. 1.02, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.27-7.24 (m, 2H), 7.13-7.08 (m, 3H), 6.95-6.91 (m, 2H), 6.83-6.78 (m, 2H), 4.83 (d, 1H, *J* = 11.9 Hz), 4.64 (d, 1H, *J* = 11.9 Hz), 3.22 (dd, 1H, *J* = 9.3, 7.5 Hz), 2.28 (dd, 1H, *J* = 9.3, 5.2 Hz), 1.97 (dd, 1H, *J* = 7.5, 5.2 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 171.5, 135.2, 133.6, 132.9, 130.9, 128.0, 128.0, 126.8, 121.5, 94.9, 74.4, 36.6, 33.9, 20.2; IR (film): 3031, 2953, 1732, 1151 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{14}O_2BrCl_3Na$ 468.9135; found 468.9140; The ee was determined by chiral HPLC: OJ-H column, 1 mL/min, 1 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 9.5 min, Minor: 6.5 min, 96% ee.




**2,2,2-trichloroethyl (1*S*,2*R*)-1-(4-(*tert*-butyl)phenyl)-2-phenylcyclopropane-1-carboxylate (5.18a):** The diazo (175 mg, 0.5 mmol, 1.0 equiv.) in 5 mL DCM was added dropwise over 30 minutes to a solution of $Rh_2$(*R*-BPCP)$_4$ (4.4 mg, 0.5 mol %) and styrene (0.12 mL, 1.0 mmol, 2.0 equiv.) in 2 mL DCM at room temperature. The solvent was removed, and the crude residue was purified by column chromatography (2% $Et_2O$ in pentane) to give the product as a white solid (156 mg, 73% yield). $[\alpha]^{20}_D$: 3.4 (c. 1.15, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.13 (d, 2H, *J* = 8.2 Hz), 7.06-7.03 (m, 3H), 6.97 (d, 2H, *J* = 8.2 Hz), 6.79-6.75 (m, 2H), 4.82 (d, 1H, *J* = 11.9 Hz), 4.64 (d, 1H, *J* = 11.9 Hz), 3.18 (dd, 1H, *J* = 9.3, 7.4 Hz), 2.27 (dd, 1H, *J* = 9.3, 5.0 Hz), 1.96 (dd, 1H, *J* = 5.0, 7.4 Hz), 1.21 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 172.2, 150.1, 135.9, 131.6, 130.5, 128.1, 127.7, 126.4, 124.6, 95.2, 74.3, 36.9, 34.4, 33.7, 31.3, 20.4; IR (film): 3031, 2961, 2867, 1732, 1152 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{23}O_2Cl_3Na$ 447.0656; found 447.0657; The ee was determined by chiral HPLC: OJ-H column, 1 mL/min, 1 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 5.2 min, Minor: 3.3 min, 98% ee.

