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Jeremiah B. Varelman December 8, 2020

Structural Requirements of the Sulfonyl Prolinate Ligands for Dirhodium Catalysis

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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
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Abstract

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Previous experimental studies have indicated that arylsulfonyl prolinate ligands might be a structural requirement in dirhodium tetraprolinate catalysis. The research presented here expands upon and tests this notion using aryl carbene precursors and two N-alkylsulfonyl prolinate catalysts, N-dodecylsulfonyl and N-methylsulfonyl. The results of this research demonstrate that arylsulfonyl prolinate ligands are not a structural requirement for achieving high enantioselectivity in cyclopropanation and C-H functionalization reactions. Currently, extensive computational studies are in progress by other members of the Davies group to develop a new model to explain the enantioselectivity of the N-sulfonylprolinate catalysts. The experimental data presented herein show that an alkylsulfonyl prolinate ligand is similarly effective at asymmetric induction as the arylsulfonyl derivatives used previously. Therefore, the new model from the computational calculations will need to address the notion that the aryl component of the sulfonyl ligand is not a critical requirement for achieving high asymmetric induction.

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Finally, I would like to thank Dr. O'Toole for integrating a lot of chemistry and biological topics together in her courses. It provided me with a wide and more cohesive knowledge of the material I learned throughout my college education.

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Figures and Tables

1. Introduction

1.1 The Requirement of Stereoselective Synthesis in Chemistry

If two compounds contain the same number and type of atoms (referred to as the empirical formula), but differ from each other in the way that the atoms are arranged; these compounds are called isomers. A specific type of isomer, a stereoisomer, is where the compounds have the same connectivity, but differ only in the spatial arrangement of the atoms[1]. This concept is illustrated in Figure 1.1.1.

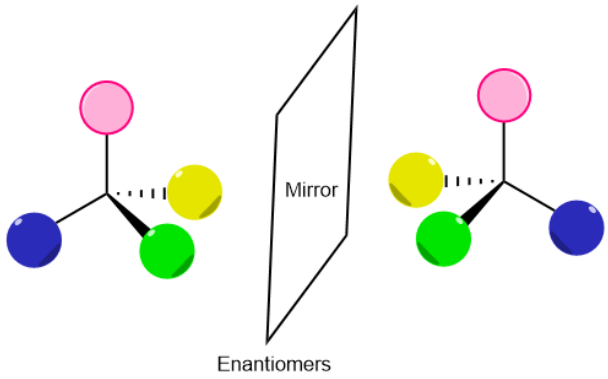

Figure 1.1.1: Visualization of stereoisomers (enantiomers). Bolded wedge represents the atom coming out of the page. Hashed wedge represents the atom coming into the page

These molecules represented in Figure 1.1.1 are a special type of stereoisomers called enantiomers. Enantiomers are chiral molecules that have a non-superimposable mirror image counterpart[1]. A common example to illustrate this concept is a person's right and left hand; your left hand, a mirror image of your right hand, cannot be superimposed onto each other making them "enantiomers". Additionally, some molecules are said to be prochiral if the addition of a group to the central atom results in a chiral center. An example of this is illustrated in Figure 1.1.2.

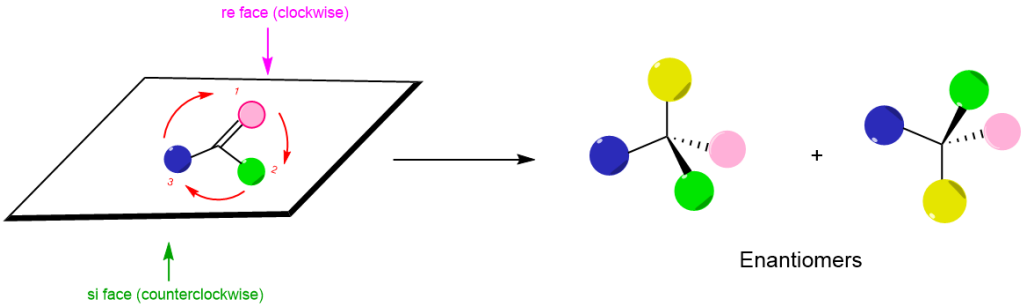

Figure 1.1.2: Diagram of sp^2 prochiral center and the resulting possible enantiomers

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The sp^2 hybridized molecule in Figure 1.1.2 has two faces denoted re and si. The re face is the face that when looking at, forms a clockwise circle using Cahn-Ingold-Prelog priority rules, while the si face forms a counterclockwise circle. During a chemical reaction, this prochiral molecule can form a chiral center if the group that binds is unique. The consideration of chirality in chemical reactions is extremely important due to its biological consequences. Changing the spatial arrangement of atoms in a molecule can affect the way enzymes interact with the molecule. For example, it has been shown that d-propranolol can inhibit the conversion of thyroxin to triiodothyronine, while l-propranolol allows the conversion[2] (Fig. 1.1.3).

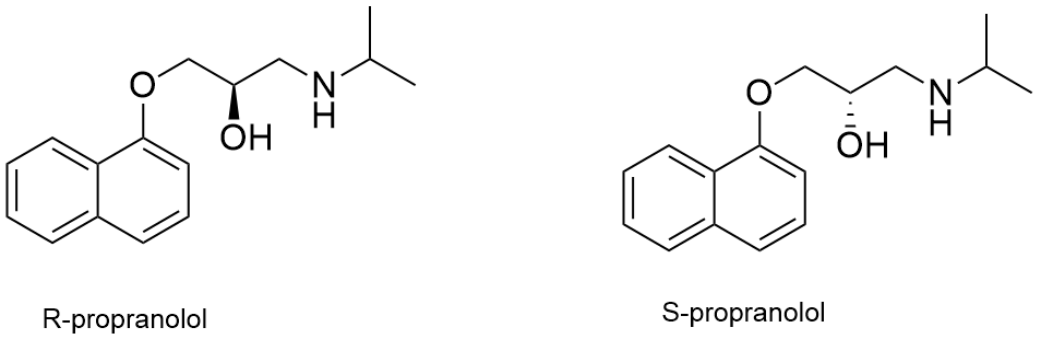


Figure 1.1.3: Two enantiomers of propranolol

This opens up different avenues for medical treatments based on enantiomerically pure drugs; this is evident in the pharmaceutical companies where fifty-six percent of drugs are

chiral[3]. Thus, when performing chemical reactions, it is imperative to control for the stereochemistry of the product. Catalyst-controlled synthesis is a method to control the stereochemical outcome of the products. In the Davies group, chiral dirhodium carbenes are used to selectively control the stereochemical outcome of chemical reactions.

1.2 Carbene Formation with Diazoacetates and Diazo Modification Effect on Selectivity

The Davies group uses carbenes in the majority of their C-H functionalization reactions. Carbenes are "zwitterionic-like" species that can be classified as either a singlet or triplet carbenes depending on the two electrons' spin on the carbon center. A singlet carbene's two electrons have opposite spin in a single orbital, while a triplet carbene's two electrons have parallel spin in two different orbitals (Fig. 1.2.1). These two different types of carbenes result in very diverse reactivity profiles. Singlet carbenes have an unfilled p-orbital that tends to make them act as electrophiles, while triplet carbenes act as diradical species. Hence, singlet carbene reactions can be considered stereospecific, while triplet carbene reactions can be considered stereoselective[4].

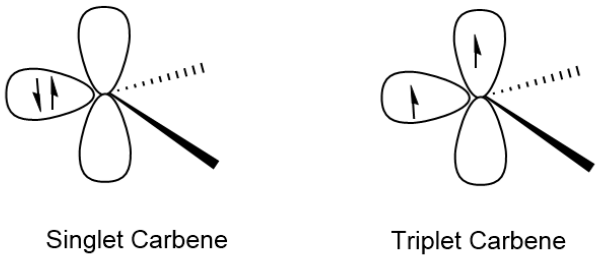


Figure 1.2.1: Depiction of Singlet and Triplet Carbene

In the Davies group, carbenes are generated through the metal-catalyzed decomposition of nitrogen precursors, such as diazoacetates and triazoles. The chiral dirhodium catalysts form a

paddlewheel complex where the rhodium atoms are bridged, connected to four carboxylate ligands, and have two positions available to form carbenes[4,6]. As shown in the Figure 1.2.2a, the diazo compound coordinates to the rhodium catalyst and then gets displaced by the back-bonding from the rhodium metal, producing an electrophilic carbene; this reaction is favored by the loss of nitrogen gas which acts as a thermodynamic sink[5]. Traditionally, carbenes were formed from diazo compounds that had either two electron with-drawing groups (EWG) or a sole EWG, denoted as "acceptor-acceptor" and "acceptor-only" carbenes, respectively. The use of "acceptor-acceptor" and "acceptor-only" carbenes resulted in highly reactive, unselective reactions. Thus, the Davies group used the relatively unexplored "donor-acceptor" carbenes; the "donor-acceptor" carbenes are formed from diazo compounds that have an EWG and an electron donating group (EDG). The EDG attenuates the reactivity of the carbene by donating electron density to the carbon center[6]. This allows for enhanced stability and selectivity in chemical reactions (Fig. 1.2.2b).

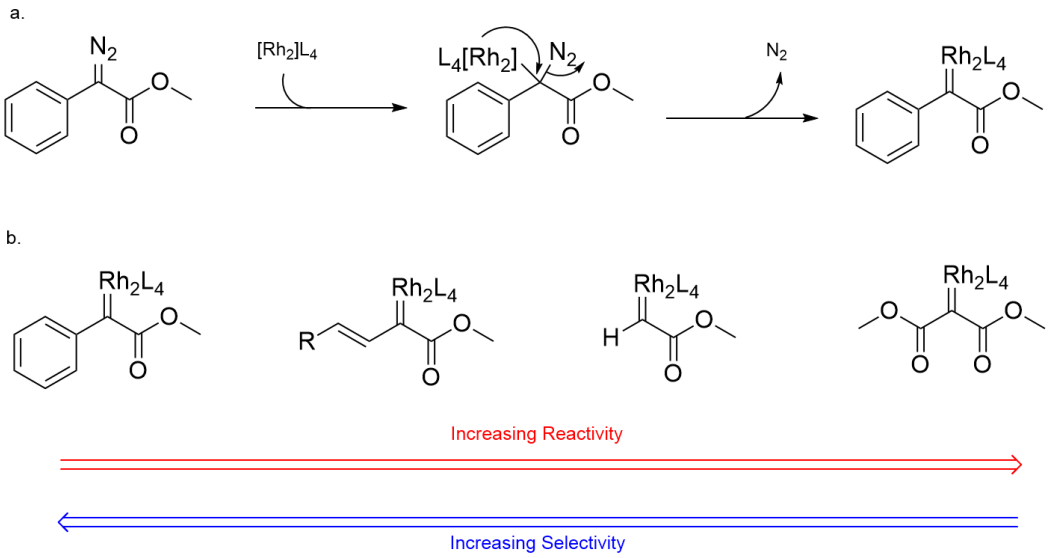


Figure 1.2.2: a.) Formation of rhodium-carbene. b.) Illustration of reactivity and selectivity with various carbene types.

Additionally, modification of the EDG and EWG of the diazoacetate impacts the enantioselectivity of the reaction. Previous research has demonstrated that the size of the EWG (typically an ester) has a large effect on the enantioselectivity of cyclopropanation reactions; increasing the size of the ester decreases the enantioselectivity of cyclopropanation reactions because it blocks the open face of the carbene due to the steric clash with the sulfonyl ligands of the catalyst[7]. Similar to the rationale behind the "donor-acceptor" carbenes, the switch from vinyl to aryl diazoacetates results in higher enantioselectivity in chemical reactions. As stated in section 1.1, stereochemical control in chemical reactions is crucial for the majority of pharmaceutical drugs and their applications in biological systems.

1.3 Two Major Reactions for Donor-Acceptor Carbenes: Cyclopropanation and C-H Functionalization Reactions

Cyclopropanation and C-H functionalization reactions are two major classes of reactions that are performed with rhodium carbenoid species. The cyclopropanation scheme is shown in Figure 1.3.1a below. The reaction of the carbenoid intermediate with an alkene generates a cyclopropane with two stereocenters. In a cyclopropanation reaction, the control of the stereochemistry of both stereocenters is of particular concern. To control the stereochemistry of both stereocenters, the Davies lab uses "donor'acceptor" carbenes; cyclopropanations with "donor-acceptor" carbenes proceed with characteristically high diastereoselectivity, while also allowing for control of the enantioselectivity through the catalyst. In the case of C-H functionalization, the carbene inserts into a C-H bond, functionalizing the hydrocarbon bonds without the need for prototypical functional groups (Figure 1.3.1b).

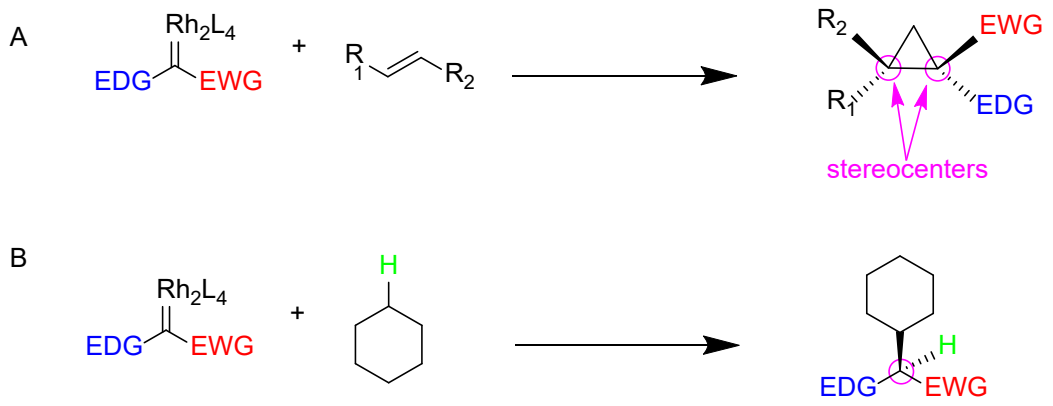


Figure 1.3.1: A) Scheme for cyclopropanation reactions and B) C-H functionalization reactions with "donor-acceptor" carbenes. Pink circles represents stereocenters.

Both cyclopropanation and C-H functionalization reactions occur without the substrate coordinating to the transition-metal. Instead, the dirhodium catalyzed cyclopropanation reaction is concerted and nonsynchronous where the electrophilic carbene attacks the alkene, forming a three membered transition state (with a build-up of positive charge on the alkene), displacing the catalyst and forming the cyclopropanation product (Fig. 1.3.2a). The cyclopropanation mechanism is similar to the C-H functionalization mechanism that proceeds via a concerted hydride transfer event, with a build-up of positive charge where carbene insertion takes place[7] (Fig. 1.3.2b).

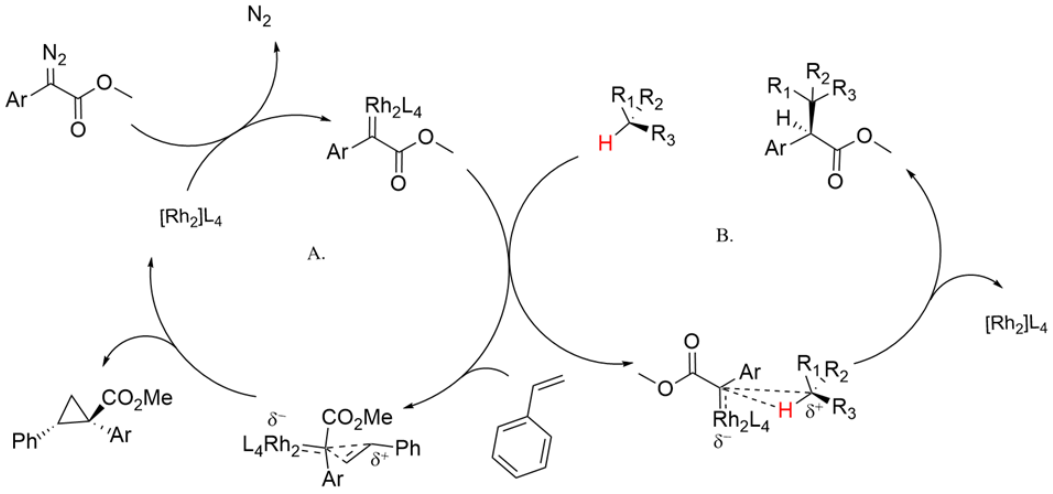


Figure 1.3.2: A.) Mechanism for cyclopropanation and B.) C-H functionalization reaction

Additionally, the dirhodium catalysts can target specific bonds in a particular substrate through catalyst control. This allows for the development of new reaction pathways that couldn't be explored with traditional directing-group chemistry.

1.4 Symmetric Models for Dirhodium Catalysts

In the Davies group, 1st, 2nd, and 3rd generation dirhodium catalyst have been designed to not only stereoselectivity control chemical reactions, but also to selectively target different C-H bonds. A major theme with these catalyst designs have been utilizing various sterically demanding ligands that afford a variety of different reactivity profiles. The sterically demanding ligands allow the catalyst to obtain three highly symmetric conformations denoted C_2, C_4, and D_2 (Fig. 1.4.1). In the C_2 symmetric model the ligands are orientated with two ligands on the top face (alpha) and two ligands on the bottom face (beta). In the C_4 symmetric model the four ligands are orientated on the alpha face, and in the D_2 symmetric model the ligands alternate between the alpha and beta face of the catalyst[6] (Fig. 1.4.1).

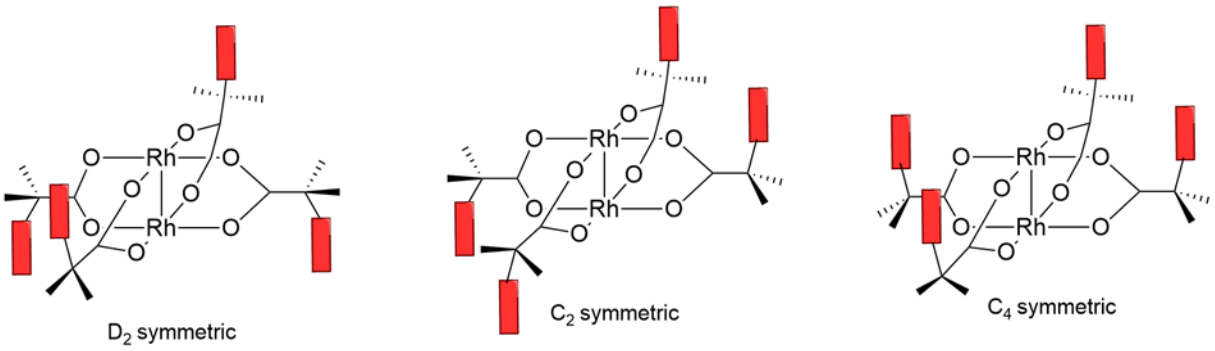
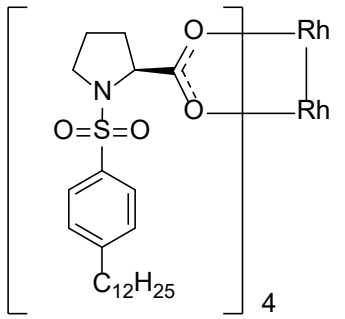


Figure 1.4.1: Depiction of the three symmetric models for the dirhodium catalyst

These higher symmetry conformations allow the researcher to preferentially select for particular C-H bonds on a substrate. For example, Tetrakis[1-[[4-alkyl(C_{11}-C_{13}) phenyl] sulfonyl] -(2*S*)-pyrrolidinecarboxylate] dirhodium (II) catalyst, $Rh_2(DOSP)_4$, (Figure 1.4.2) results in targeting the most sterically accessible secondary site.



$Rh_2(S\text{-}DOSP)_4$

Figure 1.4.2: Representative structure of the $Rh_2(DOSP)_4$ catalyst

The $Rh_2(DOSP)_4$ catalyst was hypothesized to adopt a D_2 symmetric structure due to the steric bulk of the aryl-sulfonyl ligands that were thought to not be able to exist in the periphery of the catalyst complex[6]. The ligands of $Rh_2(DOSP)_4$ aren't as sterically demanding as the next generation catalysts, allowing it target moderately sterically crowded C-H bonds (secondary C-H bonds), but disfavoring insertion of primary C-H bonds due to the more favorable electronics of a more substituted C-H bond. Consequently, $Rh_2(DOSP)_4$ can be used to target secondary C-H bonds in a substrate. This can result in the development of new synthesis pathways that were not achievable with traditional chemistry.

1.5 Previous Mechanism for Stereochemical Control in Dirhodium Tetraprolinate Catalysis

As previously stated in section 1.2, the dirhodium catalyst used in the Davies group have two carbene-formation sites. If these two sites are chemically different, it will result in low

enantioselective control because the substrate can approach either face (alpha and beta) of the catalyst. Therefore, it was hypothesized that the higher symmetry present in dirhodium catalyst (Section 1.4) is crucial to the enantioselectivity of the reaction. This model for enantioselectivity has been applied to $Rh_2(DOSP)_4$ which has been used in 47 papers from 1997 to 2011. $Rh_2(DOSP)_4$ has been proposed to adopt a D_2 symmetric structure due to the steric bulk from the aryl-sulfonyl ligands. The D_2 symmetric model has two equivalent faces and sterically large ligand groups which can block certain trajectories of the substrate. Computational studies have demonstrated that the si face of the carbenoid is blocked from the aryl-sulfonyl ligands, and that the substrate approaches the re face over the donor group; the substrate doesn't approach over the ester group because of the steric demand due to its orthogonal position relative to the carbenoid plane[8] (Fig. 1.5.1). Because the substrate approaches the re face over the donor group the resulting reaction produces a product with a predictable stereochemistry.

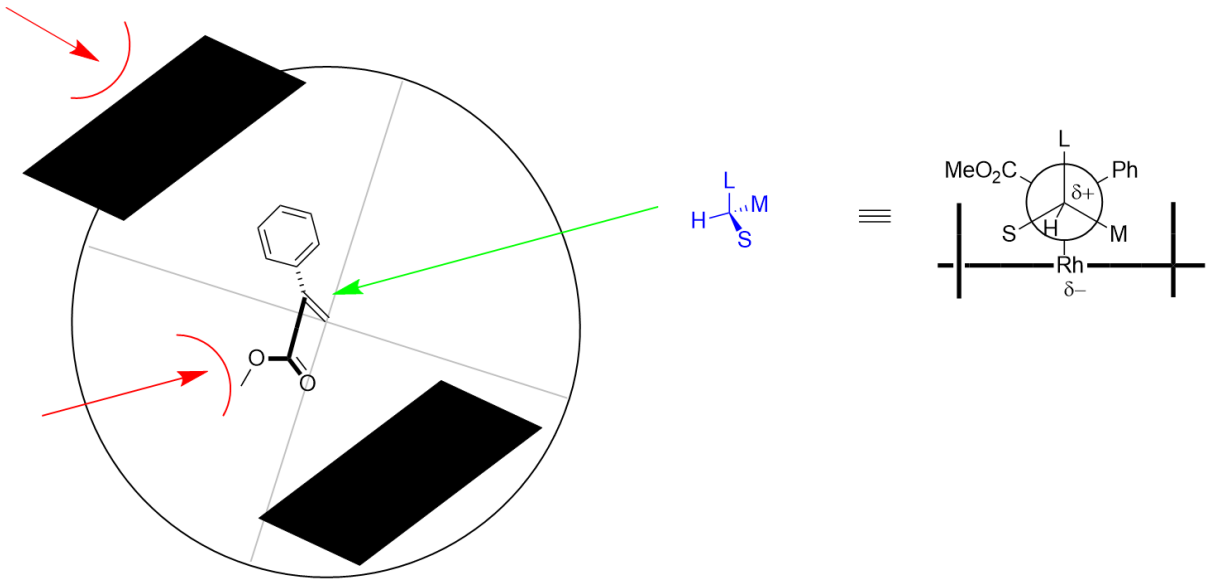


Figure 1.5.1: Illustration of the stereochemical control by catalyst. Black squares represent blocking groups. Equivalent process shown in a Newman Projection with bolden lines representing blocking groups.

As shown in the Newman Projection (Fig. 1.5.1) the diastereoselectivity can be determined based on the substituent sizes in the substrate. If there is a large size difference between the two substituents L and M (L being the large group and M being the medium group), then the L group will orient itself away from the catalyst complex; this leads to a predictable stereochemical outcome in the reaction[8]. Overall, the model of higher symmetry in the dirhodium catalysts predicts the stereochemical outcome of cyclopropanation and C-H functionalization reactions.

2. Exploration of the Structural Requirements of the Sulfonyl Prolinate Ligands for Dirhodium Catalysis

Previous computational studies of the transition state geometries of $Rh_2(DOSP)_4$ catalyzed reactions, coupled with experimental data, such as the nonpolar solvent effect have led to the hypothesized D_2 symmetric model for dirhodium tetraprolinate catalysis[6]. In this model, it was hypothesized that N-aryl sulfonyl ligands were a structural requirement of dirhodium tetraprolinate catalysis due to the low enantioselectivity (30%) seen in the N-isopropyl sulfonyl catalyzed reaction with vinyl-diazoacetate[7](Figure 2a).

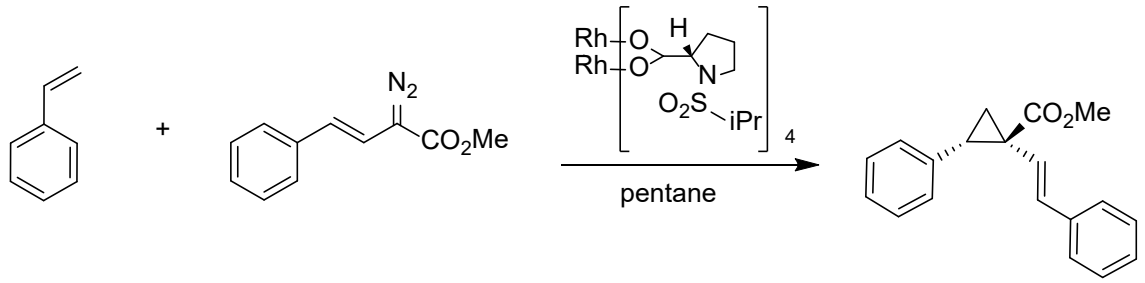


Figure 2a: Scheme of Cyclopropanation with iPr catalyst using Vinyl-diazoacetate[7]

Additionally, it was thought that ligands in $Rh_2(DOSP)_4$ had restricted conformational flexibility resulting in a defined conformation leading to the predicted D_2 symmetric model. However, recent studies have indicated that the ligands used in the $Rh_2(DOSP)_4$ catalyst aren't as

sterically demanding and could occupy the periphery of the catalyst: These studies have indicated that high enantioselectivity can be achieved with rhodium-based catalysts that cannot adopt a D_2 symmetric structure[9] (Figure 2b).

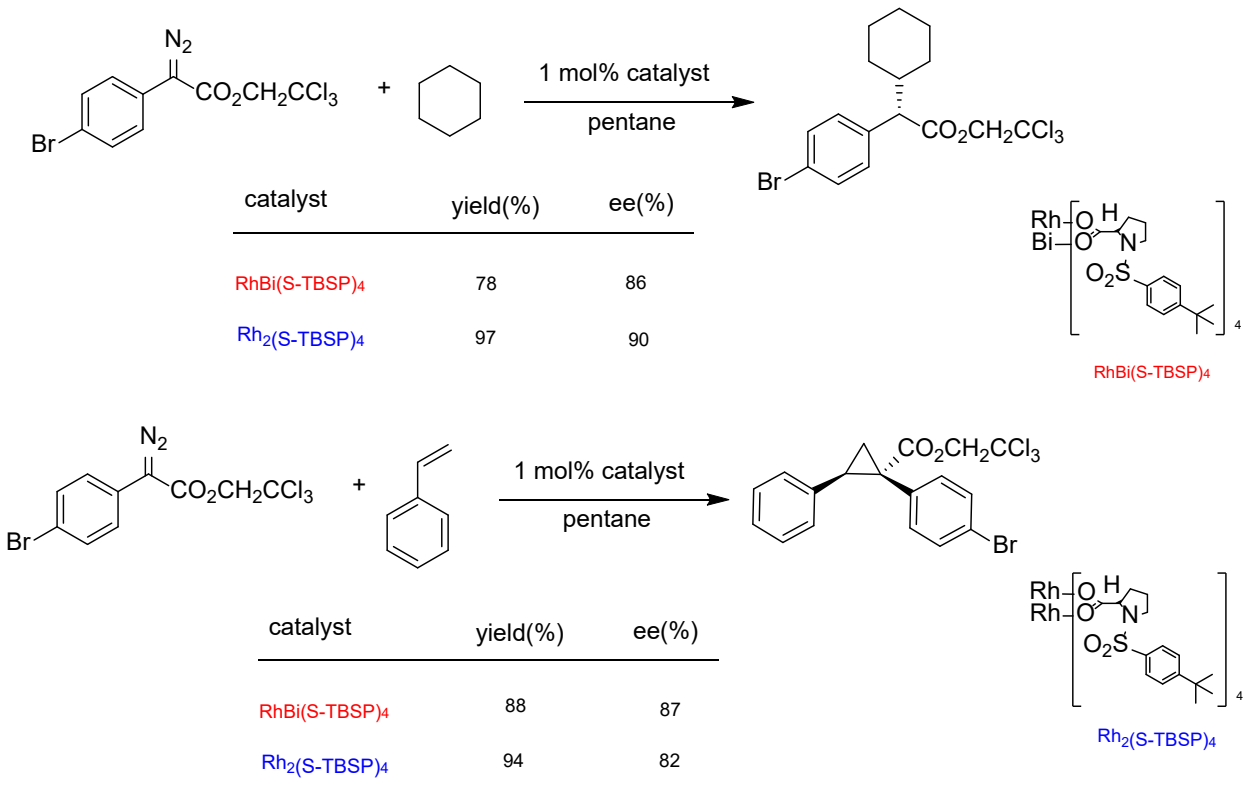


Figure 2b: Enantioselectivity of Rhodium Catalyst that cannot adopt a D_2 Symmetric Structure adapted from Davies H.M.L[9].

The present research was conducted to explore the effects that various ligands had in dirhodium tetraprolinate cyclopropanation and C-H functionalization reactions in conjuncture with the new computational studies. Assuming that the D_2 symmetric model is correct, it was postulated that dirhodium tetraprolinate catalysts with non-aryl ligands and ligands with reduced steric bulk would result in lower enantioselectivity for cyclopropanation and C-H functionalization reactions. This is due to the rationale that dirhodium catalysts with non-aryl ligands or ligands with reduced steric bulk would not be able to adopt a higher symmetry; this

would allow the substrate to approach both faces of the carbenoid in an undefine manner. However, alkylsulfonyl catalysts might be able to achieve high asymmetric induction based on the fact that aryl diazoacetates result in higher enantioselectivity compared to vinyl counterparts, and that new computational studies achieved high enantioselectivity with catalysts that cannot adopt D_2 symmetry. Thus, this study will help to elucidate on the structural requirements of dirhodium tetraprolinate catalyst. Portions of this research project were conducted in collaboration with two undergraduates, Philip Lechner and Nicholas Johnson: Any specific reactions that were not conducted by myself will be denoted with the superscript "p" or "n" in the tables and will be stated in the experimental procedures.

2.1 Synthesis of N-methylsulfonyl Catalyst for C-H functionalization reactions

The majority of catalysts used in the study were synthesized by Dr. Sidney Wilkerson Hill. However, a batch of N-methylsulfonyl catalyst was produced due to the low amount of it available for the subsequent cyclopropanation and C-H functionalization reactions. To synthesize the catalyst, Dr. Sidney Wilkerson's Hill method was used (Figure 2.1.1). L-proline was reacted with methane sulfonyl chloride to form (methylsulfonyl)-L-proline ligand (6.3% yield). A ligand exchange with rhodium acetate generated the desired catalyst in 59% yield.

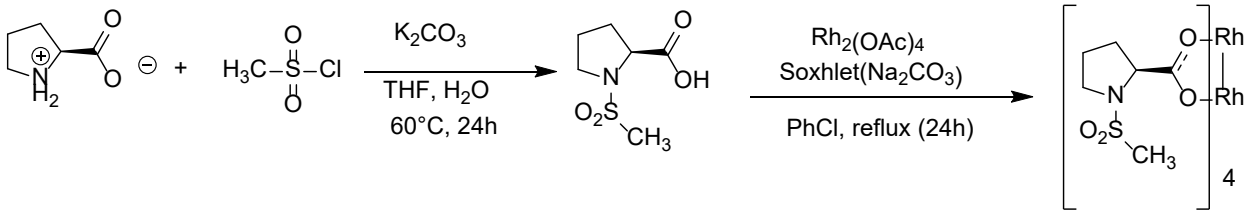
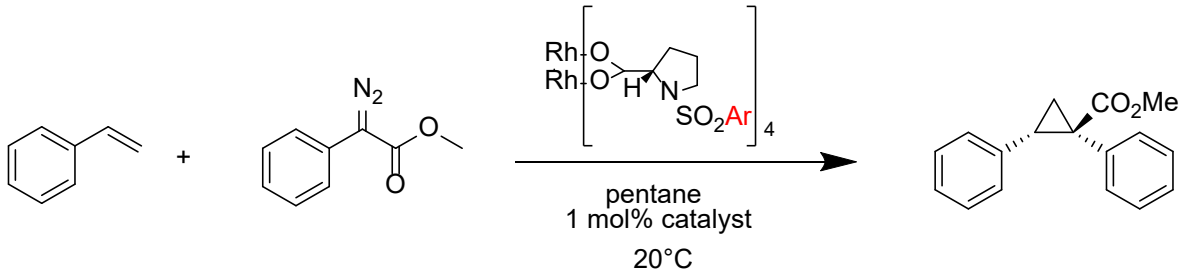


Figure 2.1.1: Scheme for synthesis of N-methylsulfonyl Catalyst[n]

After the N-methylsulfonyl catalyst was synthesized the following cyclopropanation and C-H functionalization reactions were performed.

2.2 N-arylsulfonyl Catalyst Screening via Cyclopropanation Reactions

To investigate the effects of various N-sulfonyl ligands in dirhodium tetraprolinate catalysis, a catalyst screen was performed. Cyclopropanation reactions were used to screen the various dirhodium tetraprolinate catalyst due to their heavy literature precedent and the fact that cyclopropanation reactions are non-laborious and less sensitive to air compared to C-H functionalization reactions. The cyclopropanations were ran using styrene as the substrate and methyl 2-diazo-2-phenylacetate to generate the carbene. Styrene was chosen as the substrate because of its literature precedent in dirhodium catalyzed cyclopropanations. Additionally, the methyl 2-diazo-2phenylacetate was chose as the diazoacetate in these reactions due to the fact that a smaller ester increases the enantioselectivity of $Rh_2(DOSP)_4$ catalyzed cyclopropanations[7,10]. Once the diazoacetate and substrate was picked for the catalyst screen, various N-aryl sulfonyl catalysts were used to perform the cyclopropanations. In the screening, enantiomeric excess was the most important aspect of the reaction due to the fact that it is mostly controlled by the catalyst; The reaction could always be optimized to improve yield, but changing the reaction conditions (other than changing the solvent and temperature) of the system would not drastically affect the asymmetric induction of the reaction. From Table 2.2.1, it was demonstrated that various N-aryl (S)-sulfonyl dirhodium tetraprolinate catalysts could result in high enantioselectivity in cyclopropanation reactions.



entry	Ar	yield (%)	d.r.	e.e (%)
14[p]	Ph	99	95:5	72
3	4-F Ph	73	95:5	82
10[n]	4-Br Ph	72	99:1	92
4	4-OMe Ph	65	94:6	60
1	tBut Ph	78	95:5	64
12[p]	2-naphthyl	38	95:5	60
5	R-DOSP	42	95:5	-89

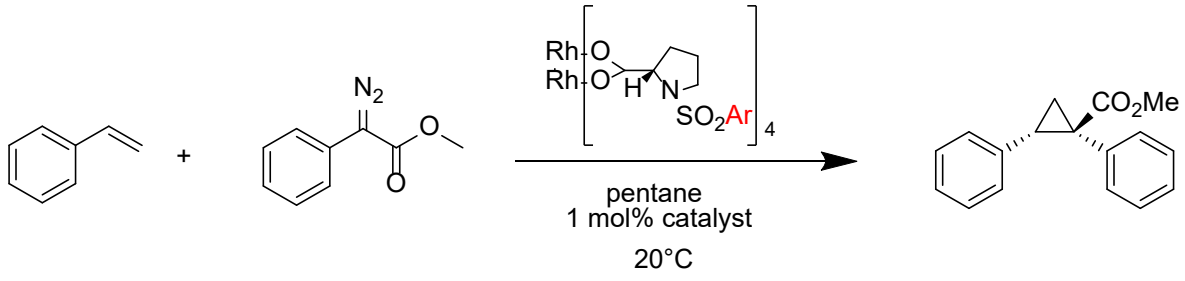
Table 2.2.1: N-arylsulfonyl Dirhodium Catalyzed Cyclopropanations

The N-arylsulfonyl catalysts showed an increase in enantioselectivity with para-substitution via a halogen. The N-2-naphthalene sulfonyl catalyst resulted in reduced enantioselectivity which might be attributed to the low solubility of this particular catalyst in pentane. This data is congruent with the previous data of N-arylsulfonyl dirhodium tetraprolinate catalyzed cyclopropanation reactions; high enantioselectivity can be achieved with various N-arylsulfonyl dirhodium catalysts. One possible explanation for this result is that the para-substitution of the N-arylsulfonyl ligands increases the steric bulk of ligands, creating a greater likelihood that the catalyst adopts a D_2 symmetric structure; this would explain the increased

enantioselectivity seen between the N-phenylsulfonyl catalyst and the para-substituted catalysts. This would also explain the differences in enantioselectivity between the para-substituted fluorine and bromine catalyst due to differences in the atomic radius of the halogens. However, additional computational studies and experiments will have to be performed in order to determine how varying the halogen in the para-substituted aryl groups results in differing enantioselectivity and how the N-methoxysulfonyl catalyzed cyclopropanation results in lower enantioselectivity.

2.3 N-alkylsulfonyl Catalyst Screening via Cyclopropanation Reactions

Studies using the N-isopropylsulfonyl dirhodium tetraprolinate catalyst coupled with previous computational studies have led to the notion that N-arylsulfonyl ligands are a structural requirement in achieving high enantioselectivity in dirhodium tetraprolinate catalysis[6,7]. To further expand upon and test this notion a N-alkylsulfonyl catalyst screen was conducted with cyclopropanation reactions. To generate comparable results to the N-arylsulfonyl catalyst screen, the same substrate and diazoacetate were used; any discrepancy in the data between the two catalyst screens would be a result of the catalyst. Additionally, linear and branched alkyl ligands were used in the screen to test the effects of increasing the steric bulk of the ligands. As seen in Table 2.3.1, it was demonstrated that N-alkyl (S)-sulfonyl dirhodium tetraprolinate catalyzed cyclopropanations could result in high enantioselectivity.

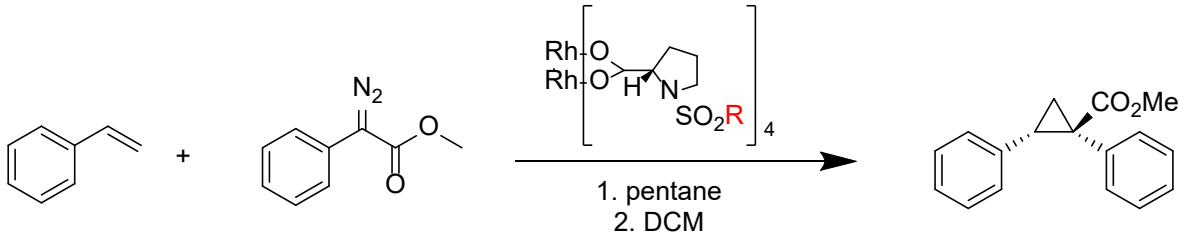


entry	R	yield (%)	d.r.	e.e (%)
16	$C_{12}H_{25}$	60	98:2	90
15^{p}	CH_3	96	97:3	92
7^{n}	Et	42	95:5	78
8^{n}	iPr	63	99:1	76
9^{n}	tBu	74	95:5	24
5	R-DOSP	42	95:5	-89

Table 2.3.1: N-alkylsulfonyl Catalyzed Cyclopropanations

These results demonstrate that high enantioselectivity can be achieved with N-alkylsulfonyl catalysts, specifically the N-dodecyl and methylsulfonyl dirhodium tetraprolinate catalysts. This contradicts the previously held notion that N-arylsulfonyl ligands are a requirement for achieving high enantioselectivity due to the fact that the N-alkylsulfonyl catalysts wouldn't adopt a D_2 symmetry: The ligands have high conformational flexibility and could exist in the periphery of the catalyst. Additionally, the decrease in enantioselectivity of branched alkyl ligands compared to linear alkyl ligands contradicts the hypothesis that increasing the steric bulk of ligand would result in higher enantioselectivity. These results indicate that the mechanism for controlling enantioselectivity in dirhodium tetraprolinate catalysis might be more complicated than the previous mechanism where the higher symmetry of the catalysts was the driving factor.

Furthermore, cyclopropanations with the N-dodecyl and methyl catalyst were ran using styrene and methyl 2-diazo-2-phenylacetate with varying solvents to determine if the solvent effect is seen in N-alkylsulfonyl catalysts. The results seen in Table 2.3.2 indicated that the solvent effect seen in dirhodium tetraprolinate catalyzed reactions is seen with N-alkylsulfonyl catalysts.



entry	R	Solvent	d.r.	e.e (%)
16	$C_{12}H_{25}$	n-pentane	98:2	90
29[p]	$C_{12}H_{25}$	DCM	98:2	74
15[p]	CH_3	n-pentane	97:3	92
30[p]	CH_3	DCM	97:3	78

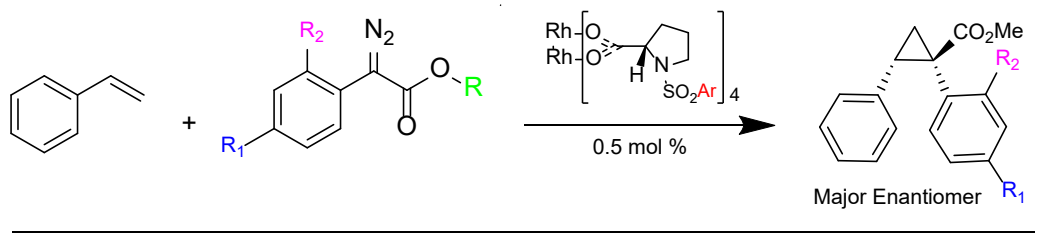
Table 2.3.2: Solvent Effect in N-alkylsulfonyl Catalyzed Cyclopropanations

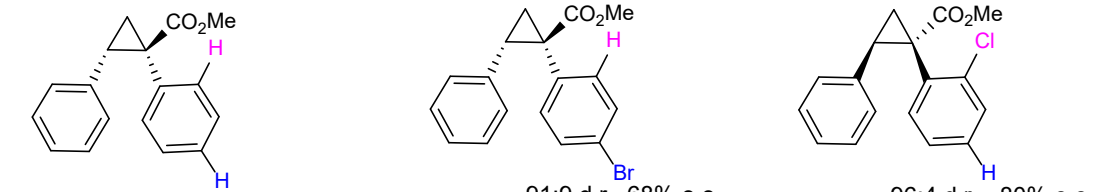
The data in the table demonstrates that using a nonpolar solvent (pentane) compared to a polar solvent (dichloromethane) results in higher enantioselectivity in N-dodecyl and methyl catalyzed cyclopropanations. This is equivalent to the drastic nonpolar solvent effect seen in other dirhodium catalyzed reactions[10]. Overall, this

indicates that the selectivity of the reaction at the carbene-binding site is enhanced with a nonpolar solvent regardless of the ligands used in dirhodium tetraprolinate catalysis.

2.4 Diazoacetate Screen via N-methyl/dodecylsulfonyl Catalyzed Cyclopropanations

The two catalysts, N-(S)-methylsulfonyl and N-(S)-dodecylsulfonyl catalyst, were used in a variety of cyclopropanation reactions to determine the effect that "donor-acceptor" carbenes had in N-alkylsulfonyl dirhodium catalysis; By using a variety of diazoacetates the EDG and EWG could be varied and the subsequent effects of the variation could be analyzed with the cyclopropanation reactions. To perform these reactions, styrene was used as the substrate to provide continuity in the cyclopropanation reactions and to allow for a direct comparison between the data in section 2.2. The results of the diazoacetate screen are presented in Figure 2.4.1.

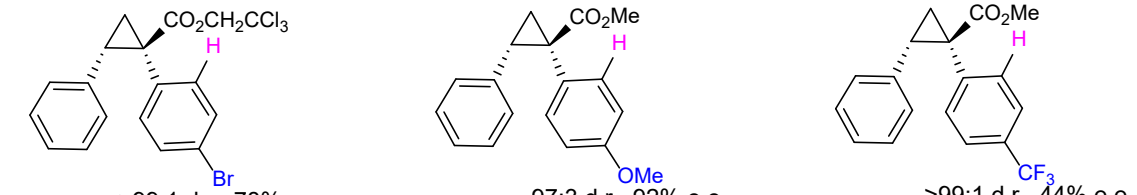




Ar = CH_3 , 97:3 d.r., 92% e.e.
Ar = $C_{12}H_{25}$,98:2 d.r.,90% e.e

Ar = CH_3 , 91:9 d.r., 68% e.e.
Ar = $C_{12}H_{25}$,95.5:4.5 d.r.,96% e.e

Ar = CH_3 , 96:4 d.r., -80% e.e.
Ar = $C_{12}H_{25}$,96:4 d.r.,-92% e.e



Ar = CH_3 , >99:1 d.r., 78% e.e.
Ar = $C_{12}H_{25}$,>99:1 d.r.,88% e.e

Ar = CH_3 , 97:3 d.r., 92% e.e.
Ar = $C_{12}H_{25}$, 95:5 d.r.,>99% e.e

Ar = CH_3 , >99:1 d.r., 44% e.e.
Ar = $C_{12}H_{25}$, 98:2 d.r., 88% e.e

Figure 2.4.1: Diazoacetate Screen via Cyclopropanation Reactions

The results of the diazoacetate screen indicate that the two N-alkylsulfonyl dirhodium catalysts are able to perform highly enantioselective cyclopropanation reactions with a variety of "donor-acceptor" carbene species. Increasing the size of the ester on the electron withdrawing group of the carbene resulted in a decrease in the enantioselectivity of the cyclopropanation reaction. This is congruent with the previous literature that rationalized that the increase in ester size blocked the open face of the carbene[7]. Furthermore, para-substitution of the electron donating group did not drastically affect the enantioselectivity of the cyclopropanation reaction with the exception of the para-substituted trifluoromethyl group. This could be due to the fact that the electron donating group attenuates the reactivity of the carbene and increases the selectivity[6]. Therefore, if the electron donating group is made more electron deficient with the substitution of an electron withdrawing group such as trifluoromethyl then this could result in a carbene that is more similar to an "acceptor-acceptor" carbene. Additionally, the reaction with methyl 2-(2-chlorophenyl)-2-diazoacetate gave the product with the opposite enantiomer. More research will have to be conducted in order to rationalize why the ortho-chloro diazoacetate resulted in forming the opposite enantiomer of the major product. An interesting generalization from the experimental data showed that the majority of cyclopropanations with N-dodecylsulfonyl catalyst resulted in higher enantioselectivity compared to N-methylsulfonyl catalyst when using aryl diazoacetates. This generalization doesn't hold up for all cyclopropanations. This is evident in the cyclopropanation reaction with methyl (E)-2-diazo-4-phenylbut-3-enoate. In this reaction, the N-methylsulfonyl catalyst achieved higher enantioselectivity compared to N-dodecylsulfonyl catalyst (Figure 2.4.2).

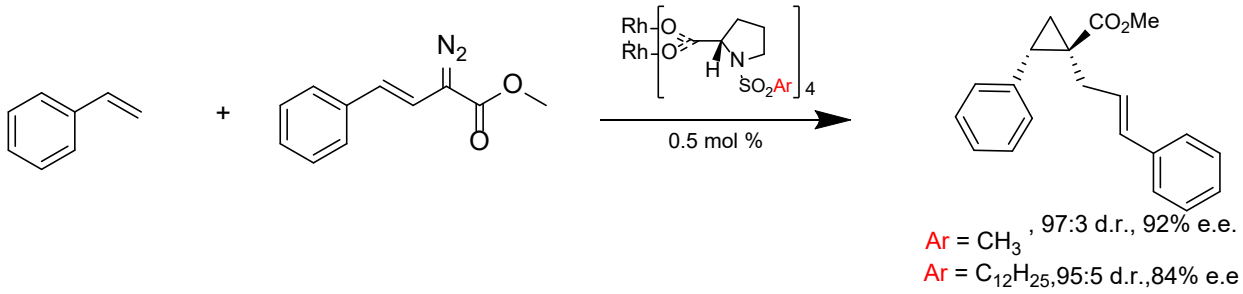


Figure 2.4.2: Cyclopropanation Reaction with the styryl diazoacetate

The reaction with the styryl diazoacetate expands on the previous study with styryl diazoacetates and an alkylsulfonyl catalyst, isopropylsulfonyl. Based on the results of the previous study, aryl ligands were thought to be structural requirement. Thus, the diazoacetate screen showed that the once held thought wasn't entirely correct: highly enantioselective carbene reactions can be performed with N-alkylsulfonyl catalysts.

2.5 Dirhodium Tetraprolinate Catalyzed C-H Functionalization Reactions

The next major class of carbene reactions (C-H functionalization reactions) with N-alkylsulfonyl catalysts were conducted once it was established that high enantioselectivity and diastereoselectivity could be achieved in cyclopropanations. All the C-H functionalization reactions were conducted with the N-dodecyl and methylsulfonyl catalyst due to their relatively similar enantioselectivity when compared to $Rh_2(DOSP)_4$ in cyclopropanation reactions.

To begin the C-H functionalization scope we used 1,1-diphenylethylene as the substrate and reacted it with the methyl 2-(4-bromophenyl)-2-diazoacetate. This reaction produces methyl (R)-1-(4-bromophenyl)-2,2-diphenylcyclopropane-1-carboxylate with high enantioselective and diastereoselective control when chiral $Rh_2(DOSP)_4$ is used as the catalyst. This reaction was chosen due to its importance in the the creation of the 3rd generation catalysts:

Triarylcyclopropanecarboxylate catalysts are generated from the cyclopropanation of 1,1-diphenylethylene. Specifically, Rh_2(S-BTPCP)$_4$ is generated from the reaction with methyl 2-(4-bromophenyl)-2-diazoacetate with a subsequent ligand exchange (Figure 2.5.1).

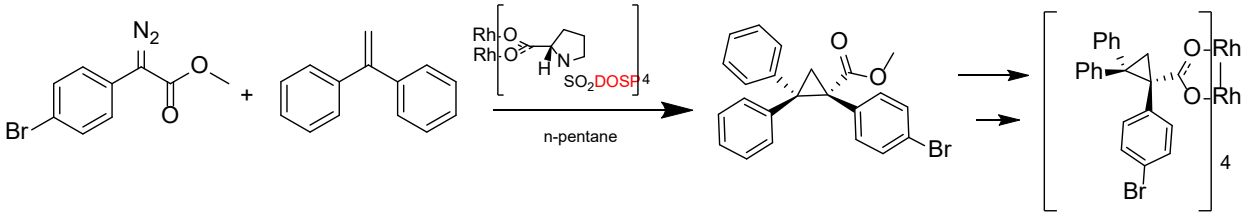
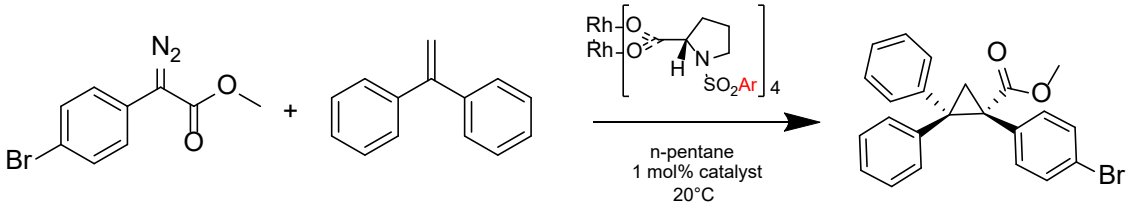


Figure 2.5.1: Development of Rh_2(S-BTPCP)$_4$ with the cyclopropanation of 1,1-diphenylethylene using the p-bromo diazoacetate

This catalyst and the other triarylcyclopropanecarboxylate catalysts have high sterically demanding ligands, which allows researchers to selectively target the less electronically favored primary and secondary C-H bonds[6]. Thus, testing the n-dodecyl and methylsulfonyl catalyst's ability to perform this cyclopropanation is not only important for determining the structural requirements needed in dirhodium tetraprolinate catalysis, but also synthetically useful in the creation of the next generation catalysts. The results in Figure 2.5.2 below demonstrate that the N-dodecyl and methylsulfonyl catalysts can perform the cyclopropanation with high enantioselective control.

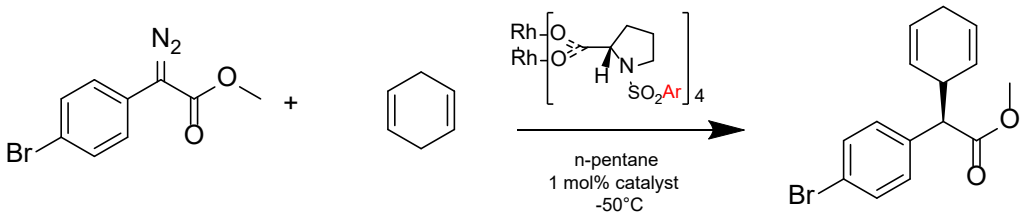


entry	Ar	yield (%)	d.r.	e.e (%)
31	$C_{12}H_{25}$	98	95:5	98
32	CH_3	78	95:5	90
45	R-DOSP	61	95:5	-94

Figure 2.5.2: Results of the Cyclopropanation with the two Alkylsulfonyl Catalysts

These results demonstrate that an aryl group is not a structural requirement for achieving high enantioselectivity in this cyclopropanation. Additionally, using these reaction conditions it is evident that n-dodecyl catalyst is slightly more enantioselective then both Rh_2(R-DOSP)$_4$ and the methysulfonyl catalyst.

After the cyclopropanation of 1,1-diphenylethylene was conducted, the C-H functionalization of 1,4-cyclohexadiene was performed. 1,4 cyclohexadiene was an ideal substrate to test if the two alkylsulfonyl catalysts were capable of performing C-H functionalization. This is due to the fact that 1,4-cyclohexadiene is an activated alkene which would be able to stabilize the partial positive charge in the transition state of the reaction. Thus, this reaction is a critical benchmark to see if it would be feasible to carry out further C-H functionalization reactions. The results of this reaction are shown in Figure 2.5.3.

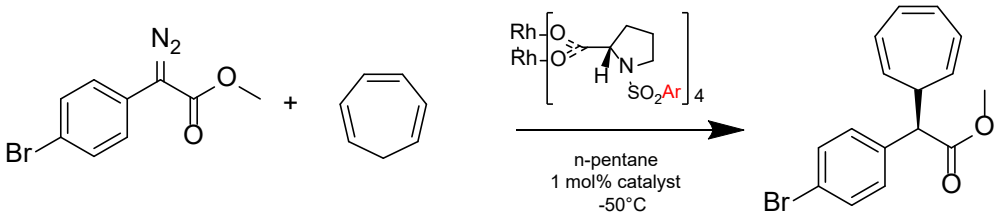


entry	Ar	yield (%)	e.e (%)
33^p	$C_{12}H_{25}$	25	99
34^p	CH_3	30	86
46	R-DOSP	87	-91

Figure 2.5.3: Results of the C-H functionalization of 1,4-cyclohexadiene

These results indicate that the N-alkylsulfonyl catalysts can functionalize highly activated C-H bonds. Additionally, as seen in the previous reaction (Fig. 2.5.2) N-dodecylsulfonyl catalyst results in the highest enantioselectivity with these reaction conditions, and give comparable enantioselectivity to the Rh_2(R-DOSP)$_4$ catalyzed reaction.

Once the functionalization of 1,4-cyclohexadiene was accomplished with the N-dodecyl and methysulfonyl catalyst more C-H functionalization reactions were conducted. The C-H functionalization of 1,3,5-cyclohepatriene was another substrate used in this scope. 1,3,5-cyclohepatriene was picked due to the fact that it is a highly favorable substrate for C-H functionalization reactions. This is due to the homoaromatic stabilization of the hydride transfer transition state in the C-H functionalization reaction. This stabilization favors the insertion of the carbene to form the product. Thus, this is another benchmark reaction that would help determine if an aryl ligand is a structural requirement for enantioselective dirhodium tetraprolinate catalysis. The results of the functionalization of 1,3,5-cyclohepatriene are shown in Figure 2.5.4.

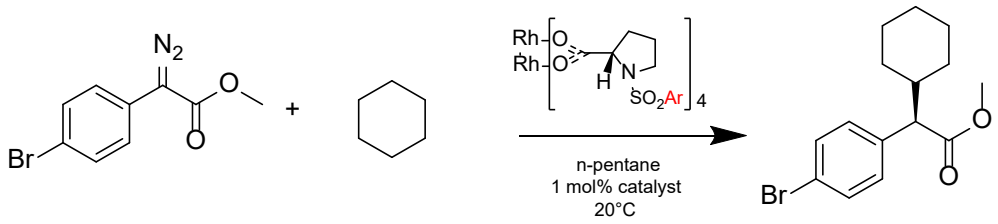


entry	Ar	yield (%)	e.e (%)
35[p]	$C_{12}H_{25}$	25	90
36[p]	CH_3	30	60
51	R-DOSP	65	-98

Figure 2.5.4: Results of the Functionalization of 1,3,5-cyclohepatriene

These results demonstrate that high enantioselectivity in C-H functionalization reactions without aryl ligands is achievable. Additionally, the reaction with N-dodecylsulfonyl catalyst is more enantioselective then the N-methylsulfonyl catalyst and is comparable to the Rh_2(R-DOSP)$_4$ catalyzed reaction.