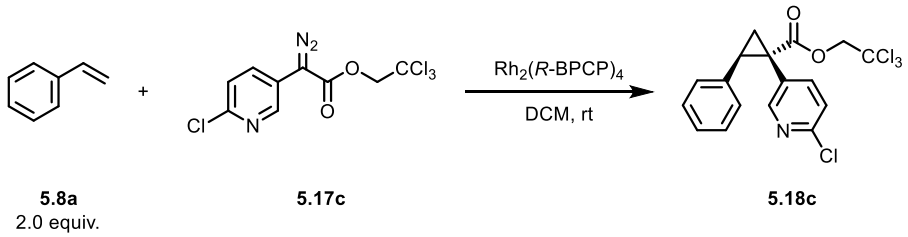



**5.8a**
2.0 equiv.

**5.17b**

**5.18b**

**2,2,2-trichloroethyl (1*S*,2*R*)-1-(4-fluorophenyl)-2-phenylcyclopropane-1-carboxylate (5.18b):** The diazo (156 mg, 0.5 mmol, 1.0 equiv.) in 5 mL DCM was added dropwise over 30 minutes to a solution of $Rh_2$(*R*-BPCP)$_4$ (4.4 mg, 0.5 mol %) and styrene (0.12 mL, 1.0 mmol, 2.0 equiv.) in 2 mL DCM at room temperature. The solvent was removed, and the crude residue was purified by column chromatography (2% $Et_2O$ in pentane) to give the product as a white solid (112 mg, 58% yield). $[\alpha]^{20}_D$: 11.9 (c. 1.28, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.11-7.07 (m, 3H), 7.04-7.00 (m, 2H), 6.84-6.77 (m, 4H), 4.82 (d, 1H, *J* = 11.9 Hz), 4.64 (d, 1H, *J* = 11.9 Hz), 3.21 (dd, 1H, *J* = 9.3, 7.5 Hz), 2.28 (dd, 1H, *J* = 9.3, 5.2 Hz), 1.97 (dd, 1H, *J* = 7.5, 5.2 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 172.0, 161.9 (d, *J* = 246.2 Hz), 135.4, 133.6 (d, *J* = 8.3 Hz), 129.6 (d, *J* = 3.4 Hz), 128.1, 127.9, 126.8, 114.7 (d, *J* = 21.4), 95.0, 74.4, 36.4, 34.0, 20.4; IR (Film): 3032, 2954, 1732, 1513, 1239 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+NH_4]^+$ calcd for $C_{18}H_{18}O_2NCl_3F$ 404.0382; found 404.0389; The ee was determined by chiral HPLC: OJ-H column, 1 mL/min, 1 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 9.1 min, Minor: 6.2 min, 93% ee.

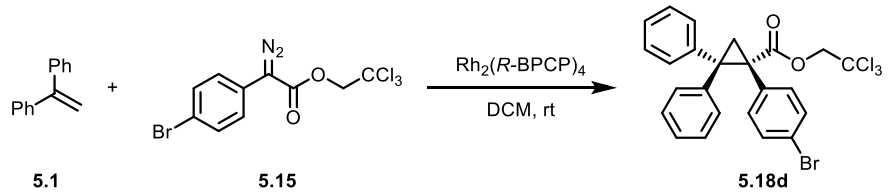



**5.8a**
2.0 equiv.

**5.17c**

**5.18c**

**2,2,2-trichloroethyl (1*S*,2*R*)-1-(6-chloropyridin-3-yl)-2-phenylcyclopropane-1-carboxylate (5.18c)**: The diazo (156 mg, 0.5 mmol, 1.0 equiv.) in 5 mL DCM was added dropwise over 30 minutes to a solution of $Rh_2$(*R*-BPCP)$_4$ (4.4 mg, 0.5 mol %) and styrene (0.12 mL, 1.0 mmol, 2.0 equiv.) in 2 mL DCM at room temperature. The solvent was removed, and the crude residue was purified by column chromatography (9:1 hexanes:EtOAc) to give the product as an oil with a yellow tint (124 mg, 61% yield). $[\alpha]^{20}_D$: -5.2 (c. 1.27, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 8.14 (d, 1H, *J* = 2.4 Hz), 7.27 (dd, 1H, *J* = 8.3, 2.4 Hz), 7.16-7.10 (m, 3H), 7.06 (d, 1H, *J* = 8.3 Hz), 6.87-6.81 (m, 2H), 4.84 (d, 1H, *J* = 11.9 Hz), 4.66 (d, 1H, *J* = 11.9 Hz), 3.28 (dd, 1H, *J* = 9.4, 7.5 Hz), 2.35 (dd, 1H, *J* = 9.4, 5.4 Hz), 2.06 (dd, 1H, *J* = 7.5, 5.4 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 170.9, 152.4, 150.3, 142.4, 134.2, 129.1, 128.4, 128.1, 127.4, 123.3, 94.8, 74.5, 33.9, 33.9, 19.5; IR (film): 3031, 2955, 1732, 1110 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{13}O_2NCl_4Na$ 425.9593; found 425.9596; The ee was determined by chiral HPLC: OJH column, 1 mL/min, 1 % iPrOH in hexanes, λ = 230 nm. $t_R$: Major: 21.0 min, Minor: 17.7 min, 93% ee.




**2,2,2-trichloroethyl (*R*)-1-(4-bromophenyl)-2,2-diphenylcyclopropane-1-carboxylate (5.18d):** The diazo (186 mg, 0.5 mmol, 1.0 equiv.) in 5 mL DCM was added dropwise over 30 minutes to a solution of $Rh_2$(*R*-BPCP)$_4$ (8.8 mg, 1 mol %) and 1,1-diphenylethylene (0.18 mL, 1.0 mmol) in 2 mL DCM at room temperature. The solvent was removed, and the crude residue was purified by column chromatography (2% $Et_2O$ in pentane) to give the product as a colorless, sticky oil (202 mg, 77% yield). $[\alpha]^{20}_D$: -54.4 (c. 1.17, $CHCl_3$); $^1$H NMR (600 MHz; $CDCl_3$) δ 7.53-7.49 (m, 2H), 7.33-7.21 (m, 7H), 7.04-6.95 (m, 5H), 4.51 (d, 1H, *J* = 11.9 Hz), 4.11 (d, 1H, *J* = 11.9 Hz), 2.74 (d, 1H, *J* = 5.7 Hz), 2.48 (d, 1H, *J* = 5.7 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 169.1, 141.3, 138.9, 134.0, 133.6, 130.8, 130.0, 128.7, 128.6, 128.0, 127.4, 126.7, 121.5, 94.3, 75.3, 45.7, 42.2, 23.0; IR (Film): 3026, 1735, 1203, 704 cm$^{-1}$; HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{24}H_{18}O_2BrCl_3Na$ 544.9480; found 544.9461; The ee was determined by chiral HPLC: OJ-H column, 1 mL/min, 1 % *i*PrOH in hexanes, λ = 230 nm. $t_R$: Major: 6.6 min, Minor: 18.2 min, 86% ee.