The C-H functionalization reactions of non-activated substrates were conducted after the C-H functionalization reactions of activated C-H bonds were shown to give high enantioselectivity with N-alkylsulfonyl catalyst. Cyclohexane was chosen as a non-activated substrate in this C-H functionalization scope. Cyclohexane was picked due to the fact that previous kinetic studies highlighted this substrate and showed that the reaction resulted in high asymmetric induction with chiral Rh_2(DOSP)$_4$. The results of the C-H functionalization reaction with cyclohexane are shown below in Figure 2.5.5.



entry	Ar	yield (%)	e.e (%)
37	$C_{12}H_{25}$	70	86
38	CH_3	73	68
47	R-DOSP	66	-95

Figure 2.5.5: Results of the Functionalization of Cyclohexane

The results of this reaction indicate that N-alkylsulfonyl catalysts can perform highly enantioselective C-H functionalization reactions in both activated and non-activated substrates. Additionally, the trend that showed higher enantioselectivity with the N-dodecylsulfonyl catalyzed C-H functionalization of activated substrates is also apparent in the C-H functionalization of non-activated substrates.

Another non-activated substrate that was chosen for this scope was adamantane. The C-H functionalization of adamantane is crucial in the development of 2nd generation phthalimido catalysts, specifically Rh_2(S-PTAD)$_4$ (Figure 2.5.6).

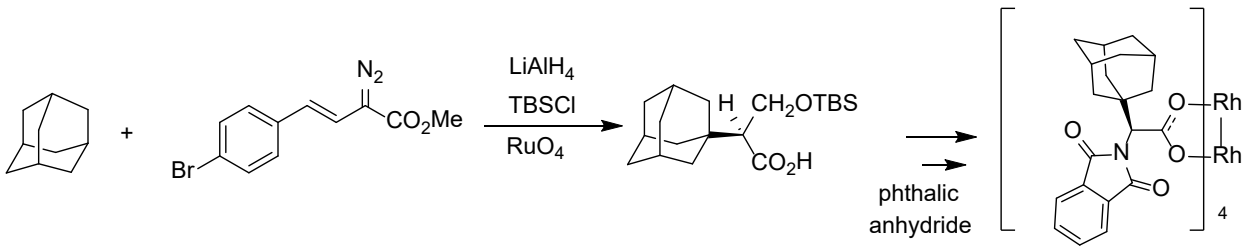
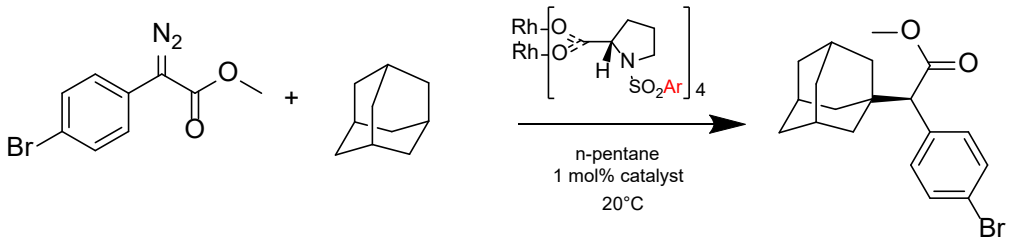


Figure 2.5.6: Synthesis of $Rh_2(S\text{-}PTAD)_4$ with the C-H functionalization of Adamantane

Here adamantane is functionalized with the para-bromo styryl diazoacetate, which then undergoes various reactions to form the phthalimido catalyst[21], $Rh_2(S\text{-}PTAD)_4$. $Rh_2(S\text{-}PTAD)_4$ isn't as synthetically useful in C-H functionalization reactions as the larger substituted phthalimido catalysts due to its lack of rigidity, but still highlights the importance of the C-H functionalization of adamantane. The results of the C-H functionalization of adamantane with the two N-alkylsulfonyl catalysts are shown below in Figure 2.5.7.

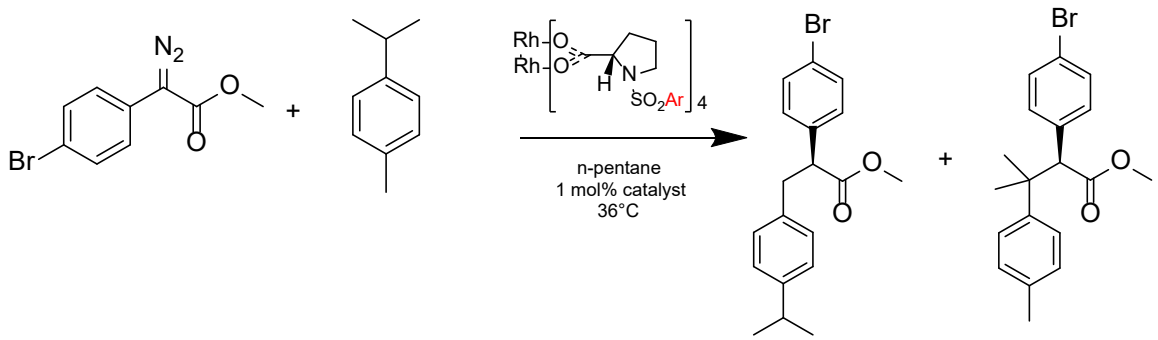


entry	Ar	yield (%)	e.e (%)
40	$C_{12}H_{25}$	79	76
39	CH_3	73	54
48[19]	S-DOSP	70	96

Figure 2.5.7: C-H functionalization of Adamantane with two N-alkylsulfonyl catalyst

The results of the reaction show that the C-H functionalization of adamantane occurs with moderate asymmetric induction. The enantioselectivity of N-dodecylsulfonyl catalyst is higher compared to the N-methylsulfonyl in this reaction which seems to be a major trend in these C-H functionalization reactions. Additionally, the results of this experiment led to using p-cymene as the next substrate of interest.

Para-Cymene was chosen as a substrate in the C-H functionalization scope due to the results of the previous reaction with adamantane (Fig. 2.5.7). The previous reaction showed a possible discrepancy in the selectivity between the N-alkylsulfonyl and $Rh_2(DOSP)_4$ catalyst. It is relatively known that $Rh_2(DOSP)_4$ favors insertion at secondary C-H sites[6]. However, the selectivity of the N-alkylsulfonyl catalysts has not been thoroughly explored. Thus, the C-H functionalization reactions with p-cymene will demonstrate the effects that N-alkylsulfonyl ligands have on enantioselectivity and bond selectivity. The results of the p-cymene reactions are shown in Figure 2.5.8.

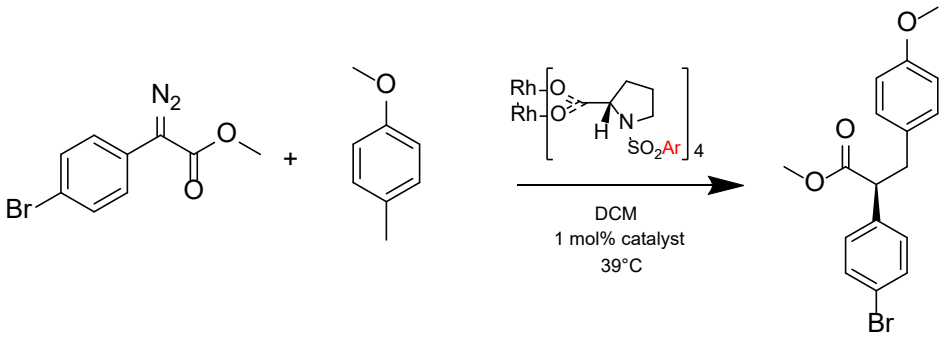


entry	Ar	yield (%)	e.e (%)
43	$C_{12}H_{25}$	57	64 (1°) 19 (3°)
44	CH_3	31	60 (1°) 32 (3°)
50[20]	S-DOSP	72	73 (1°) 55 (3°)

Figure 2.5.8: C-H functionalization of Adamantane with two N-alkylsulfonyl catalyst

These results indicate that the two N-alkylsulfonyl catalyst, based on crude ^{1}H NMR selectivity functionalized tertiary over primary (5:1) while $Rh_2(DOSP)_4$ favored tertiary over primary slightly less (3:1). Additionally, enantioselectivity was the highest for the primary insertion for both catalysts, while the N-methylsulfonyl catalyst resulted in higher enantioselectivity in the tertiary insertion compared to the N-dodecylsulfonyl catalyst.

After the C-H functionalization of p-cymene was conducted we tested the ability of N-alkylsulfonyl catalyst to functionalize 4-methylanisole. It is well known in the literature that $Rh_2(DOSP)_4$ functionalizes the benzylic position over the methyl carbon. This is due most likely to the resonance stabilization of the benzylic position, while the methyl site is more electrophilic due to the adjacent heteroatom. The results of the C-H functionalization of 4-methylanisole are presented in Figure 2.5.9.



entry	Ar	yield (%)	e.e (%)
41[p]	$C_{12}H_{25}$	80	70
42[p]	CH_3	42	64
49	R-DOSP	72	-65

Figure 2.5.9: C-H functionalization of 4-methylanisole

The results demonstrate that N-alkylsulfonyl catalysts selectivity target the benzylic C-H bond over the methyl C-H bond. Additionally, the enantioselectivity of all three catalysts are similar. This indicates that aryl ligands aren't a structural requirement for achieving high asymmetric induction. Also, it repeats a major trend in the majority of the data that shows that N-dodecylsulfonyl catalyzed reactions result in higher enantioselectivity compared to N-methylsulfonyl catalyzed reactions.

3. Conclusions

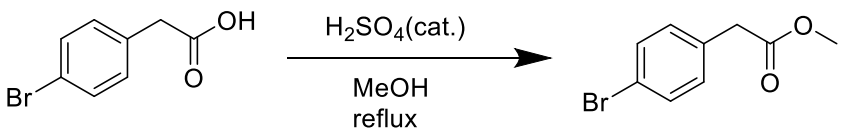
The results of these experiments indicated that arylsulfonyl ligands are not a structural requirement for achieving high asymmetric induction in both major types of carbene reactions (C-H functionalization and cyclopropanation). The results demonstrate that branched alkylsulfonyl ligands tend to decrease the enantioselectivity of cyclopropanation reactions and that there is a favorable structural component with the methyl and the n-dodecyl chain. An important note is the fact that N-dodecylsulfonyl catalyst outperformed the N-methylsulfonyl catalyst in the vast majority of cyclopropanation and C-H functionalization reactions. This indicates that there could be some benefit to having a long, linear alkyl chain in dirhodium tetraprolinate catalysis; more studies would have to be completed to test this hypothesis. Currently, extensive computational studies are in progress by other members of the group to develop a new model to explain the enantioselectivity of the N-sulfonylprolinate catalysts. The experimental data presented herein show that an alkyl sulfonyl ligand is similarly effective at asymmetric induction as the arylsulfonyl derivatives used previously. Therefore, the new model from the computational calculations will need to also demonstrate that the aryl component of the sulfonyl is not a critical requirement for high asymmetric induction.

4. Experimental

4.1 General Remarks

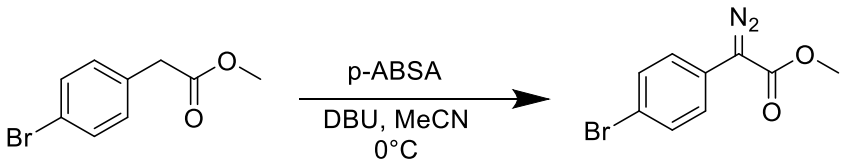
All reactions were conducted in flame-dried or oven-dried glassware under an inert atmosphere of dry argon. All reagents were used as received from commercial suppliers, unless otherwise stated. In the cyclopropanation reactions, styrene was filtered through a plug of silica before addition. Pentane, dichloromethane, and tetrahydrofuran solvents were obtained from drying columns (Grubbs type solvent purifier). Cyclohexane was kept in a flame-dried round-bottom flask that contained activated molecular sieves (4Å) under dry argon. The molecular sieves were activated under vacuum at 300 °C for 5 h and stored in a drying oven. Flash chromatography was performed on silica gel, while thin layer chromatography (TLC) was performed on aluminum backed plates that were precoated with silica gel (0.25 mm, 60 F_{254}). TLC were analyzed using ultraviolet fluorescence (254 nm) and Cerium Molybdate (Hanessian's Stain). ^{1}H NMR spectra were recorded on 400, 500, or 600 MHz spectrometers. Deuterated chloroform ($CDCl_3$) or $CDCl_3$ with tetramethylsilane (TMS) were used as the internal standards, δ = 7.26 parts per million (ppm) or δ = 7.26 and 0.00 ppm, respectively. ^{1}H NMR data are reported as follows; chemical shift, multiplicity (s = singlet, d= doublet, t= triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublets, and etc.), integration, and coupling constants in Hz.

4.2 General Procedure for the Synthesis of Diazoacetates

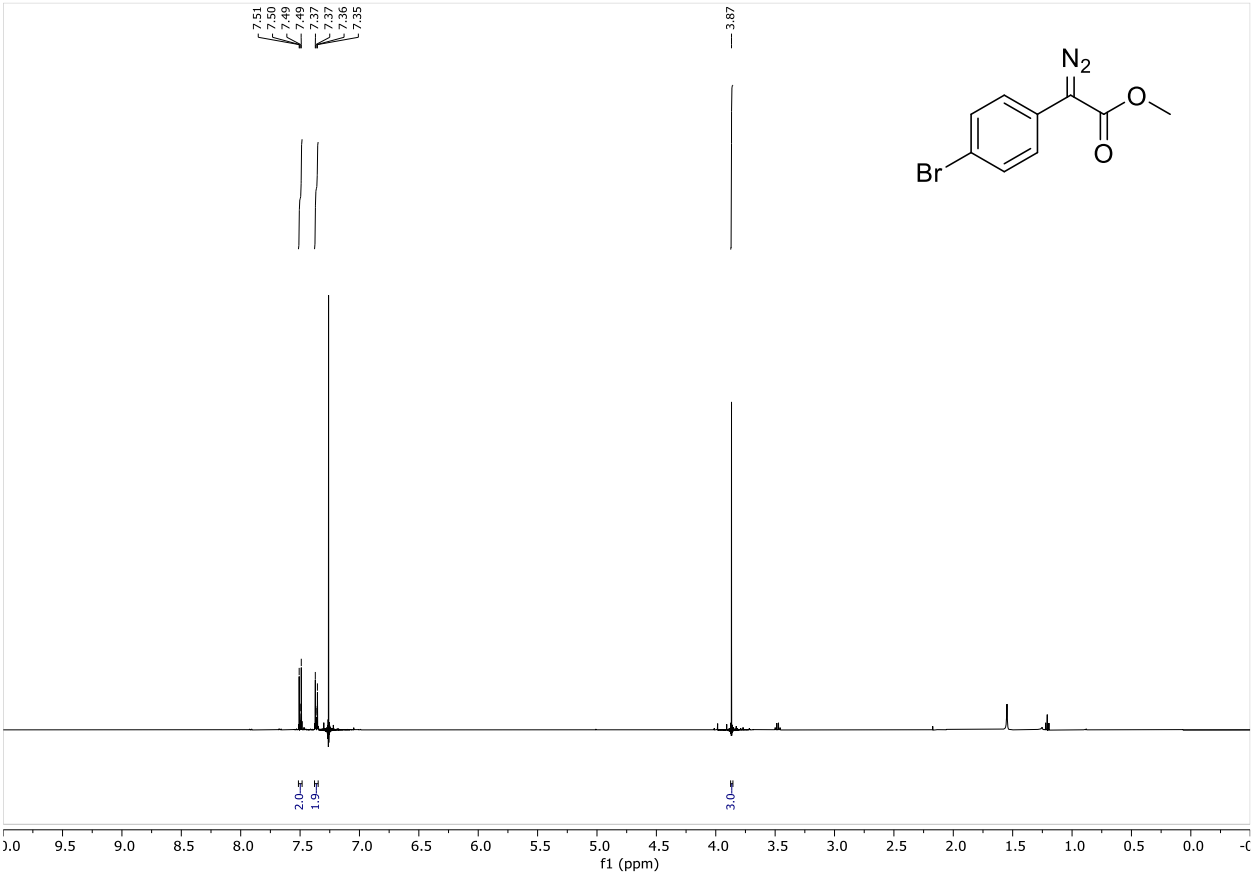


Methyl 2-(4-bromophenyl) acetate: A stirring solution of 4-bromophenylacetic acid (10 mmol, 1.0 equiv., 2.15 g) in methanol (10 mL) was added to a 50 mL oven-dried round-bottom flask

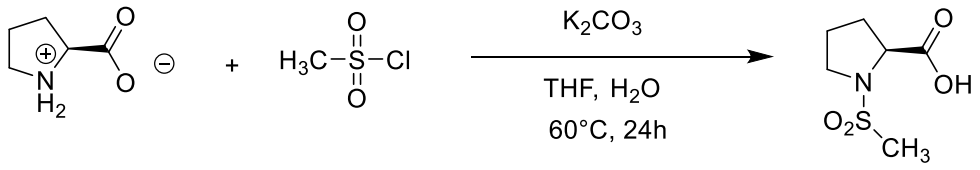
under argon. Then sulfuric acid (9.38 mmol, 0.938 equiv., 0.5 mL) was added to the stirring solution via syringe. The resulting solution was heated to 68°C and stirred for 5 h before the reaction was cooled to ambient temperature. The following reaction mixture was diluted with sodium bicarbonate (35 mL) and then a liquid-liquid extraction was performed with ethyl acetate (50 mL) and washed with brine. The resulting solution was subjected to gravity filtration and dried with magnesium sulfate. The resulting filtrate was concentrated *in vacuo* producing a clear oil. The product was used without further purification to synthesize the methyl 2-(4-bromophenyl)-2-diazoacetate.



Methyl 2-(4-bromophenyl)-2-diazoacetate: Methyl 2-(4-bromophenyl) acetate (4.1 mmol, 1equiv., 996.4 mg) and p-ABSA (6.2 mmol, 1.5equiv., 1.49 g) were dissolved in acetonitrile (20 mL) and the following solution was cooled to 0° using an ice bath. DBU (9.02 mmol, 2.2 equiv., 1.37g) was added dropwise via syringe and stirred for 24 hours. The reaction mixture was then quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate 3 times. The organic layer was then washed with water and brine twice, dried with sodium sulfate, and filtered. The resulting product was concentrated *in vacuo* and purified via flash column chromatography (15% diethyl ether/ hexanes). The resulting reaction produced methyl 2-(4-bromophenyl)-2-diazoacetate (874 mg, 83% yield). 1H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.48 (m, 2H), 7.38 – 7.35 (m, 2H), 3.87 (s, 3H). Consistent with previously reported data[11].

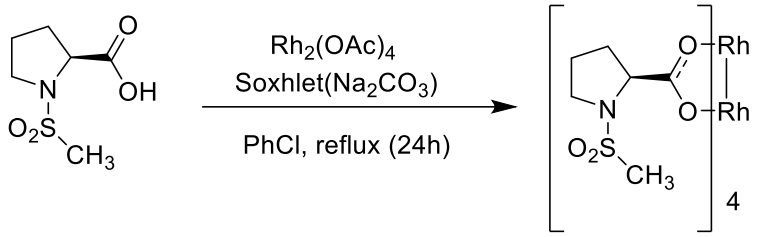


4.3 N-methylsulfonyl Catalyst Synthesis

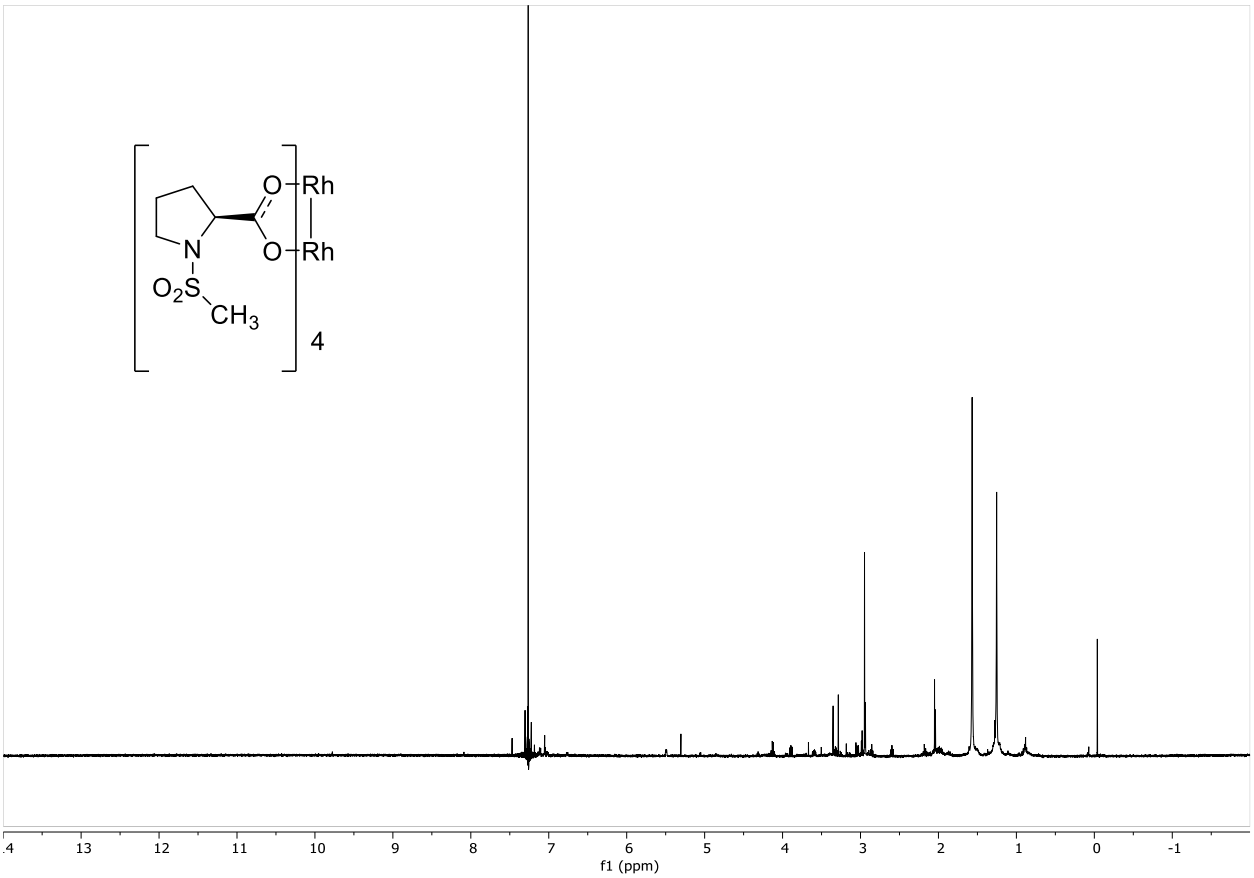


(Methylsulfonyl)-L-proline: To an oven-dried 500 mL round-bottom flask kept under a dry atmosphere of argon, was added L-proline (100 mmol, 1.0 equiv., 11.5 g), dry, degassed THF (100 mL), and water (100 mL). Potassium carbonate (150 mmol, 1.5 equiv., 20.7 g) added to the former solution and stirred till homogenous. Once the solution is homogenous, sulfonyl chloride was added to dry, degassed THF (100 mL) under argon at 60°C and stirred for 24h. The reaction mixture was then neutralized via the addition of 3M HCl to a pH= 3.0. Once the solution was

neutralized a liquid-liquid extraction was performed, concentrated *in vacuo* and flash chromatography (30% ethyl acetate/ dichloromethane) to afford pure product (1.22g) that was used in ligand exchange.



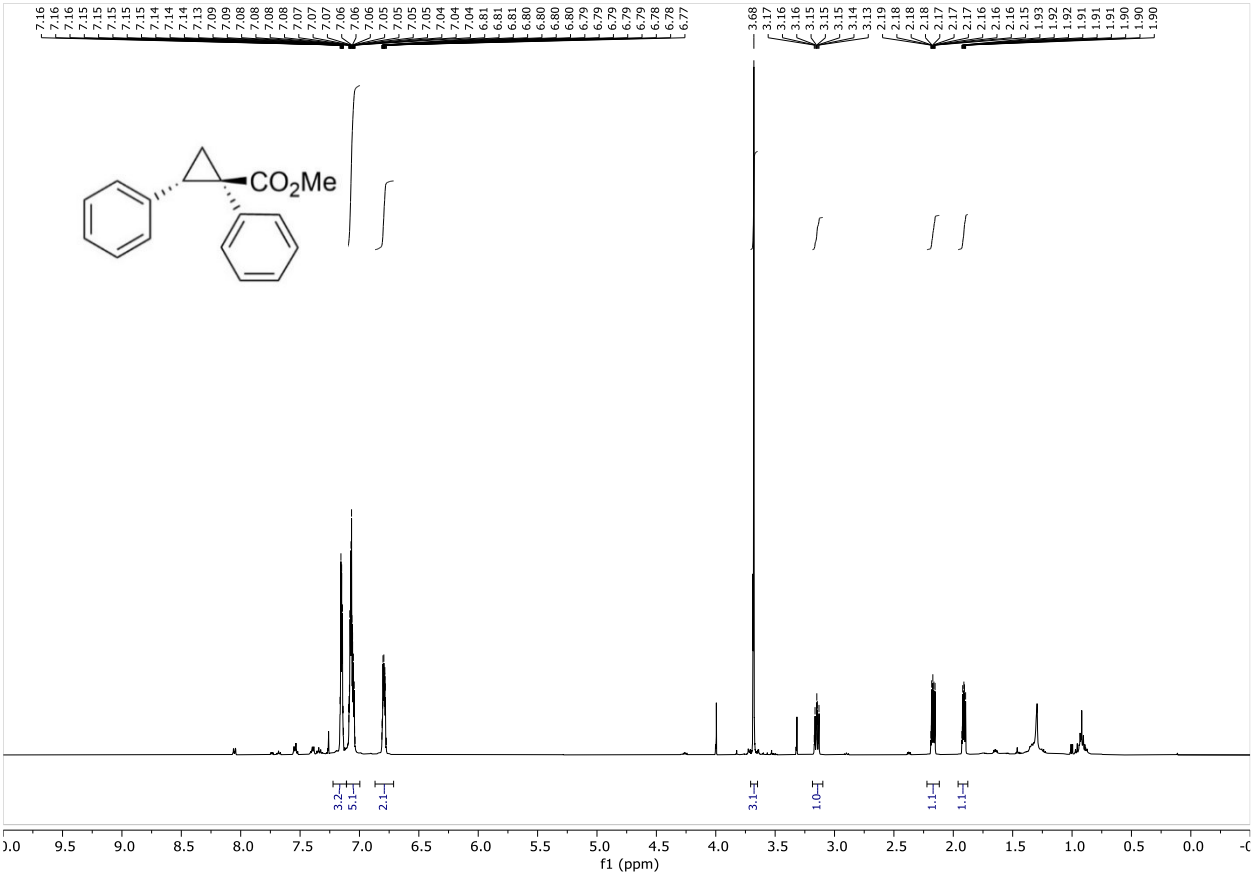
N-methylsulfonyl catalyst: To an oven-dried 100 mL round-bottom flask kept under a dry atmosphere of argon, was added (methylsulfonyl)-L-proline (5.7 mmol, 9.0 equiv., 1.10g), dry, degassed chlorobenzene (45 mL), and rhodium acetate (0.63 mmol, 1.0 equiv., 275 mg). Then the Soxhlet and sodium bicarbonate Hnimble was equipped. Inverted reflux condenser with argon balloon was added, solution was heated to reflux, and stirred for 24 h then gradually cooled to ambient temperature. The resulting solution was purified by flash chromatography (2 to 1 ethyl acetate in hexanes) and concentrated *in vacuo* to afford pure product (643 mg, 59%)



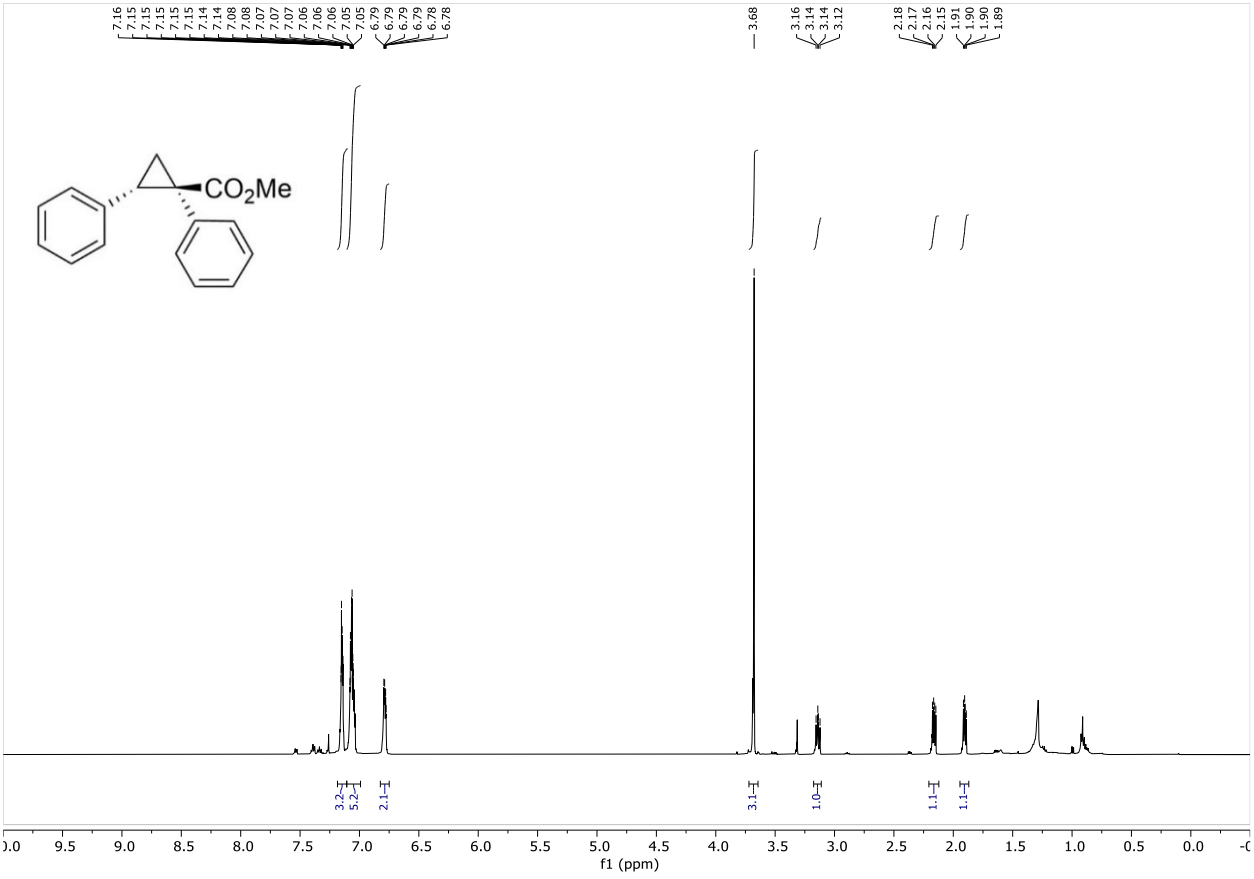
4.4 General Procedure for Cyclopropanation Reactions with Methyl 2-diazo-2-phenylacetate

To an oven-dried 25 mL round-bottom flask kept under a dry atmosphere of argon, was added dirhodium tetraprolinate catalyst (1 mol%, 0.01 equiv.) and dry, degassed pentane (2.5 mL). A solution of diazo compound (0.5 mmol, 1 equiv.) in dry, degassed pentane (6.5 mL), was then added to the former solution drop-wise over 30 min at ambient temperature. The mixture was allowed to stir for 30 min after addition, and then concentrated *in vacuo*. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (SiO_2, 1% Et_2O/Hexane) to afford the pure cyclopropane.

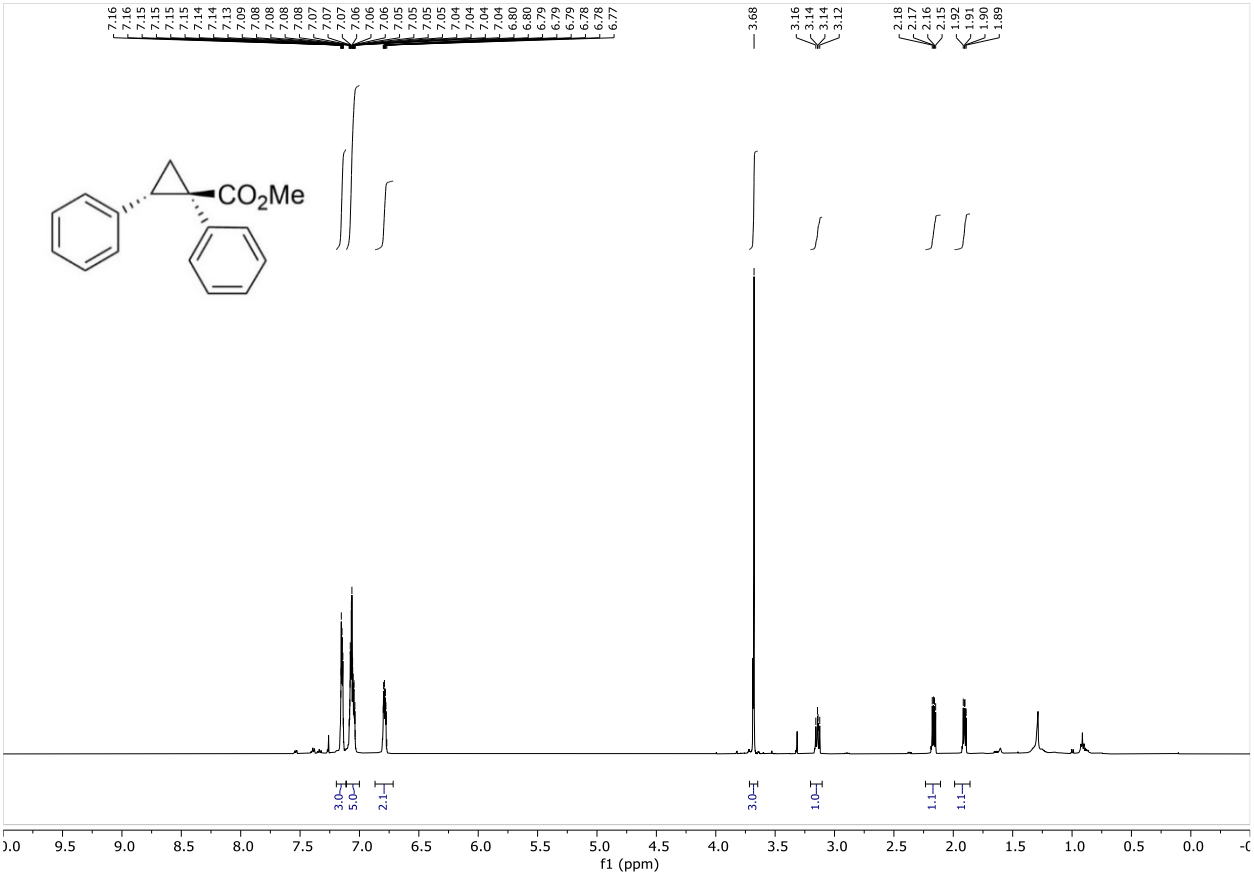
Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (1): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 155mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using SMH III-003C (1 mol%, 0.01 equiv., 8.0 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (99mg, 78%) was obtained as a 95:5 mixture of diastereomers. 1H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.11 (m, 3H), 7.11 – 6.99 (m, 5H), 6.87 – 6.71 (m, 2H), 3.68 (s, 3H), 3.15 (dd, J = 7.1, 3.2 Hz, 1H), 2.17 (dd, 1H), 1.91 (dd, 1H). Consistent with previously reported data[12]. HPLC conditions: Registech Pirkle Covalent S,S-Whelk-O1, 5/100 Kromasil (5 um), 4.6x25mm, 0.7% 2-propanol in hexanes, isocratic elution, 1.5 mL/min, 230 nm detection. Retention times: 20.3 min, 24.7 min; 64% e.e.



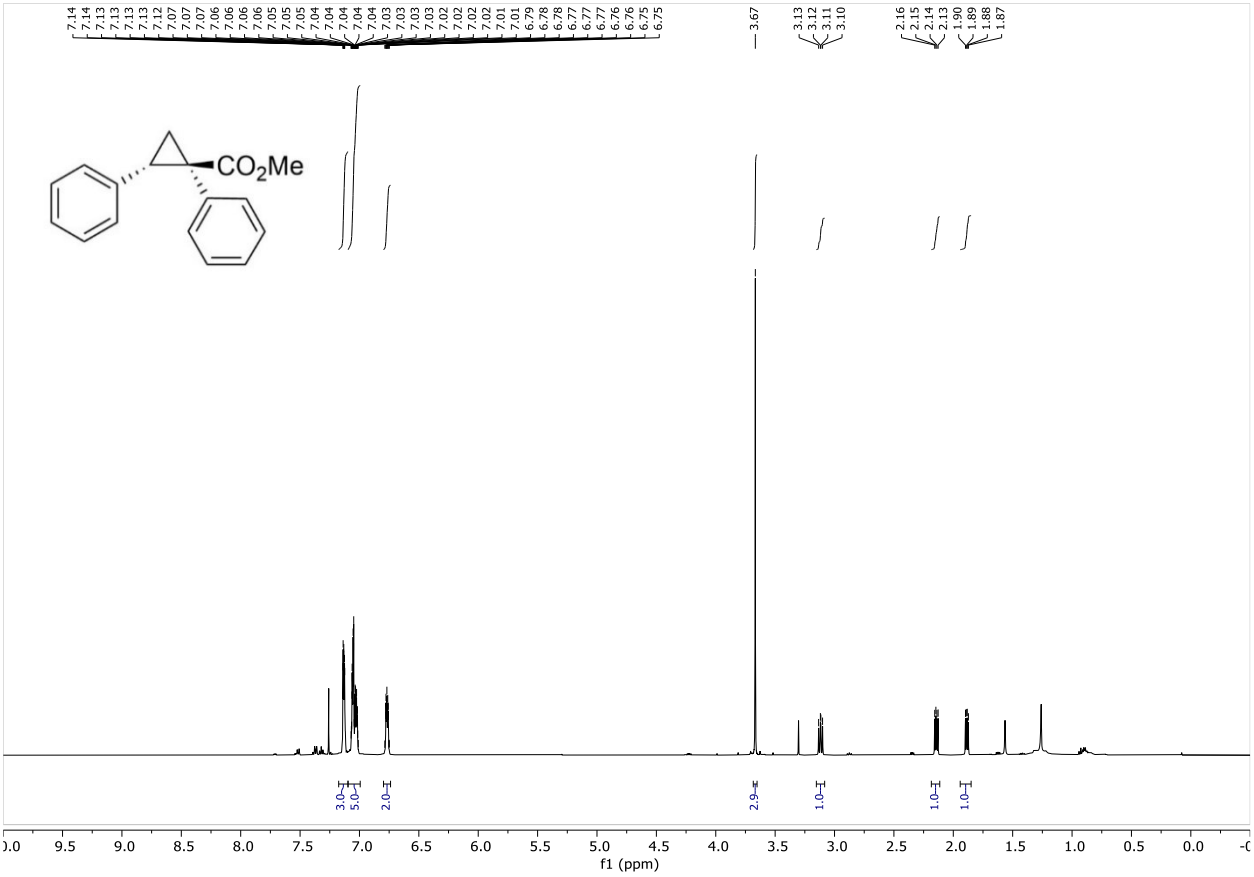
Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (2): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 157 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using SMH III-069C (1 mol%, 0.01 equiv., 7.7 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (101mg, 80%) was obtained as a 95:5 mixture of diastereomers. 1H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.11 (m, 3H), 7.11 – 6.99 (m, 5H), 6.87 – 6.71 (m, 2H), 3.68 (s, 3H), 3.15 (dd, J = 7.1, 3.2 Hz, 1H), 2.17 (dd, 1H), 1.91 (dd, 1H). Consistent with previously reported data[12]. HPLC conditions: Registech Pirkle Covalent S,S-Whelk-O1, 5/100 Kromasil (5 um), 4.6x25mm, 0.7% 2-propanol in hexanes, isocratic elution, 1.5 mL/min, 230 nm detection. Retention times: 20.3 min, 24.7 min; 16% e.e.



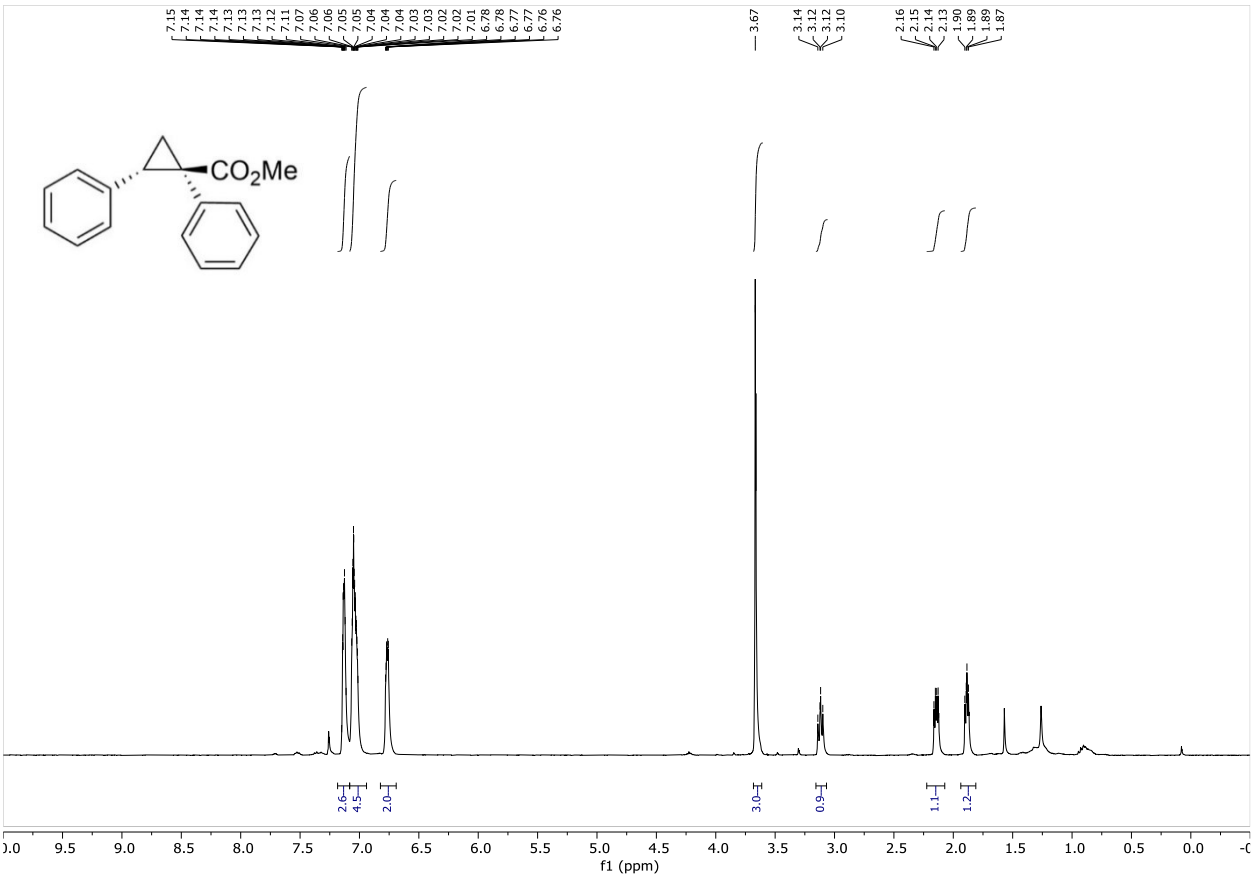
Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (3): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using SMH III-174C (1 mol %, 0.01 equiv., 6.6 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (93 mg, 73%) was obtained as a 95:5 mixture of diastereomers. ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.11 (m, 3H), 7.11 – 7.00 (m, 5H), 6.87 – 6.72 (m, 2H), 3.68 (s, 3H), 3.14 (dd, J = 9.3, 7.2 Hz, 1H), 2.16 (dd, J = 9.4, 4.9 Hz, 1H), 1.90 (dd, J = 7.3, 4.9 Hz, 1H). Consistent with previously reported data[12]. HPLC conditions: Registech Pirkle Covalent S,S-Whelk-O1, 5/100 Kromasil (5 um), 4.6x25mm, 0.7% 2-propanol in hexanes, isocratic elution, 1.5 mL/min, 230 nm detection. Retention times: 20.3 min, 24.7 min; 82% e.e.



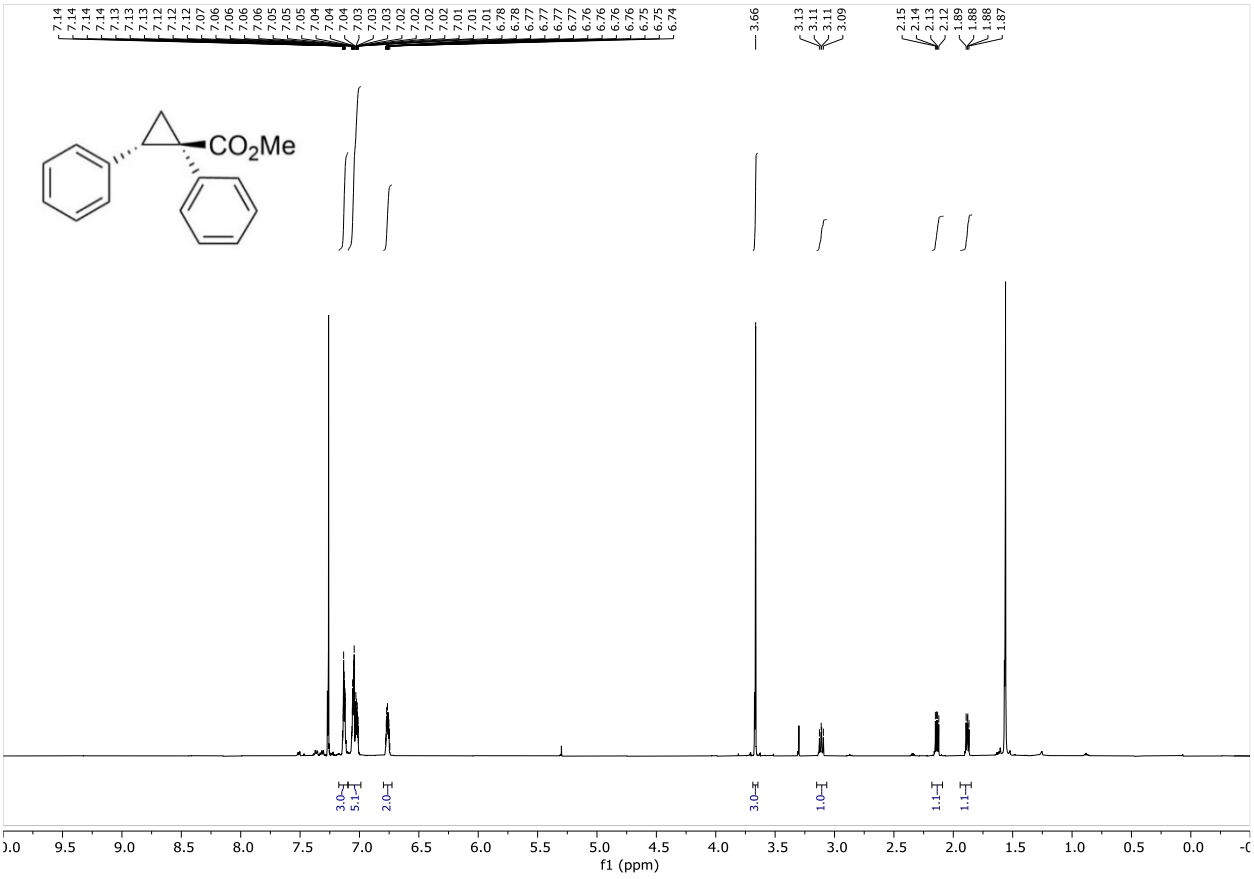
Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (4): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using SMH III-167C (1 mol%, 0.01 equiv., 6.8 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (82 mg, 65%) was obtained as a 94:6 mixture of diastereomers. ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 – 7.10 (m, 3H), 7.10 – 6.99 (m, 5H), 6.80 – 6.74 (m, 2H), 3.67 (s, 3H), 3.12 (dd, J = 9.3, 7.3 Hz, 1H), 2.14 (dd, J = 9.3, 4.9 Hz, 1H), 1.88 (dd, J = 7.3, 4.9 Hz, 1H). Consistent with previously reported data[12]. HPLC conditions: Registech Pirkle Covalent S,S-Whelk-O1, 5/100 Kromasil (5 um), 4.6x25mm, 0.7% 2-propanol in hexanes, isocratic elution, 1.5 mL/min, 230 nm detection. Retention times: 20.3 min, 24.7 min; 60% e.e.



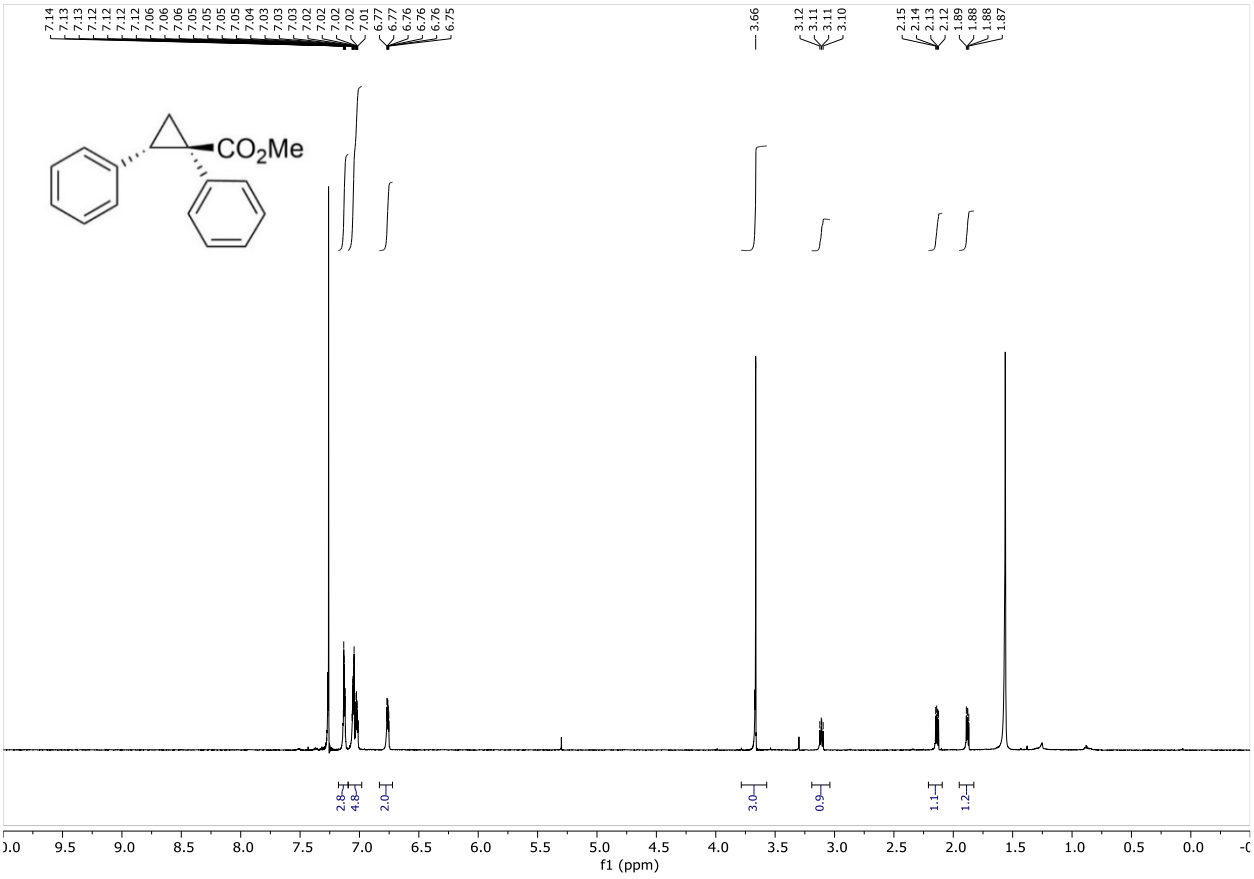
Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (5): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using Rh_2(R-DOSP)$_4$ (1mol%, 0.01 equiv., 6.3 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (82 mg, 65%) was obtained as a 95:5 mixture of diastereomers.^{1}H NMR (399 MHz, $CDCl_3$) δ 7.18 – 7.08 (m, 3H), 7.08 – 6.94 (m, 5H), 6.82 – 6.69 (m, 2H), 3.67 (s, 3H), 3.12 (dd, J = 9.4, 7.3 Hz, 1H), 2.15 (dd, J = 9.3, 4.8 Hz, 1H), 1.89 (dd, J = 7.2, 4.9 Hz, 1H). Consistent with previously reported data[12]. HPLC conditions: Registech Pirkle Covalent S,S-Whelk-O1, 5/100 Kromasil (5 um), 4.6x25mm, 0.7% 2-propanol in hexanes, isocratic elution, 1.5 mL/min, 230 nm detection. Retention times: 20.3 min, 24.7 min; -89% e.e.



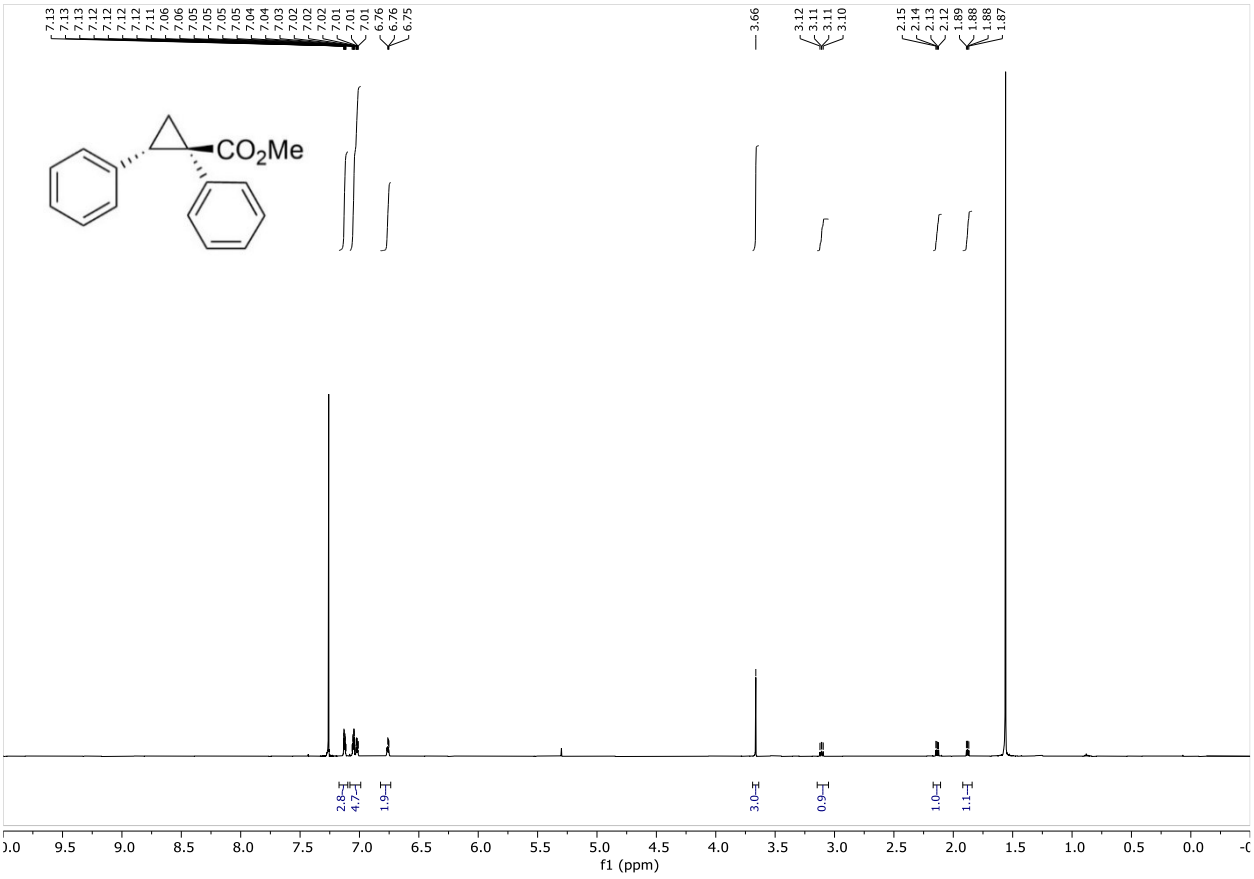
Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (6): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using methyl catalyst (1mol%, 0.01 equiv., 4.9 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (115 mg, 80%) was obtained as a 94:6 mixture of diastereomers. ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 – 7.10 (m, 3H), 7.10 – 6.99 (m, 5H), 6.80 – 6.73 (m, 2H), 3.66 (s, 3H), 3.11 (dd, J = 9.3, 7.3 Hz, 1H), 2.14 (dd, J = 9.3, 4.9 Hz, 1H), 1.88 (dd, J = 7.3, 4.9 Hz, 1H). Consistent with previously reported data[12]. HPLC conditions: Registech Pirkle Covalent S,S-Whelk-O1, 5/100 Kromasil (5 um), 4.6x25mm, 0.7% 2-propanol in hexanes, isocratic elution, 1.5 mL/min, 230 nm detection. Retention times: 20.3 min, 24.7 min; 90% e.e.