## 5.5 References

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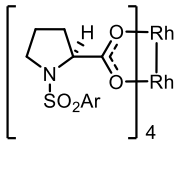
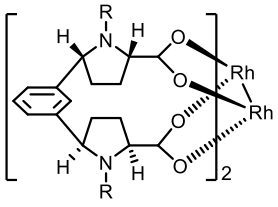
# Appendix A – Structures of Dirhodium Catalysts

## Chiral Catalysts



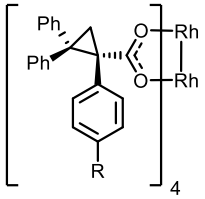
Ar = *p*-$C_{12}H_{25}C_6H_4$

**$Rh_2$(*S*-DOSP)$_4$**



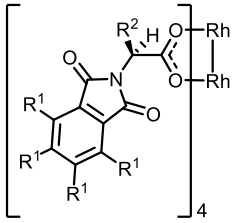
R = $SO_2$-2,4,6-tri-*i*-$PrC_6H_2$

**$Rh_2$(*S*-bi-TISP)$_2$**

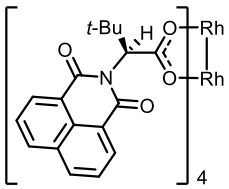


R = Br **$Rh_2$(*R*-BTPCP)$_4$**

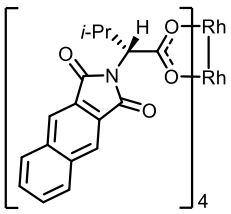
R = Ph **$Rh_2$(*R*-BPCP)$_4$**



| | |
|---|---|
| $R^1$ = H, $R^2$ = *t*-Bu | **$Rh_2$(*S*-PTTL)$_4$** |
| $R^1$ = H, $R^2$ = adamantyl | **$Rh_2$(*S*-PTAD)$_4$** |
| $R^1$ = H, $R^2$ = *i*-Pr | **$Rh_2$(*S*-PTV)$_4$** |
| $R^1$ = Cl, $R^2$ = *t*-Bu | **$Rh_2$(*S*-TCPTTL)$_4$** |
| $R^1$ = Cl, $R^2$ = adamantyl | **$Rh_2$(*S*-TCPTAD)$_4$** |
| $R^1$ = Cl, $R^2$ = *i*-Pr | **$Rh_2$(*S*-TCPTV)$_4$** |

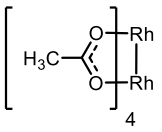


**$Rh_2$(*S*-NTTL)$_4$**

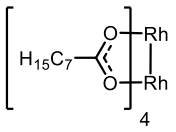


**$Rh_2$(*R*-BPTV)$_4$**

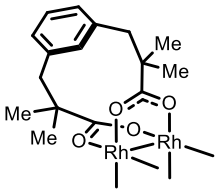
# Achiral Catalysts



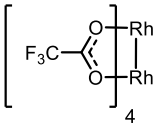
**$Rh_2(OAc)_4$**



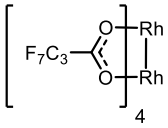
**$Rh_2(OOct)_4$**



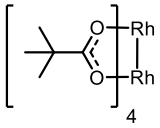
**$Rh_2(esp)_2$**



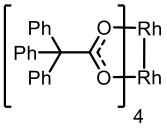
**$Rh_2(TFA)_4$**



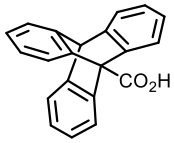
**$Rh_2(pfb)_4$**



**$Rh_2(Piv)_4$**



**$Rh_2(Piv)_4$**



9-triptycenecarboxylic acid
ligand for $Rh_2(9\text{-trp})_4$