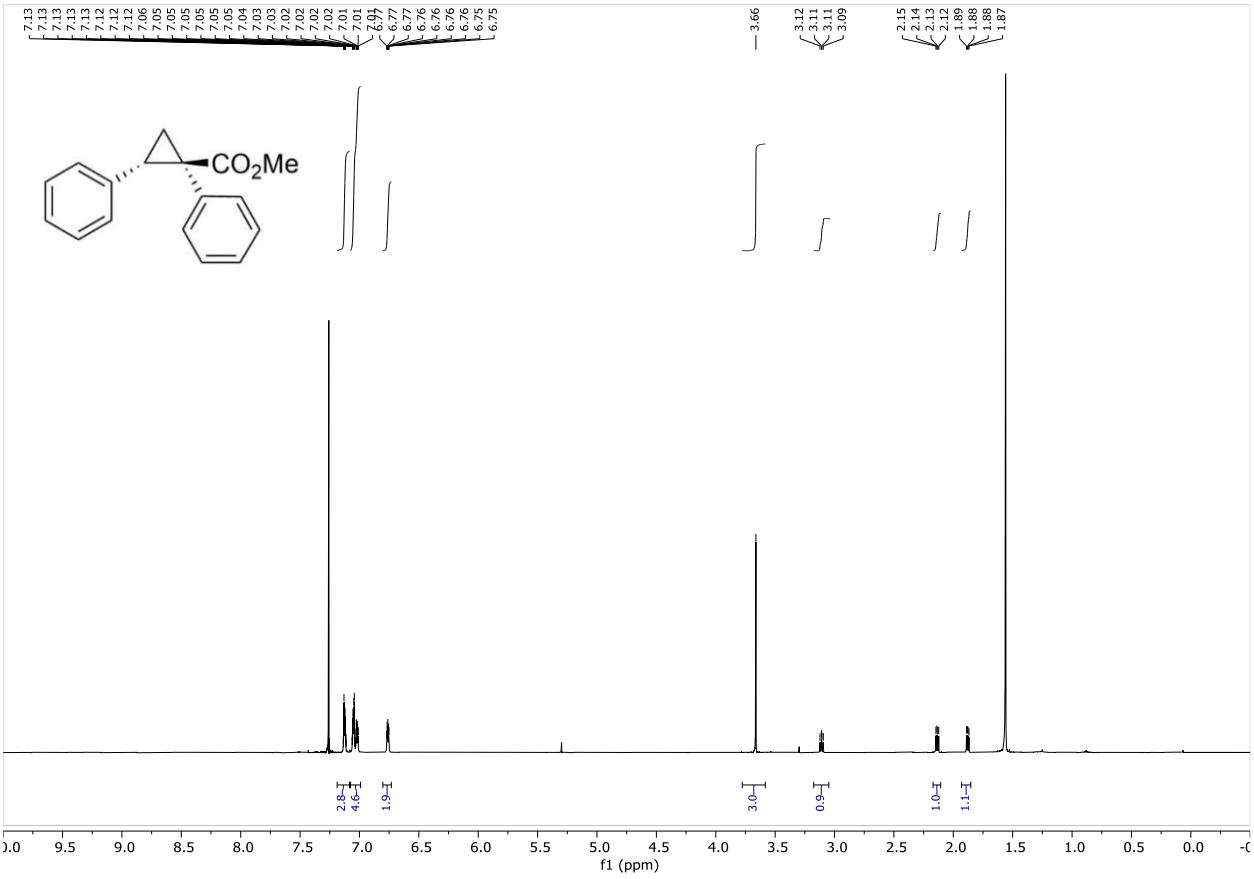
Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (7): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using ethyl catalyst (1mol%, 0.01 equiv., 5.2 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (47 mg, 42%) was obtained as a 95:5 mixture of diastereomers. ^1H NMR (600 MHz, $CDCl_3$) δ 7.18 – 7.09 (m, 3H), 7.09 – 6.98 (m, 5H), 6.83 – 6.72 (m, 2H), 3.66 (s, 3H), 3.11 (dd, J = 9.4, 7.3 Hz, 1H), 2.14 (dd, J = 9.3, 4.9 Hz, 1H), 1.88 (dd, J = 7.3, 4.9 Hz, 1H). Consistent with previously reported data[12]. HPLC conditions: Registech Pirkle Covalent S,S-Whelk-O1, 5/100 Kromasil (5 um), 4.6x25mm, 0.7% 2-propanol in hexanes, isocratic elution, 1.5 mL/min, 230 nm detection. Retention times: 20.3 min, 24.7 min; 78% e.e.



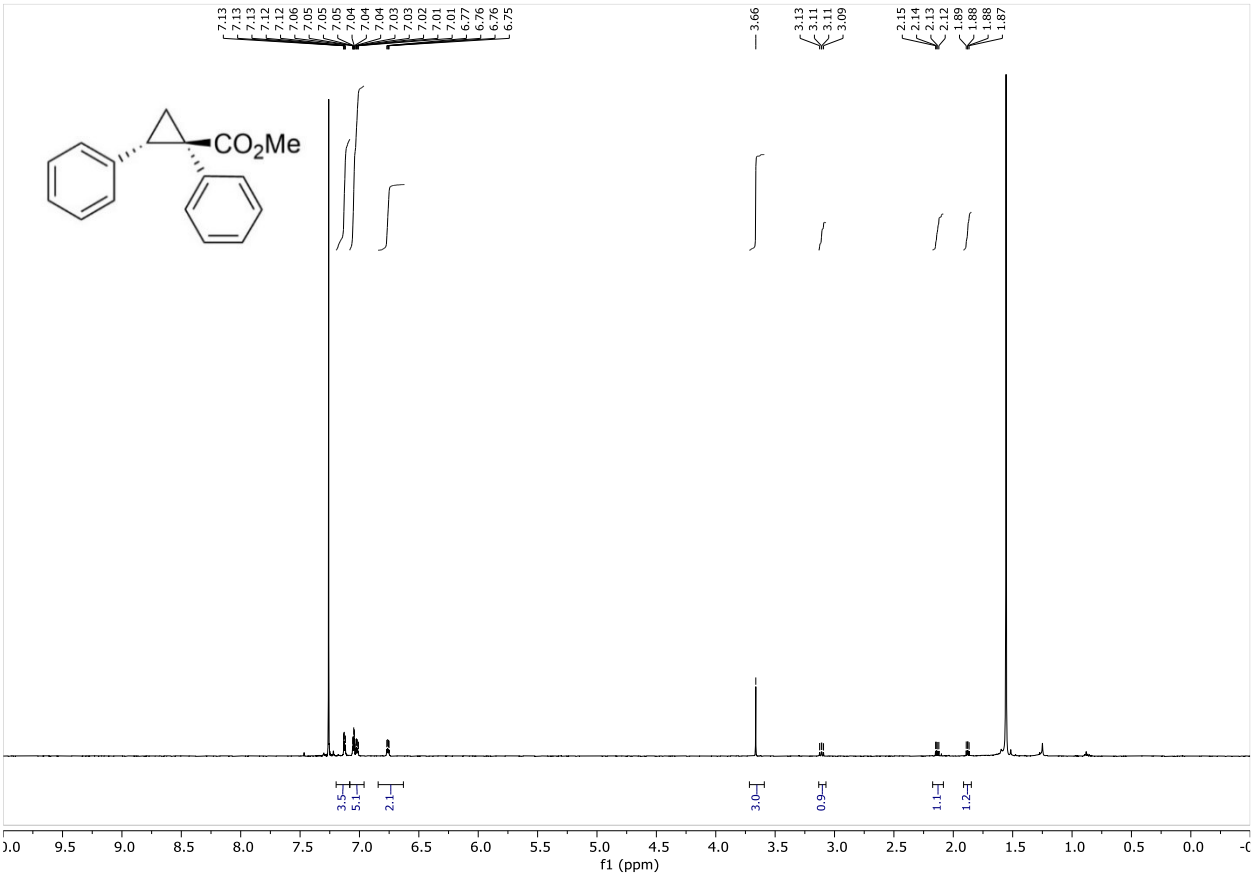
Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (8): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using isopropyl (1mol%, 0.01 equiv., 5.4 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (57 mg, 63%) was obtained as a 99:1 mixture of diastereomers. ^1H NMR (600 MHz, $CDCl_3$) δ 7.15 – 7.10 (m, 3H), 7.08 – 6.99 (m, 5H), 6.82 – 6.74 (m, 2H), 3.66 (s, 3H), 3.11 (dd, J = 9.3, 7.3 Hz, 1H), 2.14 (dd, J = 8.7, 4.7 Hz, 1H), 1.88 (dd, J = 7.2, 4.9 Hz, 1H). Consistent with previously reported data[12]. HPLC conditions: Registech Pirkle Covalent S,S-Whelk-O1, 5/100 Kromasil (5 um), 4.6x25mm, 0.7% 2-propanol in hexanes, isocratic elution, 1.5 mL/min, 230 nm detection. Retention times: 20.3 min, 24.7 min; 76% e.e.



Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (9): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using tert-butyl (1mol%, 0.01 equiv., 5.7 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (88 mg, 74%) was obtained as a 95:5 mixture of diastereomers. ^1H NMR (600 MHz, $CDCl_3$) δ 7.17 – 7.09 (m, 3H), 7.07 – 6.99 (m, 5H), 6.80 – 6.73 (m, 2H), 3.66 (s, 3H), 3.11 (dd, J = 9.3, 7.3 Hz, 1H), 2.13 (dd, J = 9.3, 4.9 Hz, 1H), 1.88 (dd, J = 7.3, 4.9 Hz, 1H). Consistent with previously reported data[12]. HPLC conditions: Registech Pirkle Covalent S,S-Whelk-O1, 5/100 Kromasil (5 um), 4.6x25mm, 0.7% 2-propanol in hexanes, isocratic elution, 1.5 mL/min, 230 nm detection. Retention times: 20.3 min, 24.7 min; 24% e.e.

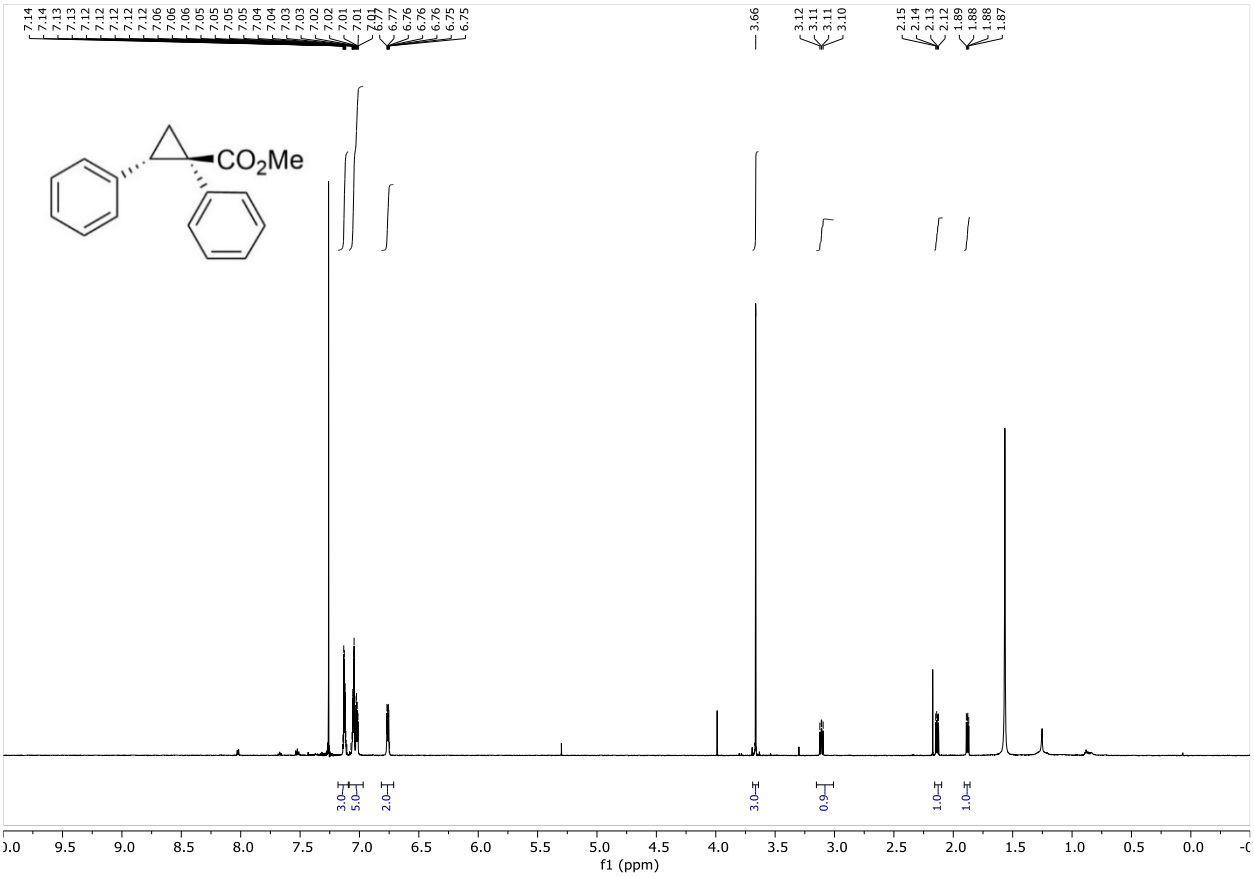


Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (10): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using para-bromo (1mol%, 0.01 equiv., 7.7 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (91 mg, 72%) was obtained as a 99:1 mixture of diastereomers. ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.08 (m, 4H), 7.08 – 6.96 (m, 5H), 6.76 (dd, J = 6.6, 3.0 Hz, 2H), 3.66 (s, 3H), 3.11 (dd, J = 9.3, 7.3 Hz, 1H), 2.14 (dd, J = 9.3, 4.6 Hz, 1H), 1.88 (dd, J = 7.3, 4.9 Hz, 1H). Consistent with previously reported data[12]. HPLC conditions: Registech Pirkle Covalent S,S-Whelk-O1, 5/100 Kromasil (5 um), 4.6x25mm, 0.7% 2-propanol in hexanes, isocratic elution, 1.5 mL/min, 230 nm detection. Retention times: 20.3 min, 24.7 min; 90% e.e.



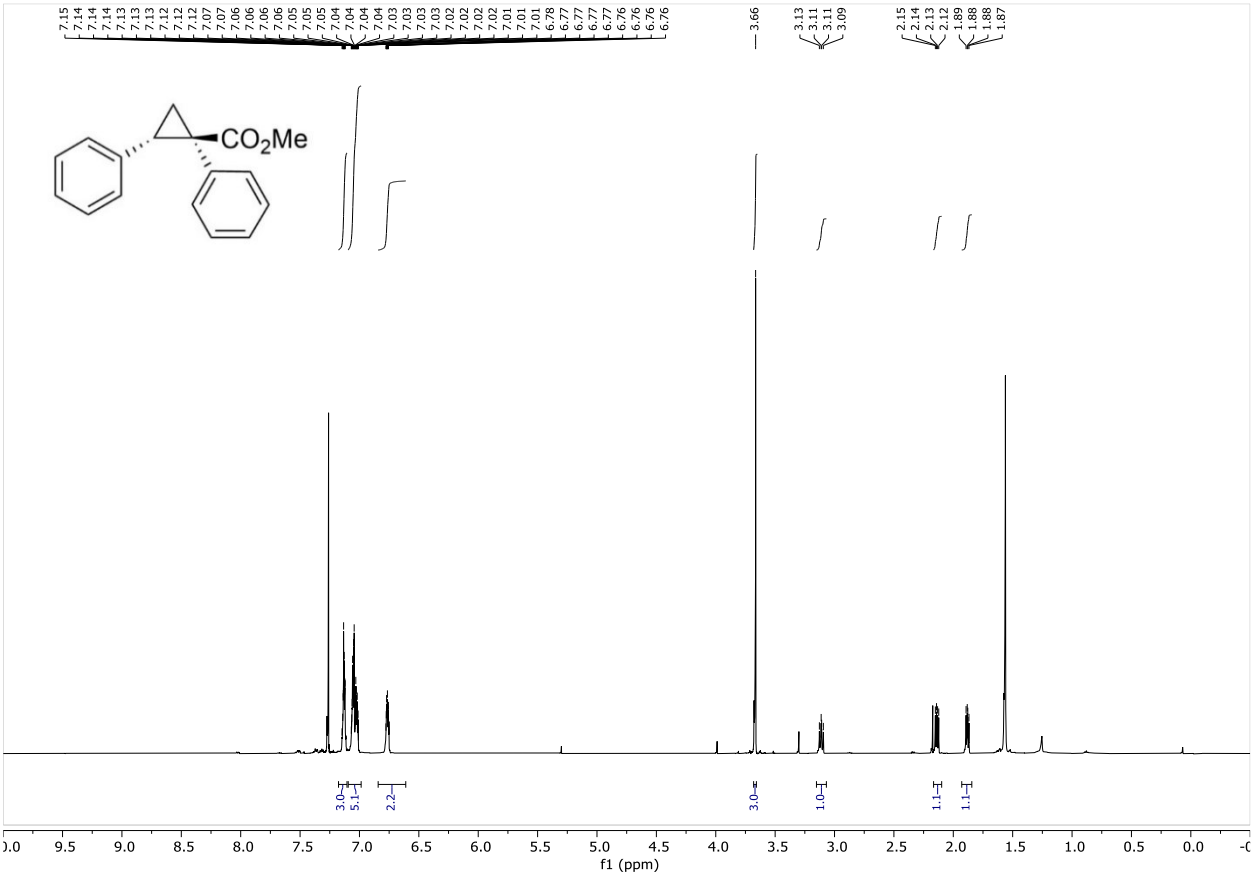
Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (11): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using Rh_2(S-DOSP)$_4$ (1mol%, 0.01 equiv., 9.48 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (151 mg, 33%) was obtained as a 95:5 mixture of diastereomers. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18 – 7.09 (m, 3H), 7.09 – 6.97 (m, 5H), 6.82 – 6.71 (m, 2H), 3.66 (s, 3H), 3.11 (dd, J = 9.3, 7.2 Hz, 1H), 2.14 (dd, J = 9.2, 5.0 Hz, 1H), 1.88 (dd, J = 7.2, 4.9 Hz, 1H). Consistent with previously reported data[12]. HPLC conditions:

Registech Pirkle Covalent S,S-Whelk-O1, 5/100 Kromasil (5 um), 4.6x25mm, 0.7% 2-propanol in hexanes, isocratic elution, 1.5 mL/min, 230 nm detection. Retention times: 20.3 min, 24.7 min; 88% e.e.



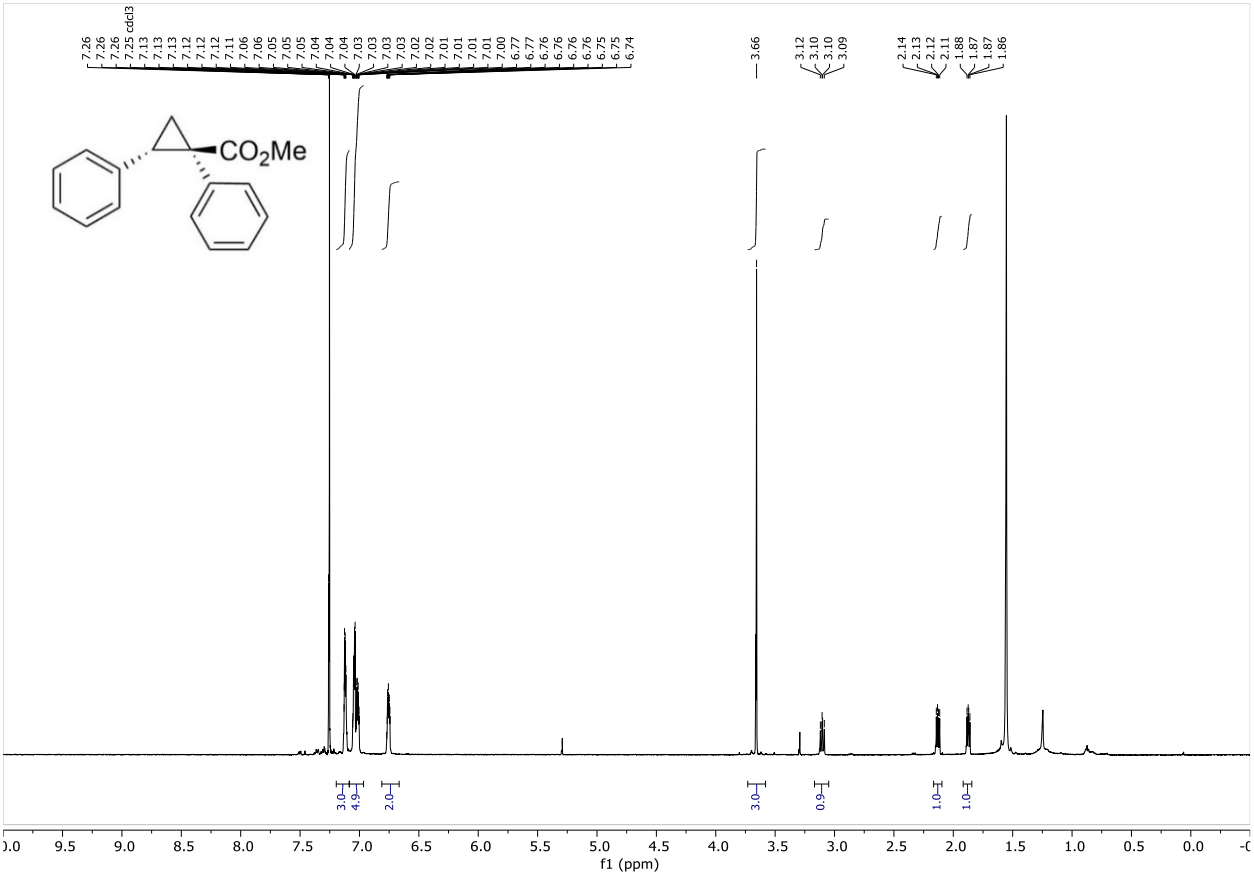
Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (12): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using 2-Napthalene (1mol%, 0.01 equiv., 8.88 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (128.2 mg, 38%) was obtained as a 95:5 mixture of diastereomers. ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.10 (m, 1H), 7.10 – 6.95 (m, 2H), 6.83 –

6.70 (m, 1H), 3.66 (s, 1H), 2.14 (dd, J = 9.3, 4.9 Hz, 1H), 1.88 (dd, J = 7.3, 4.9 Hz, 1H). Consistent with previously reported data[12]. HPLC conditions: Registech Pirkle Covalent S,S-Whelk-O1, 5/100 Kromasil (5 um), 4.6x25mm, 0.7% 2-propanol in hexanes, isocratic elution, 1.5 mL/min, 230 nm detection. Retention times: 20.3 min, 24.7 min; 60% e.e.



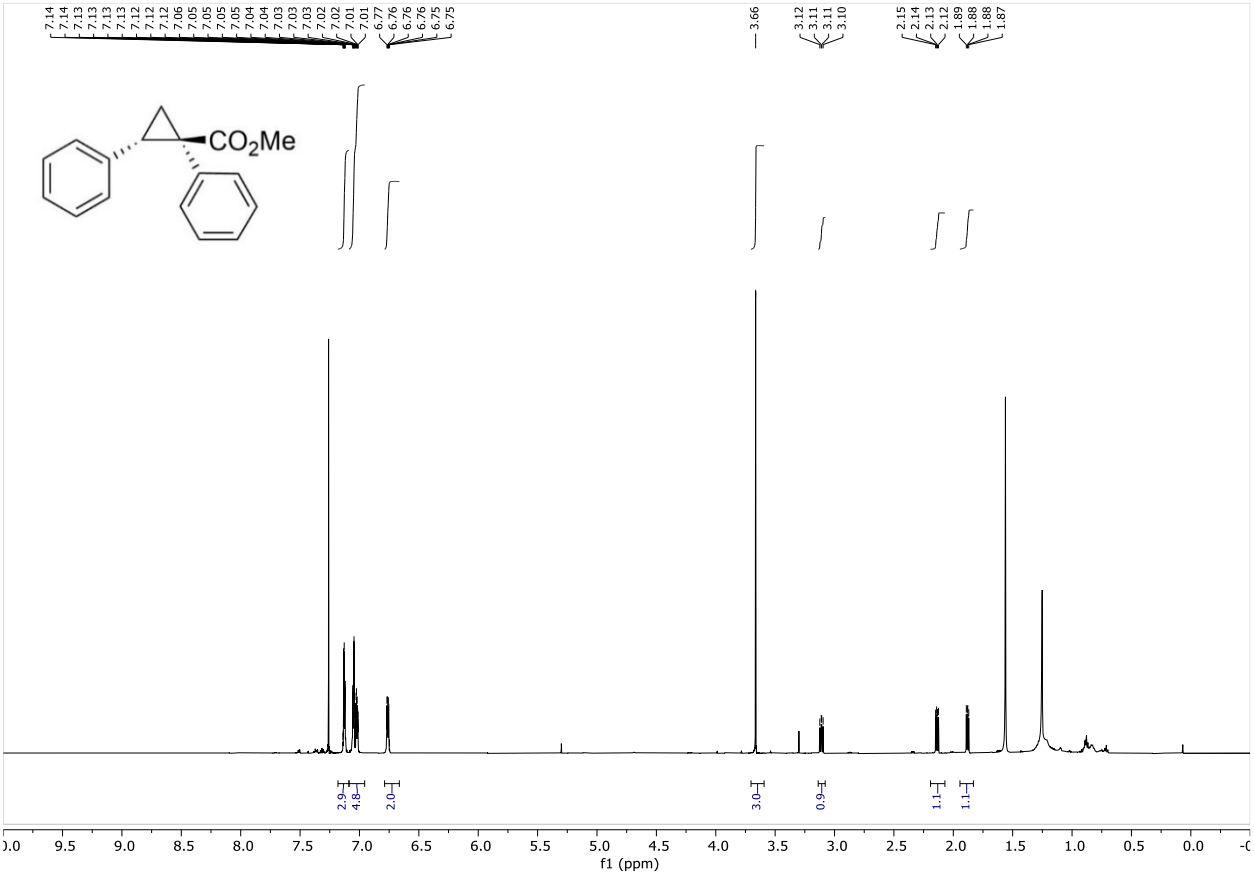
Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (13): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using Boc (1mol%, 0.01 equiv., 8.74 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (117 mg, 74%) was obtained as a 95:5 mixture of diastereomers. ^1H NMR

(500 MHz, $CDCl_3$) δ 7.20 – 7.09 (m, 3H), 7.09 – 6.97 (m, 5H), 6.81 – 6.67 (m, 2H), 3.66 (s, 3H), 3.10 (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). Consistent with previously reported data[12]. HPLC conditions: Registech Pirkle Covalent S,S-Whelk-O1, 5/100 Kromasil (5 um), 4.6x25mm, 0.7% 2-propanol in hexanes, isocratic elution, 1.5 mL/min, 230 nm detection. Retention times: 20.3 min, 24.7 min; 12% e.e.



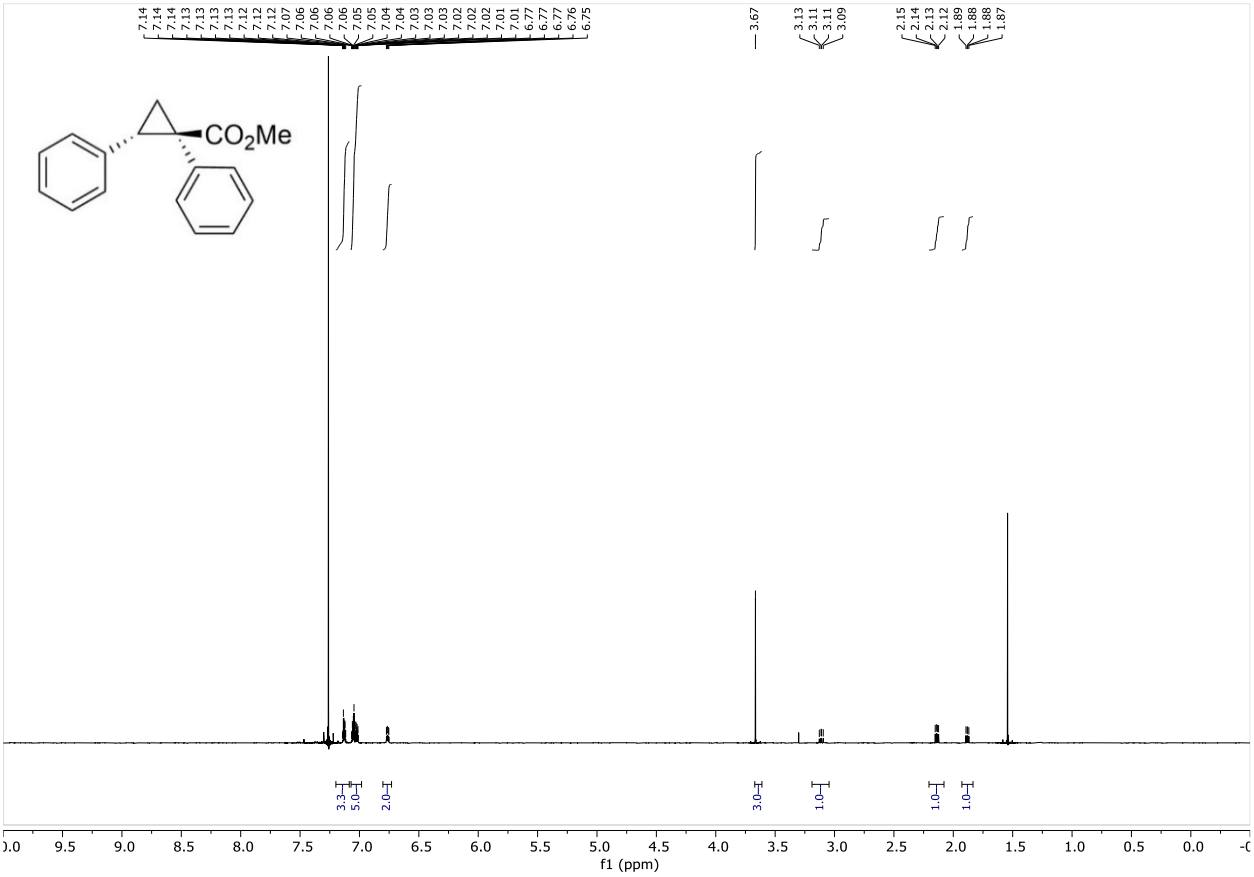
Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (14): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using Phenyl (1mol%, 0.01 equiv., 6.11 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane)

the title compound (111 mg, 72%) was obtained as a 95:5 mixture of diastereomers. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18 – 7.09 (m, 3H), 7.09 – 6.96 (m, 5H), 6.79 – 6.66 (m, 2H), 3.66 (s, 3H), 3.11 (dd, J = 9.4, 7.3 Hz, 1H), 2.14 (dd, J = 9.4, 5.0 Hz, 1H), 1.88 (dd, J = 7.2, 4.9 Hz, 1H). Consistent with previously reported data[12]. HPLC conditions: Registech Pirkle Covalent S,S-Whelk-O1, 5/100 Kromasil (5 um), 4.6x25mm, 0.7% 2-propanol in hexanes, isocratic elution, 1.5 mL/min, 230 nm detection. Retention times: 20.3 min, 24.7 min; 72% e.e.



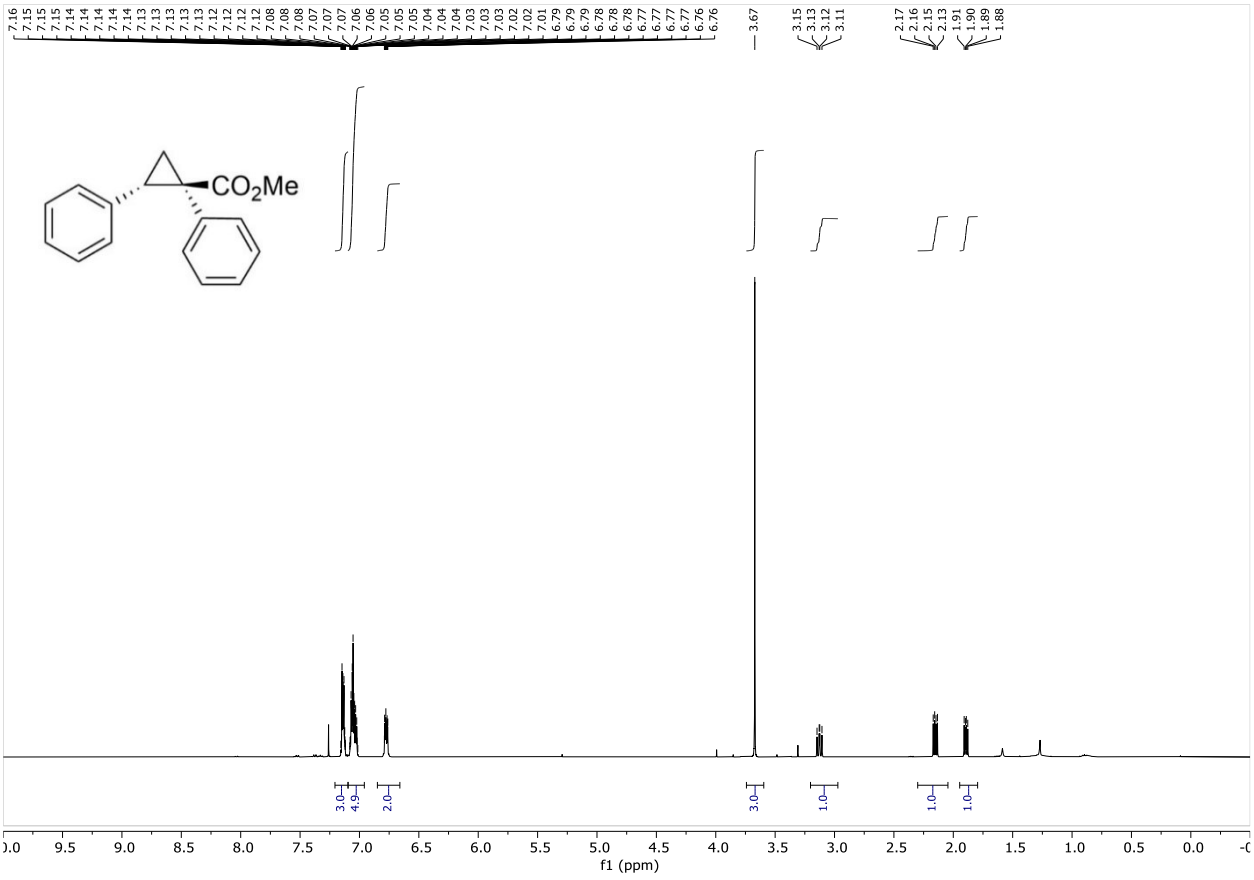
Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (15): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using methyl

(1mol%, 0.01 equiv., 4.9 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (74 mg, 58%) was obtained as a 97:3 mixture of diastereomers. ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.09 (m, 3H), 7.07 – 6.98 (m, 5H), 6.80 – 6.73 (m, 2H), 3.67 (s, 3H), 3.11 (dd, J = 9.4, 7.3 Hz, 1H), 2.14 (dd, J = 9.3, 4.9 Hz, 1H), 1.88 (dd, J = 7.3, 4.9 Hz, 1H). Consistent with previously reported data[14].



Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (16): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 154 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using n-dodecyl (1mol%, 0.01 equiv., 8.0 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (121 mg, 96%) was obtained as a 98:2 mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.10 (m, 3H), 7.10 – 6.96 (m, 5H), 6.85 –

6.66 (m, 2H), 3.67 (s, 3H), 3.13 (dd, J = 9.4, 7.3 Hz, 1H), 2.15 (dd, J = 9.3, 4.9 Hz, 1H), 1.89 (dd, J = 7.3, 4.9 Hz, 1H). Consistent with previously reported data[14].

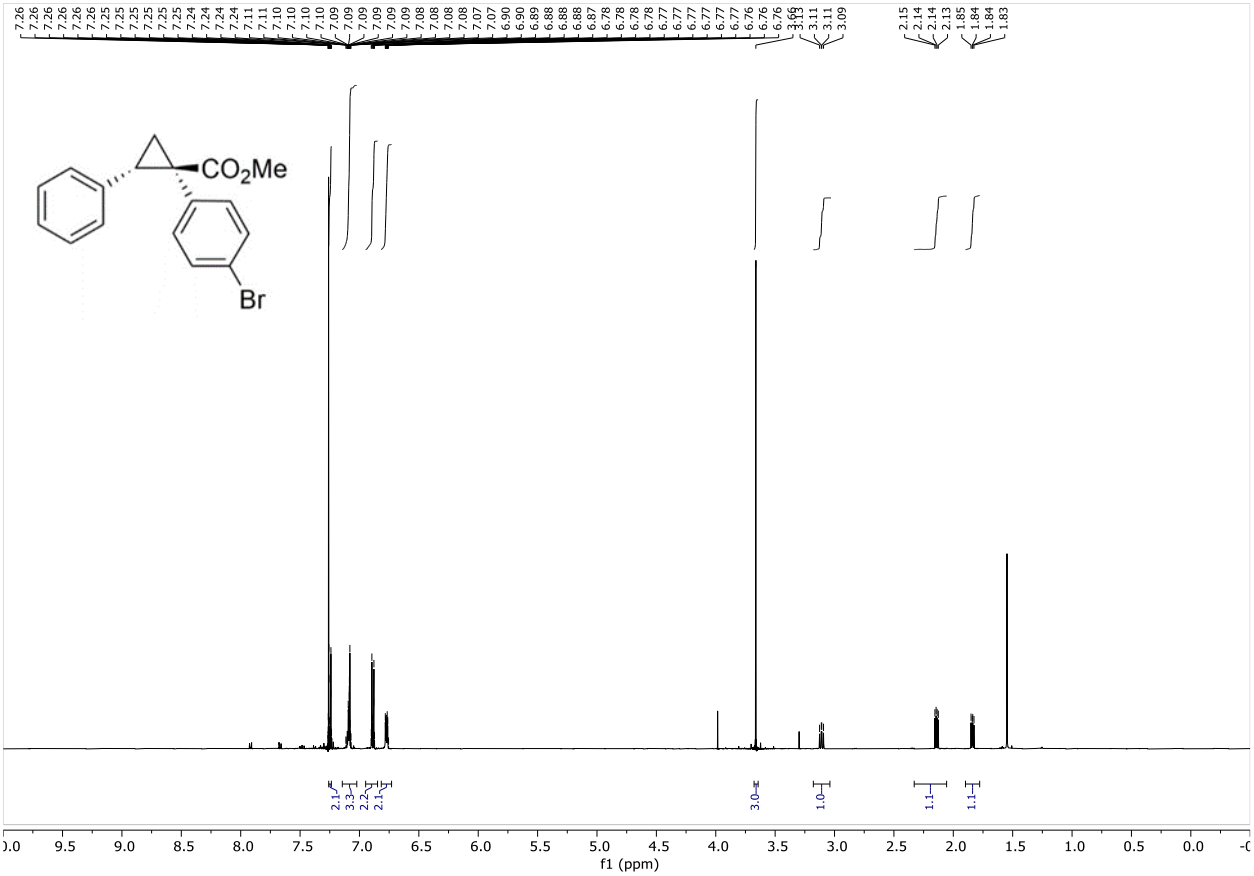


4.5 General Procedure for Cyclopropanation Reactions in Diazo Screen

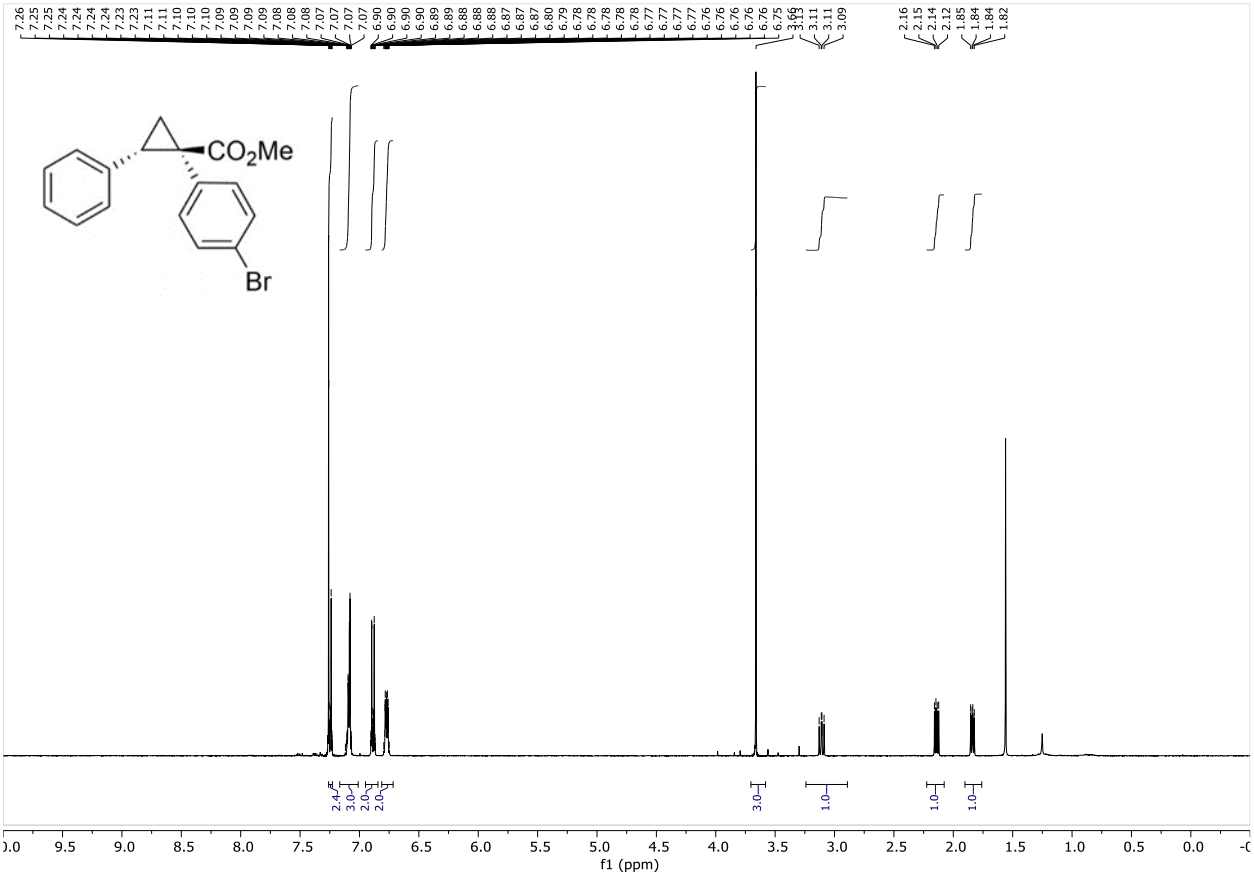
To an oven-dried 25 mL round-bottom flask kept under a dry atmosphere of argon, was added dirhodium tetraprolinate catalyst (1 mol%, 0.01 equiv.) and dry, degassed pentane (2.5 mL) and styrene (1.5 mmol, 3.0 equiv.). A solution of diazo compound (0.5 mmol, 1 equiv.) in dry, degassed pentane (6.5 mL), was then added to the former solution drop-wise over 1.5 h at -50 ^{o}C. The mixture was allowed to stir for 1.5h after addition, and then concentrated *in vacuo*. The

crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (SiO_2, 1% Et_2O/Hexane) to afford the pure cyclopropane.

Methyl (1R,2S)-1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate(17): The general procedure for cyclopropanation reactions in diazo screen was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 154 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (0.5 mmol, 1 equiv., 128 mg) using methyl (1mol%, 0.01 equiv., 4.9 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (55 mg, 33%) was obtained as a 99:1 mixture of diastereomers. ^{1}H NMR (500 MHz, , $CDCl_3$) δ 7.26 – 7.24 (m, 2H), 7.14 – 7.02 (m, 3H), 6.95 – 6.85 (m, 2H), 6.82 – 6.73 (m, 2H), 3.66 (s, 3H), 3.11 (dd, J = 9.3, 7.3 Hz, 1H), 2.14 (dd, J = 9.3, 5.0 Hz, 1H), 1.84 (dd, J = 7.3, 5.0 Hz, 1H). Consistent with previously reported data[14].

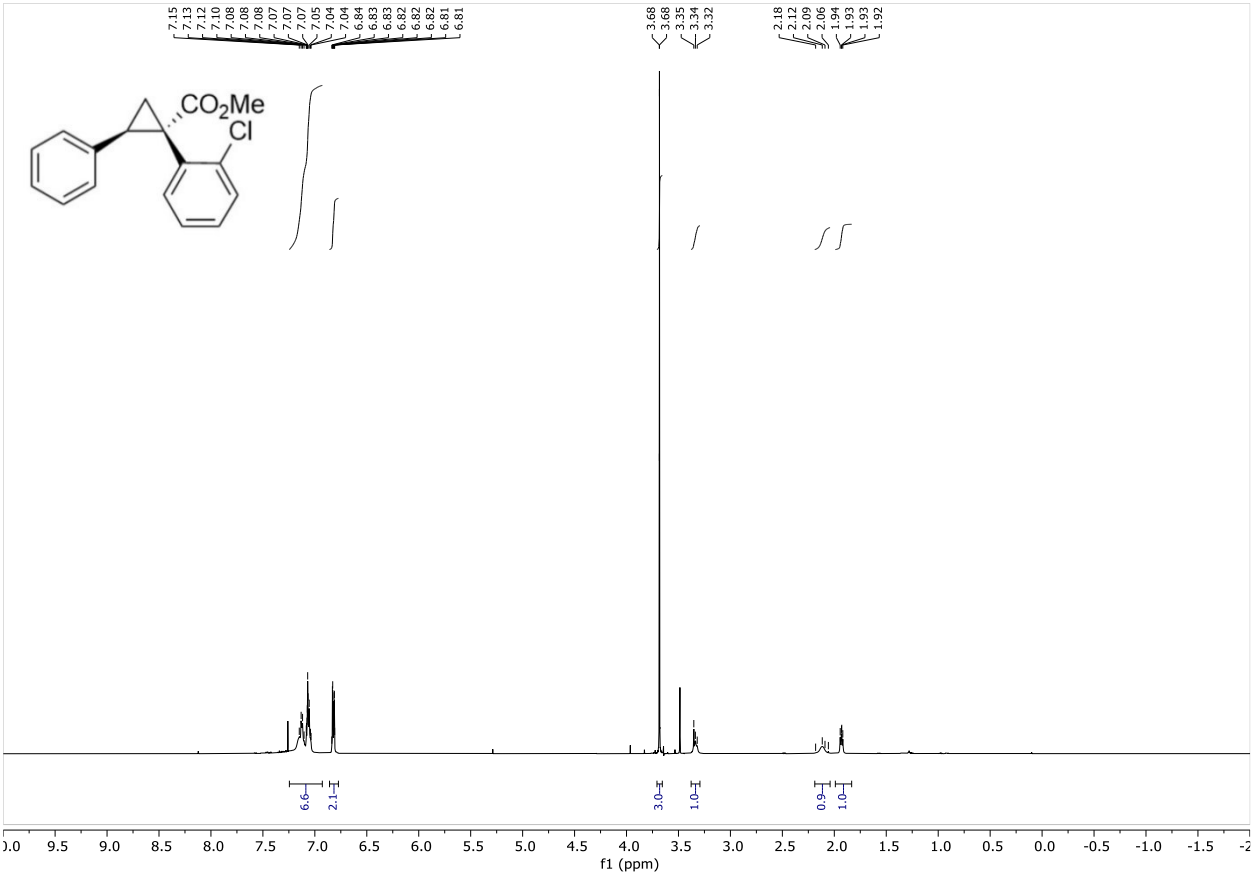


Methyl (1R,2S)-1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate(18): The general procedure for cyclopropanation reactions in diazo screen was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (0.5 mmol, 1 equiv., 128 mg) using n-dodecyl (1mol%, 0.01 equiv., 7.9 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (135 mg, 81%) was obtained as a 99:1 mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 3H), 7.17 – 7.01 (m, 3H), 6.95 – 6.84 (m, 2H), 6.82 – 6.72 (m, 2H), 3.66 (s, 3H), 3.11 (dd, J = 9.3, 7.3 Hz, 1H), 2.14 (dd, J = 9.4, 5.0 Hz, 1H), 1.84 (dd, J = 7.3, 5.0 Hz, 1H). Consistent with previously reported data[14].



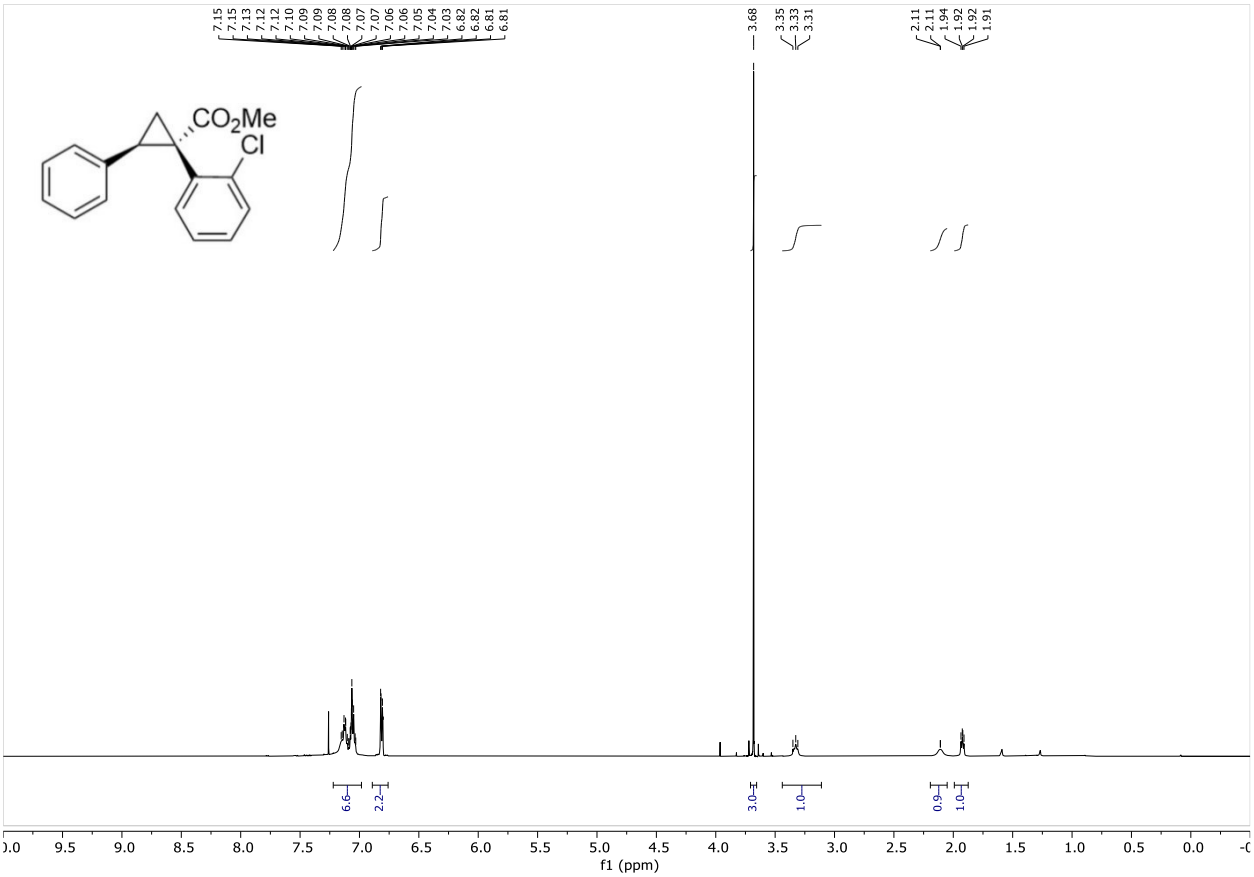
Methyl (1S,2R)-1-(2-chlorophenyl)-2-phenylcyclopropane-1-carboxylate(19): The general procedure for cyclopropanation reactions in diazo screen was employed for the cyclopropanation

of styrene (1.5 mmol, 3 equiv., 154 mg) with methyl 2-(2-chlorophenyl)-2-diazoacetate (0.5 mmol, 1 equiv., 97 mg) using methyl (1mol%, 0.01 equiv., 4.9 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (116 mg, 92%) was obtained as a 96:4 mixture of diastereomers. ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.01 (m, 6H), 6.86 – 6.77 (m, 2H), 3.68 (s, 3H), 3.34 (t, J = 7.6 Hz, 1H), 2.20 – 2.04 (m, 1H), 1.93 (dd, 1H). Consistent with previously reported data[14].



Methyl (1S,2R)-1-(2-chlorophenyl)-2-phenylcyclopropane-1-carboxylate(20): The general procedure for cyclopropanation reactions in diazo screen was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-(2-chlorophenyl)-2-diazoacetate (0.5 mmol, 1 equiv., 105 mg) using n-dodecyl (1mol%, 0.01 equiv., 7.9 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (52 mg, 71%) was obtained as a

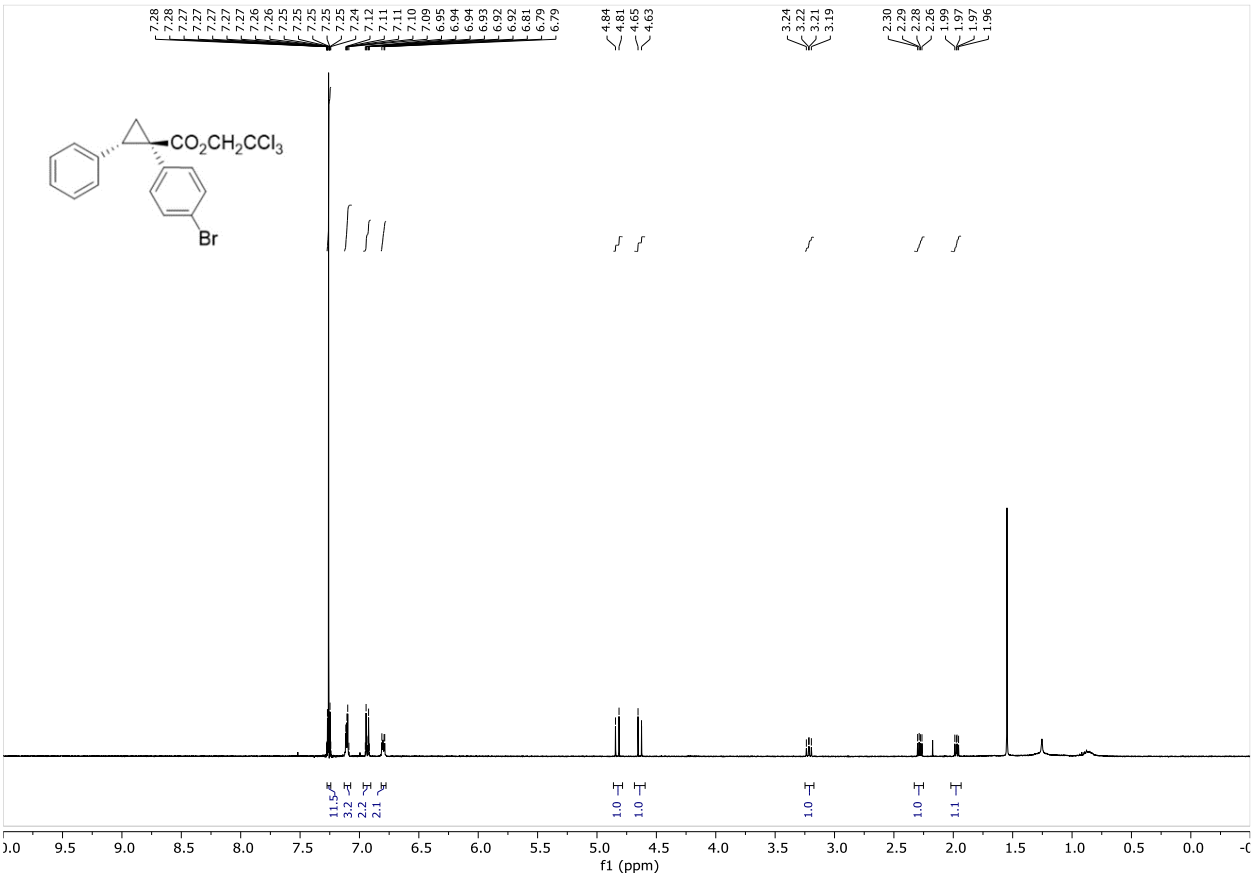
96:4 mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 6.98 (m, 7H), 6.89 – 6.76 (m, 2H), 3.68 (s, 3H), 3.39 – 3.26 (m, 1H), 2.19 – 2.05 (m, 1H), 1.92 (dd, J = 7.5, 5.3 Hz, 1H). Consistent with previously reported data[14].



2,2,2-trichloroethyl (1R,2S)-1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate(21):

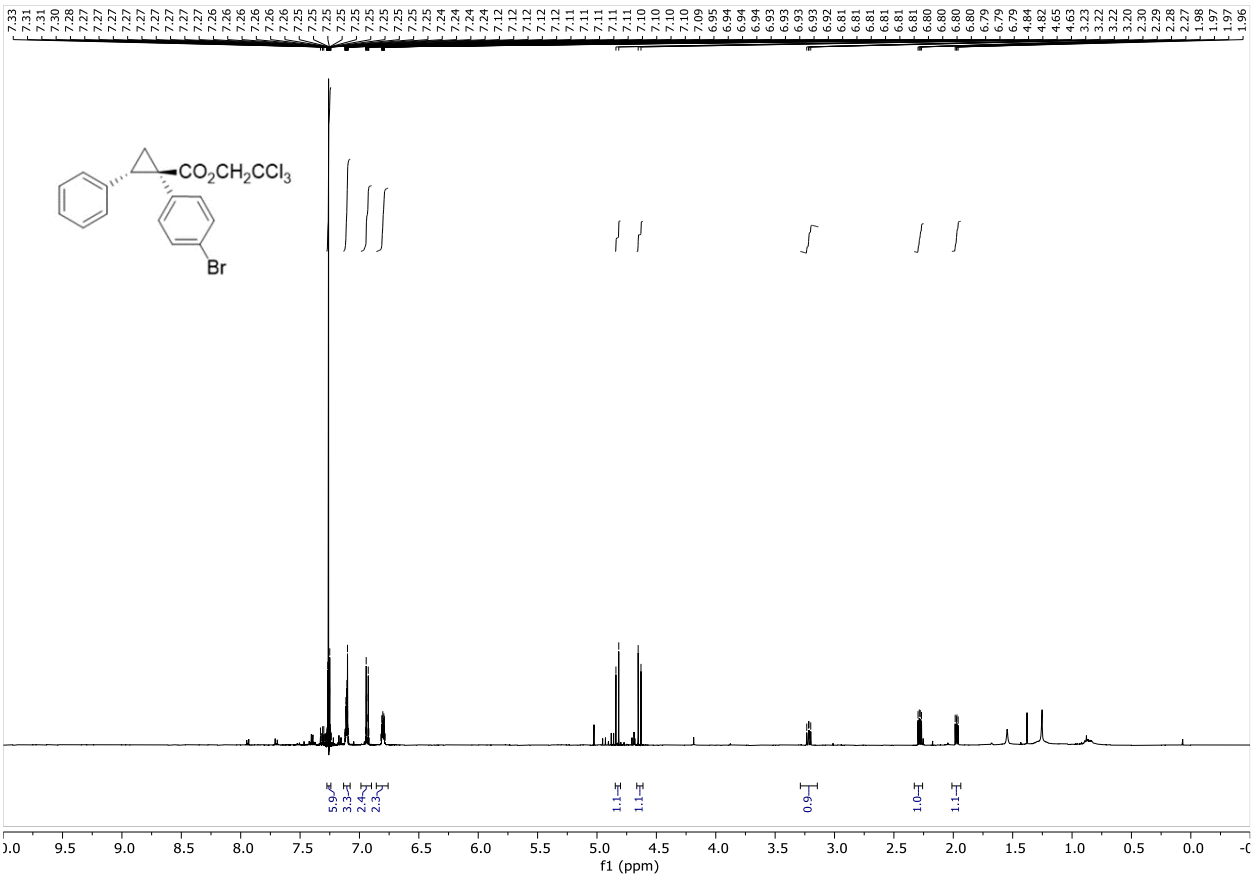
The general procedure for cyclopropanation reactions in diazo screen was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (0.5 mmol, 1 equiv., 173 mg) using n-dodecyl (1mol%, 0.01 equiv., 7.9 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (217 mg, 97%) was obtained as a 99:1 mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 12H), 7.14 – 7.07 (m, 3H), 6.97 – 6.89 (m, 2H), 6.83 – 6.76 (m, 2H),

4.83 (d, J = 11.9 Hz, 1H), 4.64 (d, J = 11.7 Hz, 1H), 3.22 (dd, J = 9.4, 7.4 Hz, 1H), 2.28 (dd, J = 9.4, 5.2 Hz, 1H), 1.97 (dd, J = 7.5, 5.2 Hz, 1H). Consistent with previously reported data[15].



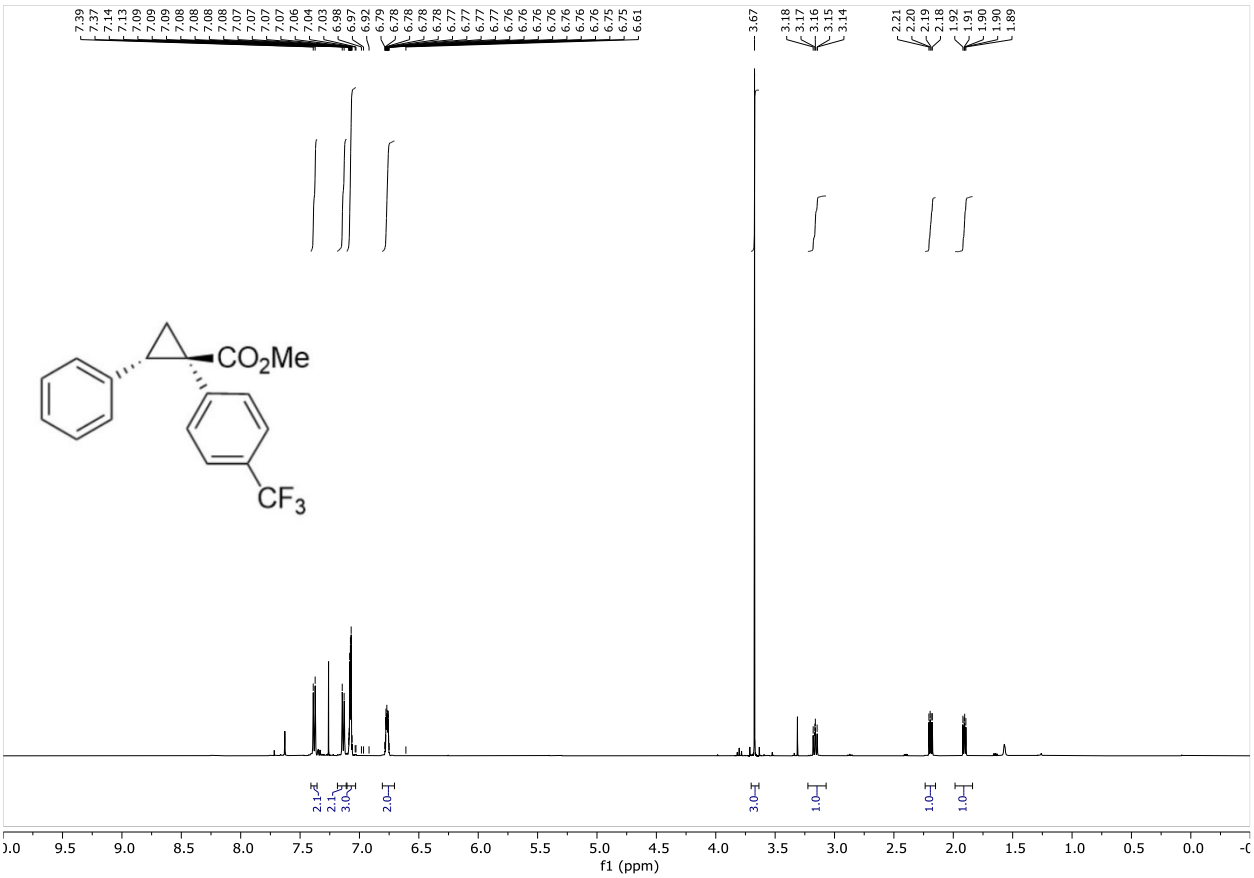
2,2,2-trichloroethyl (1R,2S)-1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate(22):

The general procedure for cyclopropanation reactions in diazo screen was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (0.5 mmol, 1 equiv., 186 mg) using methyl (1mol%, 0.01 equiv., 4.9 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (136 mg, 75%) was obtained as a 99:1 mixture of diastereomers. ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.24 (m, 6H), 7.13 – 7.08 (m, 3H), 6.99 – 6.90 (m, 2H), 6.86 – 6.76 (m, 2H), 4.83 (d, J = 11.9 Hz, 1H), 4.64 (d, J = 11.7 Hz, 1H), 3.22 (dd, J = 9.4, 7.4 Hz, 1H), 2.28 (dd, J = 9.4, 5.2 Hz, 1H), 1.97 (dd, J = 7.5, 5.2 Hz, 1H). Consistent with previously reported data[15].



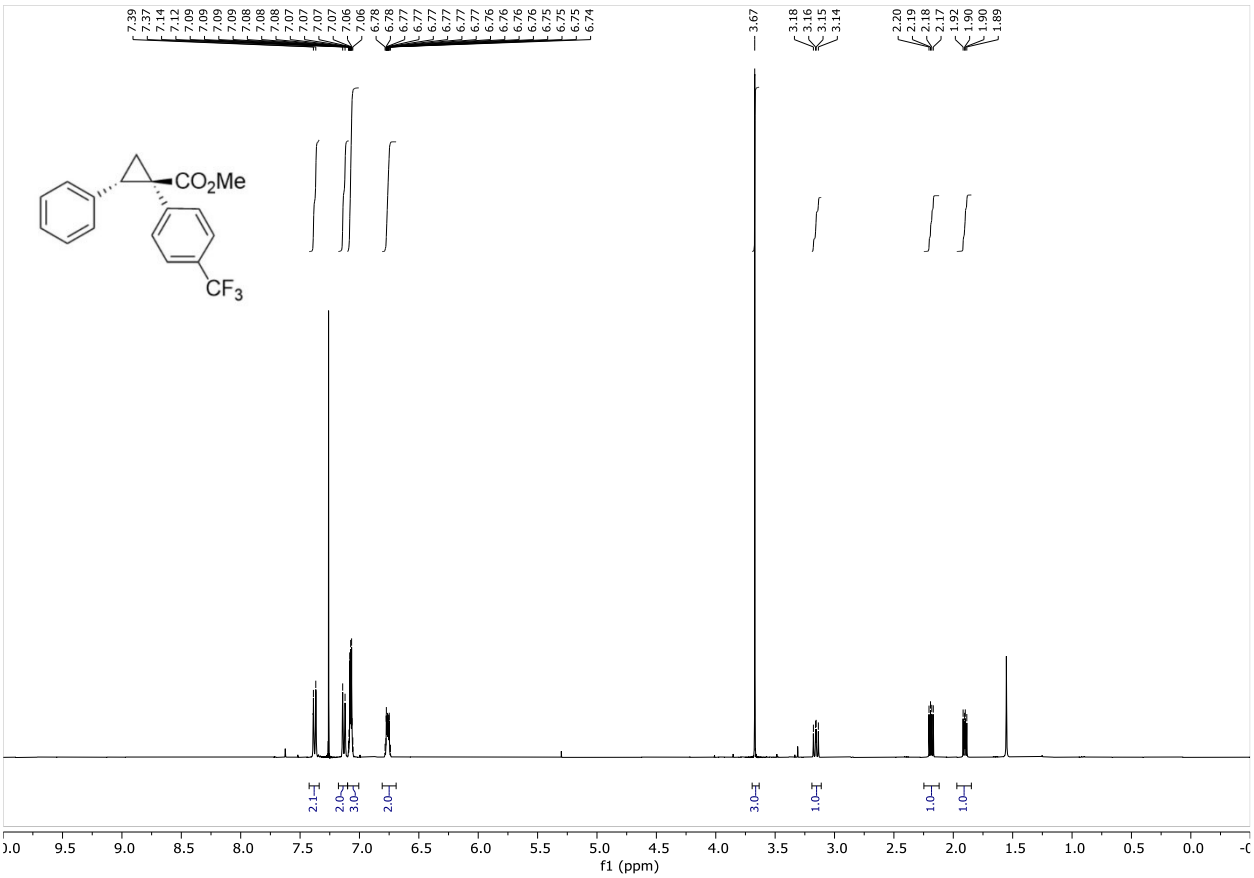
Methyl (1R,2S)-2-phenyl-1-(4-(trifluoromethyl) phenyl) cyclopropane-1-carboxylate(23):

The general procedure for cyclopropanation reactions in diazo screen was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-(4-trifluoromethylphenyl)-2-diazoacetate (0.5 mmol, 1 equiv., 122 mg) using methyl (1mol%, 0.01 equiv., 4.9 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (72 mg, 50%) was obtained as a 99:1 mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 7.11 – 7.02 (m, 3H), 6.81 – 6.71 (m, 2H), 3.67 (s, 3H), 3.16 (dd, J = 9.3, 7.3 Hz, 1H), 2.19 (dd, J = 9.3, 5.1 Hz, 1H), 1.91 (dd, J = 7.4, 5.1 Hz, 1H). Consistent with previously reported data[14].

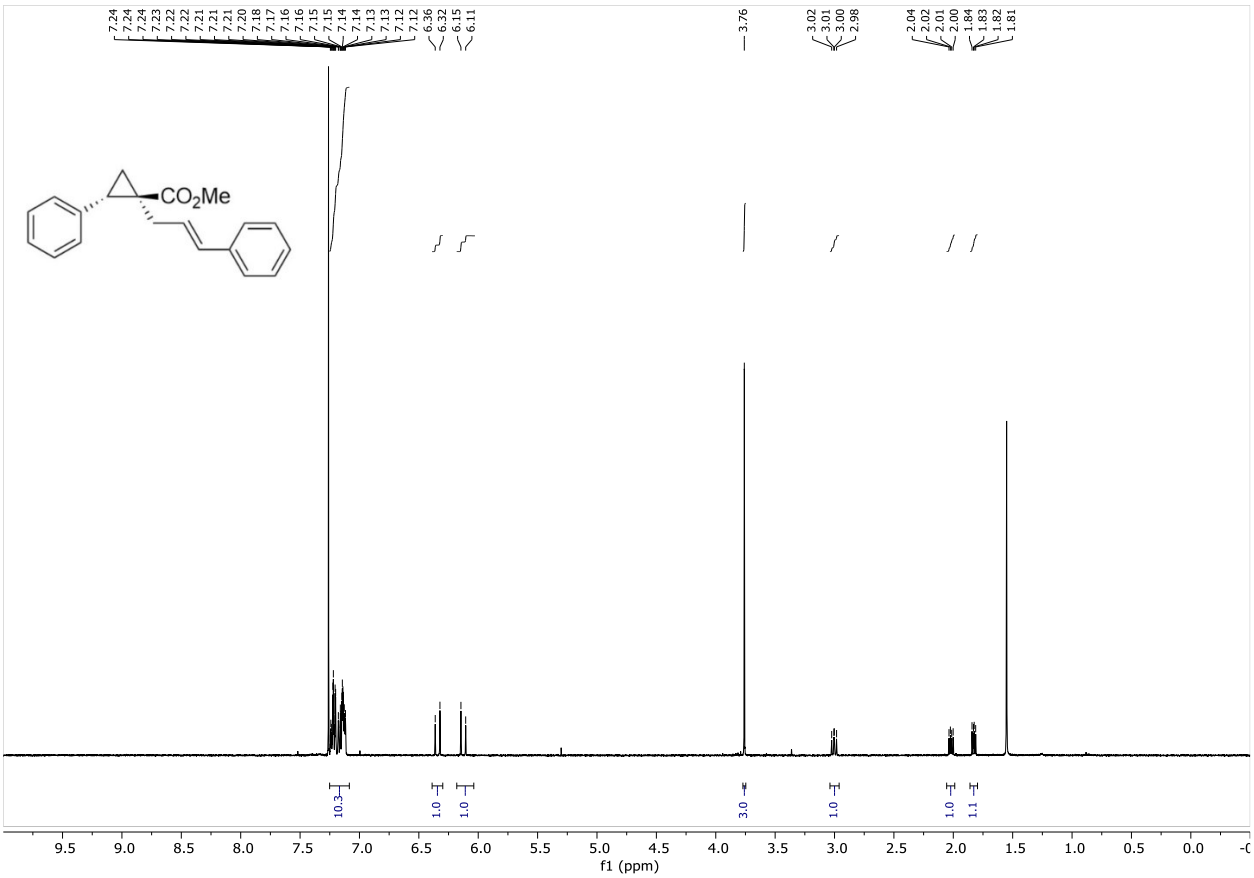


Methyl (1R,2S)-2-phenyl-1-(4-(trifluoromethyl) phenyl) cyclopropane-1-carboxylate(24):

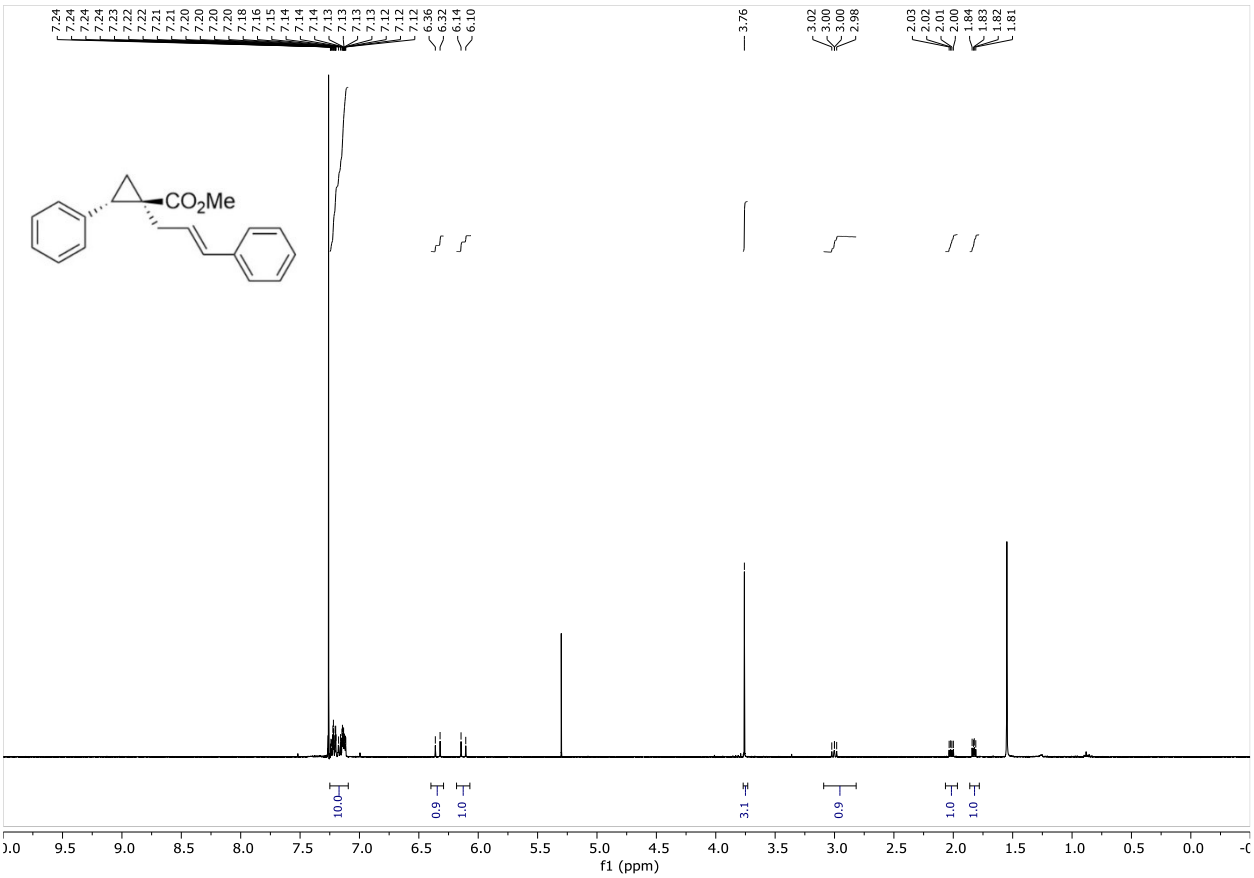
The general procedure for cyclopropanation reactions in diazo screen was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-(4-trifluoromethylphenyl)-2-diazoacetate (0.5 mmol, 1 equiv., 122 mg) using n-dodecyl (1mol%, 0.01 equiv., 7.9 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (63 mg, 39%) was obtained as a 98:2 mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 7.9 Hz, 2H), 7.10 – 7.01 (m, 3H), 6.81 – 6.69 (m, 2H), 3.67 (s, 3H), 3.16 (dd, J = 9.3, 7.4 Hz, 1H), 2.19 (dd, J = 9.4, 5.1 Hz, 1H), 1.90 (dd, J = 7.4, 5.1 Hz, 1H). Consistent with previously reported data[14].



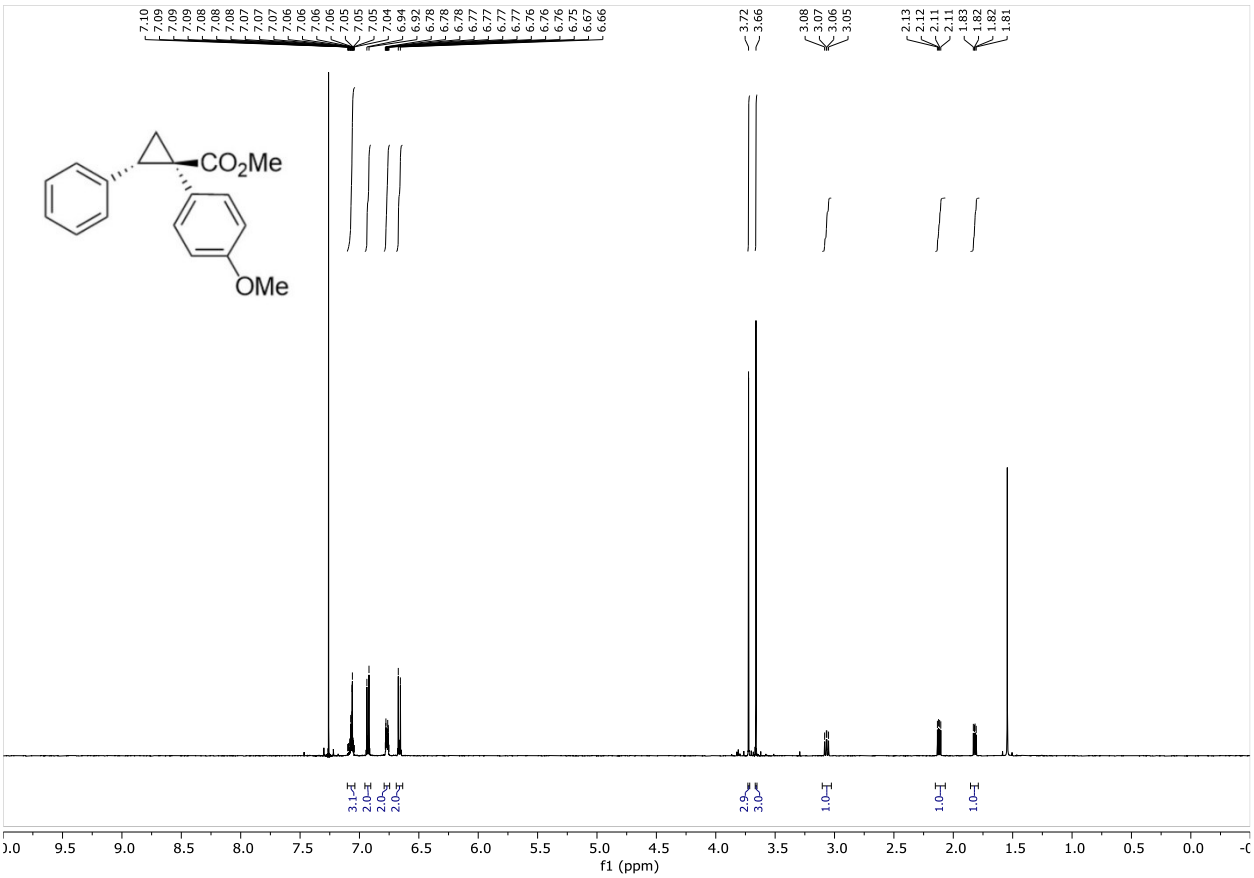
Methyl (1R,2S)-1-cinnamyl-2-phenylcyclopropane-1-carboxylate(25): The general procedure for cyclopropanation reactions in diazo screen was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl (E)-2-diazo-4-phenylbut-3-enoate (0.5 mmol, 1 equiv., 88 mg) using n-dodecyl (1mol%, 0.01 equiv., 7.9 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (71 mg, 59%) was obtained as a 99:1 mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.09 (m, 10H), 6.34 (d, J = 15.9 Hz, 1H), 6.13 (d, J = 16.0 Hz, 1H), 3.76 (s, 3H), 3.00 (dd, J = 9.2, 7.3 Hz, 1H), 2.02 (dd, J = 9.2, 4.8 Hz, 1H), 1.83 (dd, J = 7.3, 5.0 Hz, 1H). Consistent with previously reported data[16].



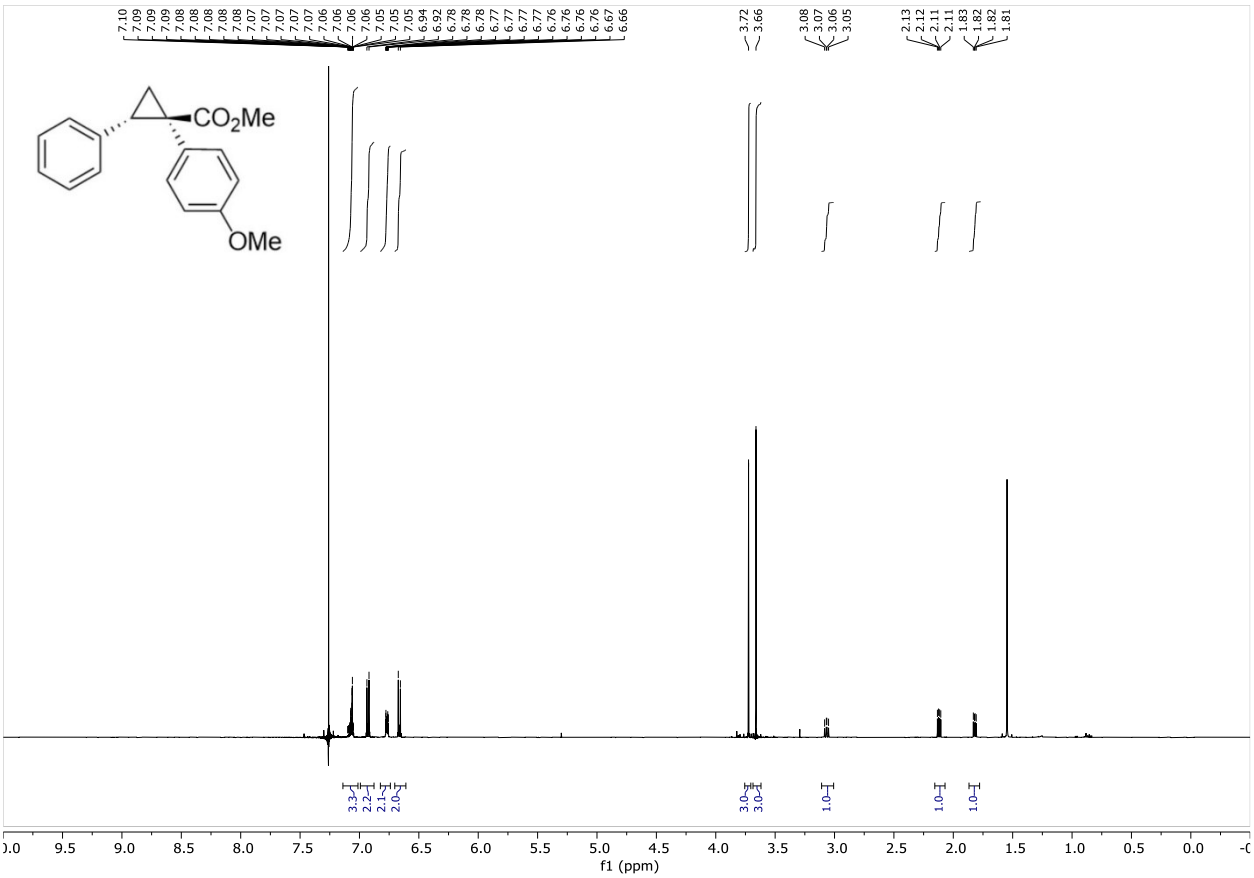
Methyl (1R,2S)-1-cinnamyl-2-phenylcyclopropane-1-carboxylate(26): The general procedure for cyclopropanation reactions in diazo screen was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl (E)-2-diazo-4-phenylbut-3-enoate (0.5 mmol, 1 equiv., 88 mg) using methyl (1mol%, 0.01 equiv., 4.9 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (43 mg, 36%) was obtained as a 99:1 mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.09 (m, 10H), 6.34 (d, J = 16.0 Hz, 1H), 6.12 (d, J = 15.9 Hz, 1H), 3.76 (s, 3H), 3.00 (dd, 1H), 2.02 (dd, J = 9.1, 5.0 Hz, 1H), 1.83 (dd, J = 7.3, 5.0 Hz, 1H). Consistent with previously reported data[16].



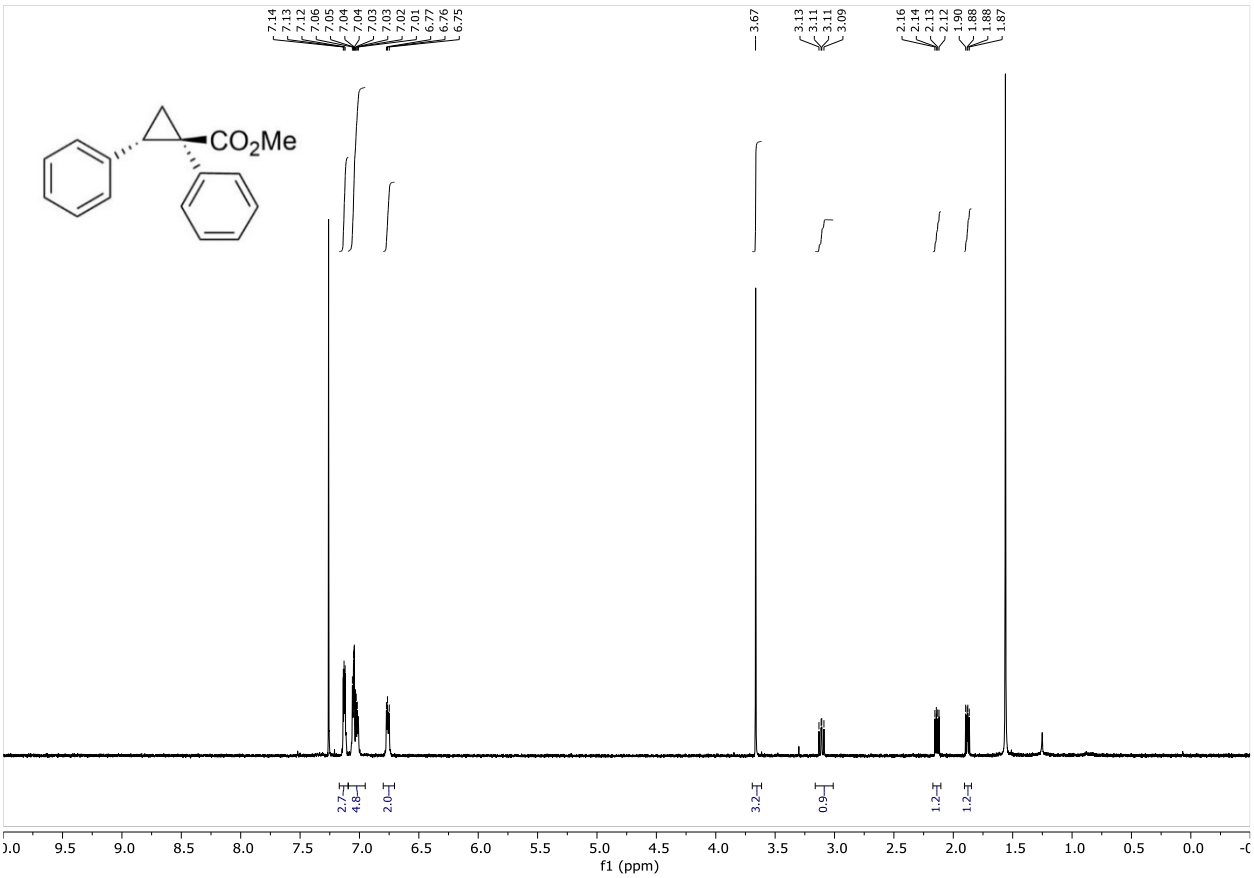
Methyl (1R,2S)-1-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate (27): The general procedure for cyclopropanation reactions in diazo screen was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-(4-methoxyphenyl)-2-diazoacetate (0.5 mmol, 1 equiv., 122 mg) using n-dodecyl (1mol%, 0.01 equiv., 7.9 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (127 mg, 90%) was obtained as a 99:1 mixture of diastereomers. ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 – 7.04 (m, 3H), 6.93 (d, J = 8.9 Hz, 2H), 6.79 – 6.75 (m, 2H), 6.66 (d, J = 8.8 Hz, 2H), 3.72 (s, 3H), 3.66 (s, 3H), 3.07 (dd, J = 9.3, 7.3 Hz, 1H), 2.12 (dd, J = 9.3, 4.8 Hz, 1H), 1.82 (dd, J = 7.3, 4.8 Hz, 1H). Consistent with previously reported data[14].



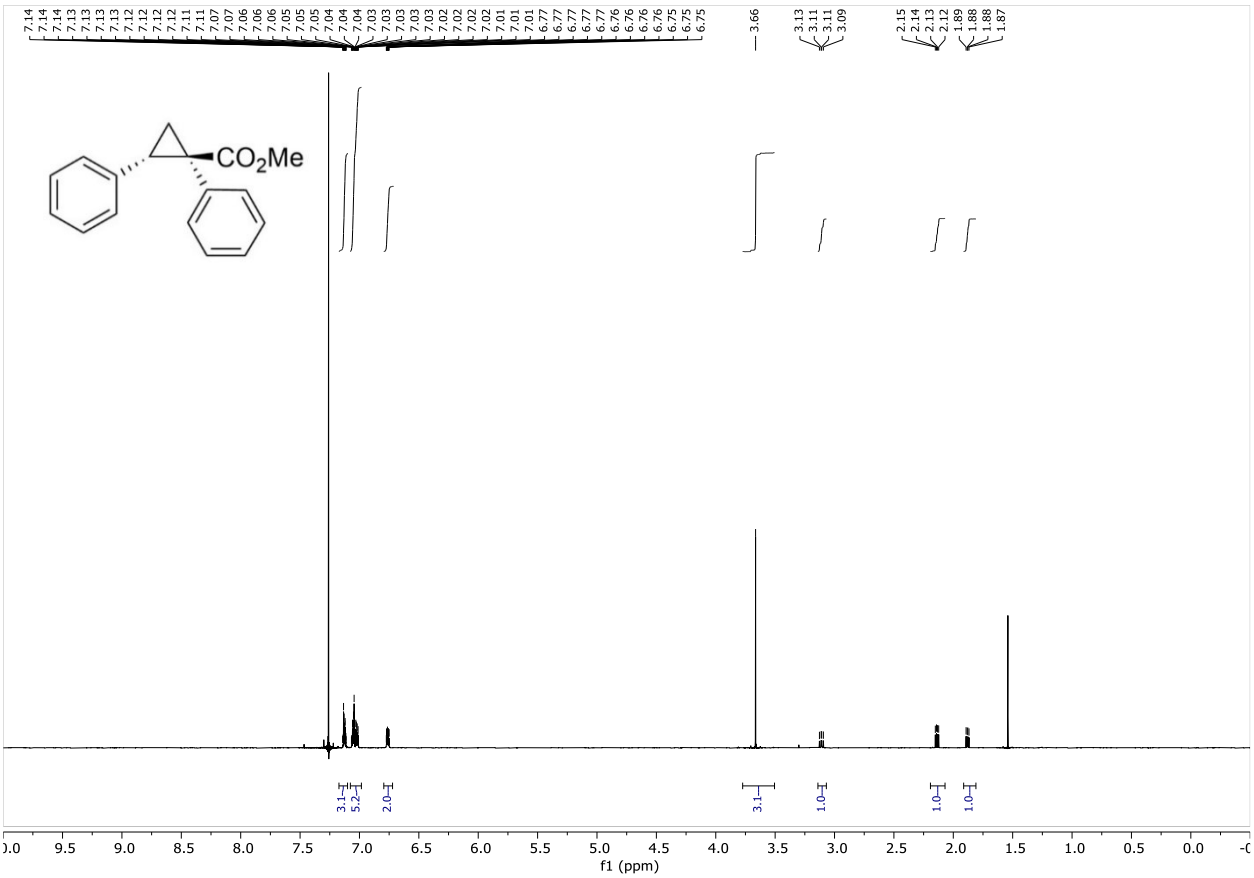
Methyl (1R,2S)-1-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate (28): The general procedure for cyclopropanation reactions in diazo screen was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 156 mg) with methyl 2-(4-methoxyphenyl)-2-diazoacetate (0.5 mmol, 1 equiv., 122 mg) using methyl (1mol%, 0.01 equiv., 4.9 mg) as catalyst. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (74 mg, 52%) was obtained as a 99:1 mixture of diastereomers. ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 – 7.01 (m, 3H), 6.93 (d, J = 8.9 Hz, 2H), 6.82 – 6.74 (m, 2H), 6.66 (d, J = 8.9 Hz, 2H), 3.72 (s, 3H), 3.66 (s, 3H), 3.07 (dd, J = 9.3, 7.3 Hz, 1H), 2.12 (dd, J = 9.3, 4.8 Hz, 1H), 1.82 (dd, J = 7.3, 4.8 Hz, 1H). Consistent with previously reported data[14].



Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (29): The general procedure for cyclopropanation reactions in diazo screen was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 154 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using n-dodecyl (1mol%, 0.01 equiv., 7.9 mg) as catalyst, except this reaction was ran in dichloromethane instead of pentane. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (86 mg, 68%) was obtained as a 95:5 mixture of diastereomers. ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.17 – 7.09 (m, 3H), 7.09 – 6.95 (m, 4H), 6.80 – 6.70 (m, 2H), 3.67 (s, 3H), 3.11 (dd, J = 9.4, 7.3 Hz, 1H), 2.14 (dd, J = 9.3, 4.7 Hz, 1H), 1.88 (dd, J = 7.3, 4.9 Hz, 1H). Consistent with previously reported data[14].



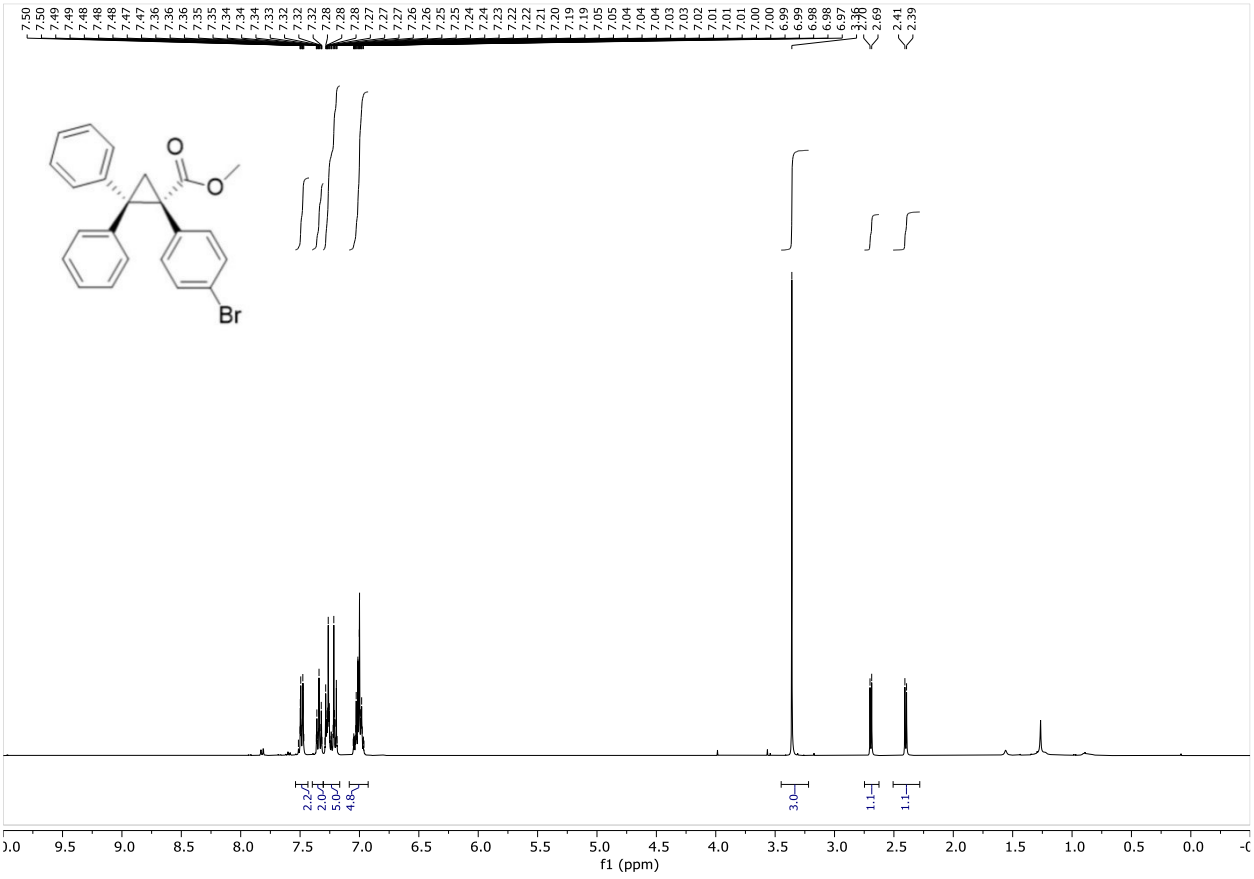
Methyl (1R,2S)-1,2-diphenylcyclopropane-1-carboxylate (30): The general procedure for cyclopropanation reactions was employed for the cyclopropanation of styrene (1.5 mmol, 3 equiv., 154 mg) with methyl 2-diazo-2-phenylacetate (0.5 mmol, 1 equiv., 88 mg) using methyl (1mol%, 0.01 equiv., 5.0 mg) as catalyst, except this reaction was ran in dichloromethane instead of pentane. After flash chromatography (SiO_2, 1% Et_2O/Hexane) the title compound (47 mg, 37%) was obtained as a 92:8 mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 – 7.10 (m, 3H), 7.08 – 6.98 (m, 5H), 6.80 – 6.72 (m, 2H), 3.66 (s, 3H), 3.11 (dd, J = 9.4, 7.3 Hz, 1H), 2.14 (dd, J = 9.3, 4.9 Hz, 1H), 1.88 (dd, J = 7.3, 4.9 Hz, 1H). Consistent with previously reported data[14].



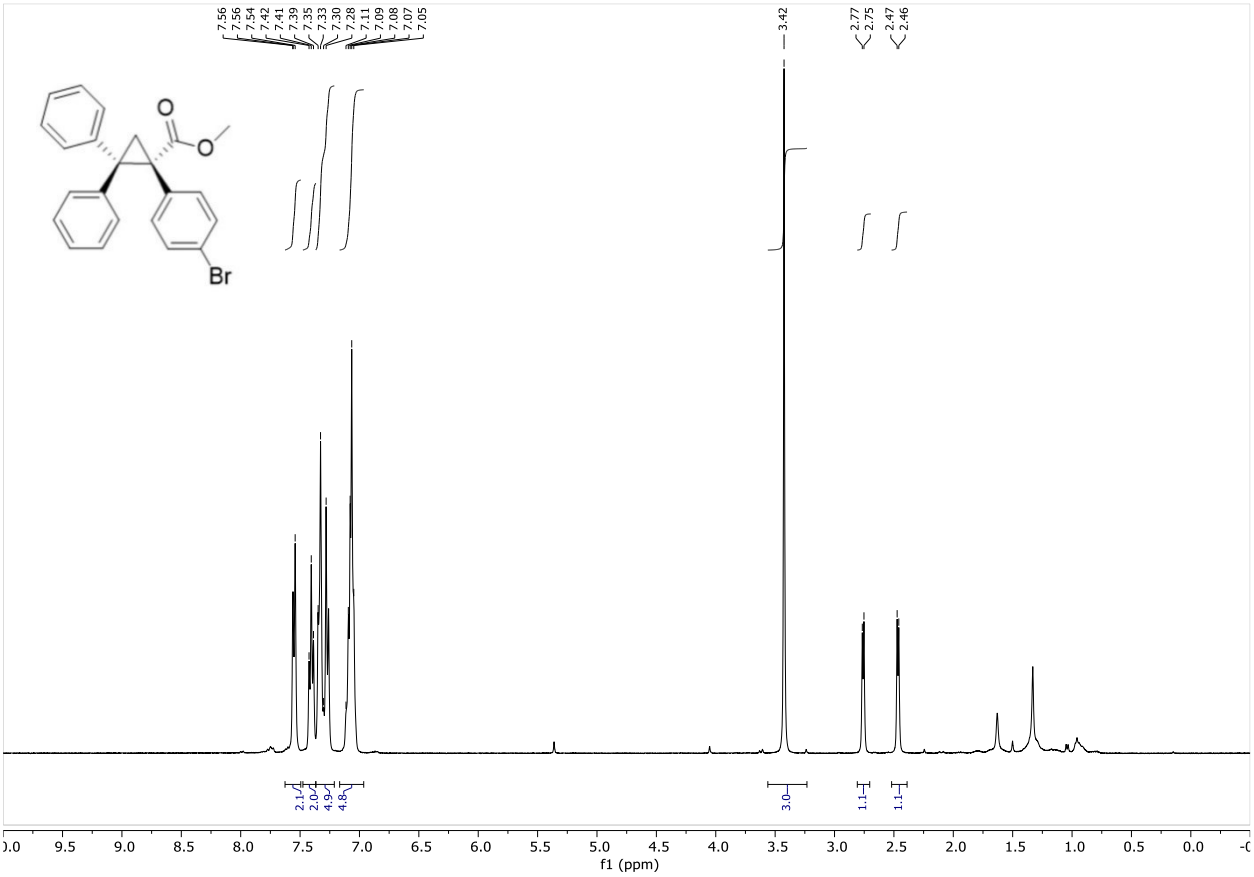
4.6 General Procedure for C-H Functionalization Reactions with N-dodecyl/methyl Catalyst

To an oven-dried 25 mL round-bottom flask kept under a dry atmosphere of argon, was added dirhodium tetraprolinate catalyst (1 mol%, 0.01 equiv.) and dry, degassed pentane (2.0 mL) and substrate (0.75 mmol, 3.0 equiv.). A solution of diazo compound (0.25 mmol, 1 equiv.) in dry, degassed pentane (4.0 mL), was then added to the former solution drop-wise over 1.5 h at ambient temperature unless otherwise noted. The mixture was allowed to stir for 1.5h after addition, and then concentrated *in vacuo*. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (Et_2O/Hexane) to afford the pure C-H functionalization product.

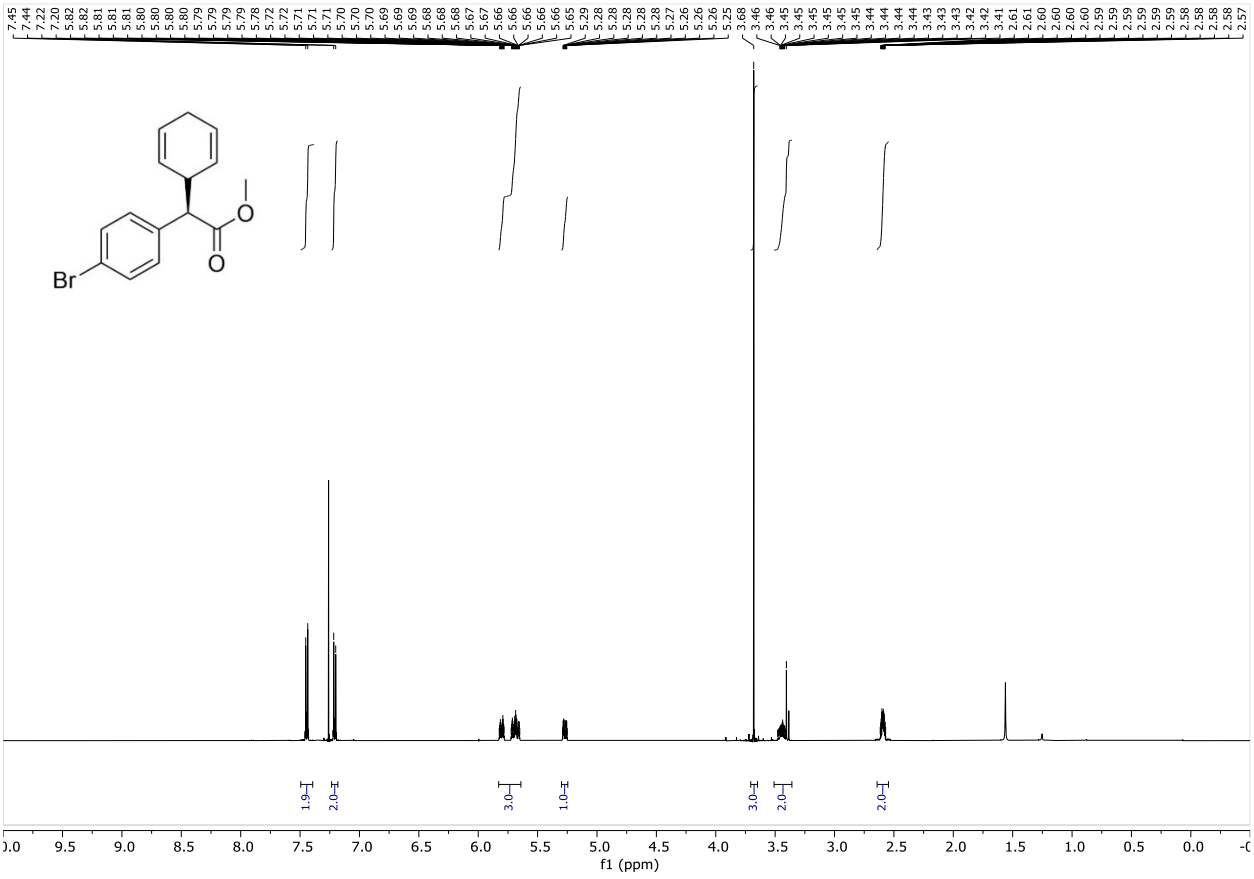
Methyl (R)-1-(4-bromophenyl)-2,2-diphenylcyclopropane-1-carboxylate (31): The general procedure for C-H functionalization reactions was employed for the cyclopropanation of 1,1-diphenylethylene (0.75 mmol, 3equiv., 134 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (0.25 mmol, 1 equiv., 72 mg) using methyl (1mol%, 0.01 equiv., 4.9 mg) as catalyst. After flash chromatography (SiO_2, 3% Et_2O/Hexane) the title compound (80 mg, 71%) was obtained. ^1H NMR (399 MHz, $CDCl_3$) δ 7.63 – 7.49 (m, 2H), 7.48 – 7.36 (m, 2H), 7.37 – 7.21 (m, 5H), 7.07 (q, J = 6.5 Hz, 5H), 3.42 (s, 3H), 2.76 (d, J = 5.6 Hz, 1H), 2.47 (d, J = 5.6 Hz, 1H). Consistent with previously reported data[17]. HPLC conditions: SS-Whelk, 60 min, 0.8 mL/min, 5% iPrOH/Hexane, 254 nm. Retention times: 9.5 min and 15.4 min; 90% e.e.



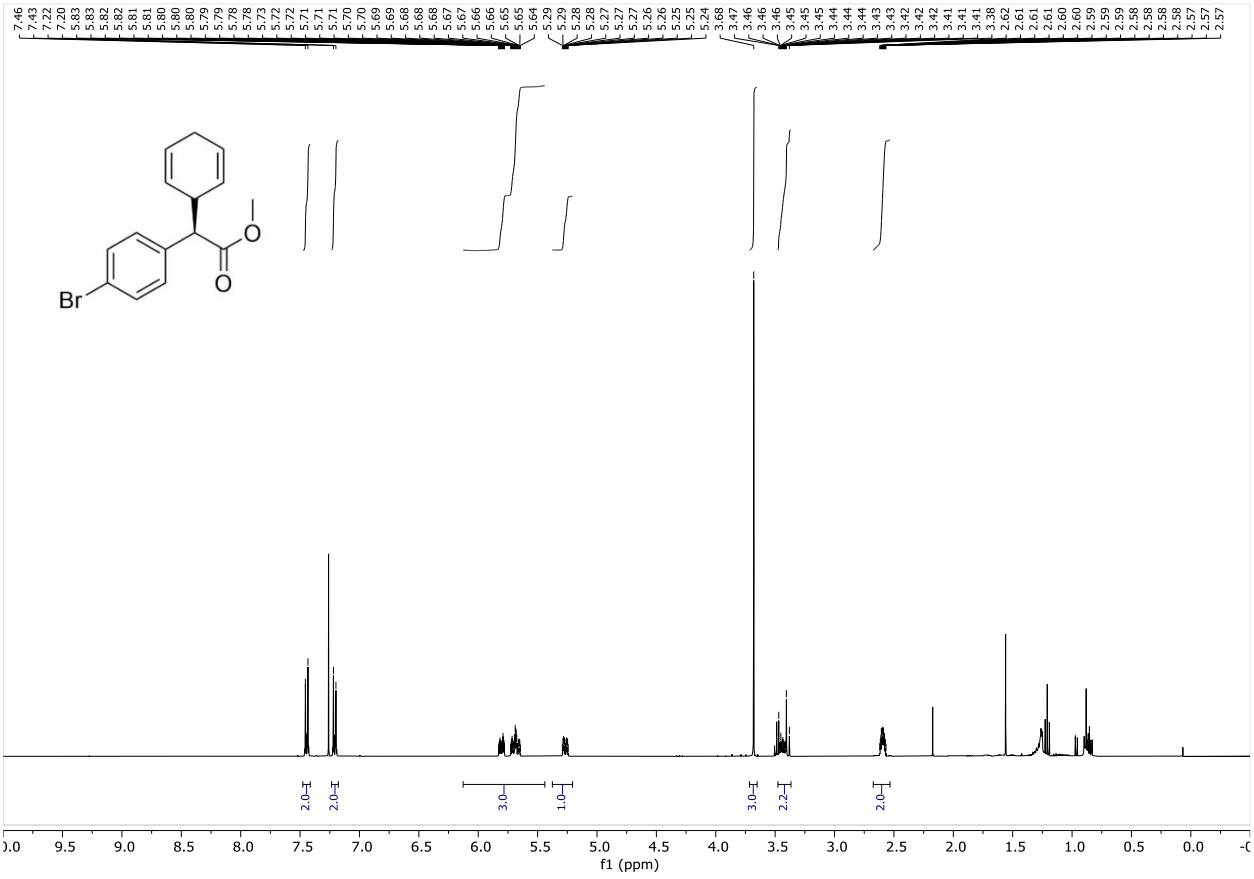
Methyl (R)-1-(4-bromophenyl)-2,2-diphenylcyclopropane-1-carboxylate (32): The general procedure for C-H functionalization reactions was employed for the cyclopropanation of 1,1-diphenylethylene (0.75 mmol, 3equiv., 134 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (0.25 mmol, 1 equiv., 72 mg) using n-dodecyl (1mol%, 0.01 equiv., 7.9 mg) as catalyst. After flash chromatography (SiO_2, 3% Et_2O/Hexane) the title compound (99.6 mg, 98%) was obtained. ^1H NMR (399 MHz, $CDCl_3$) δ 7.54 – 7.43 (m, 2H), 7.40 – 7.30 (m, 2H), 7.30 – 7.17 (m, 5H), 7.09 – 6.93 (m, 5H), 3.36 (s, 3H), 2.69 (d, J = 5.6 Hz, 1H), 2.40 (d, J = 5.6 Hz, 1H). Consistent with previously reported data[17]. HPLC conditions: SS-Whelk, 60 min, 0.8 mL/min, 5% iPrOH/Hexane, 254 nm. Retention times: 9.5 min and 15.4 min; 98% e.e.



Methyl (R)-2-(4-bromophenyl)-2-(cyclohexa-2,5-dien-1-yl) acetate (33): The general procedure for C-H functionalization reactions was employed for the functionalization of 1,4-cyclohexadiene (2.5 mmol, 1.0 equiv., 200 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (6.25 mmol, 2.5 equiv., 128 mg) using n-dodecyl (1mol%, 0.01 equiv., 7.9 mg) as catalyst at -50°C. After flash chromatography (SiO_2, 3% Et_2O/Hexane) the title compound (38 mg, 77%) was obtained. ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 5.83 – 5.64 (m, 3H), 5.30 – 5.25 (m, 1H), 3.68 (s, 3H), 3.48 – 3.40 (m, 2H), 2.63 – 2.55 (m, 2H). Consistent with previously reported data[18]. HPLC conditions: AD-H, 1mL/min, 2% iPrOH/Hexane, 230 nm. Retention times: 5.2 min and 5.5 min; 99% e.e.

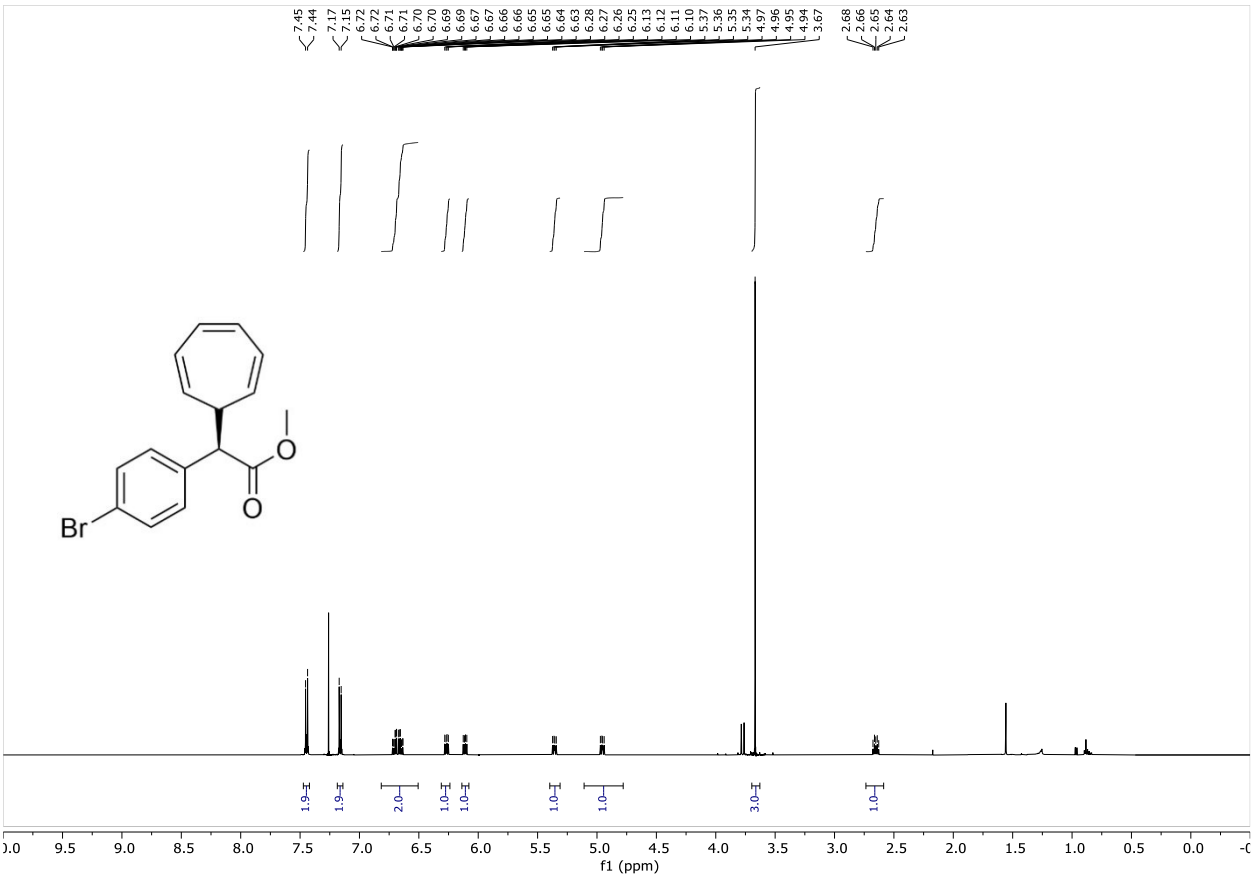


Methyl (R)-2-(4-bromophenyl)-2-(cyclohexa-2,5-dien-1-yl) acetate (34): The general procedure for C-H functionalization reactions was employed for the functionalization of 1,4-cyclohexadiene (2.5 mmol, 1.0 equiv., 200 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (6.25 mmol, 2.5 equiv., 128 mg) using methyl (1mol%, 0.01 equiv., 4.9 mg) as catalyst at -50°C. After flash chromatography (SiO_2, 3% Et_2O/Hexane) the title compound (12.3 mg, 25%) was obtained. ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 5.93 – 5.62 (m, 3H), 5.38 – 5.21 (m, 1H), 3.68 (s, 3H), 3.48 – 3.37 (m, 2H), 2.67 – 2.53 (m, 2H). Consistent with previously reported data[18]. HPLC conditions: AD-H, 1mL/min, 2% iPrOH/Hexane, 230 nm. Retention times: 5.2 min and 5.5 min; 86% e.e.

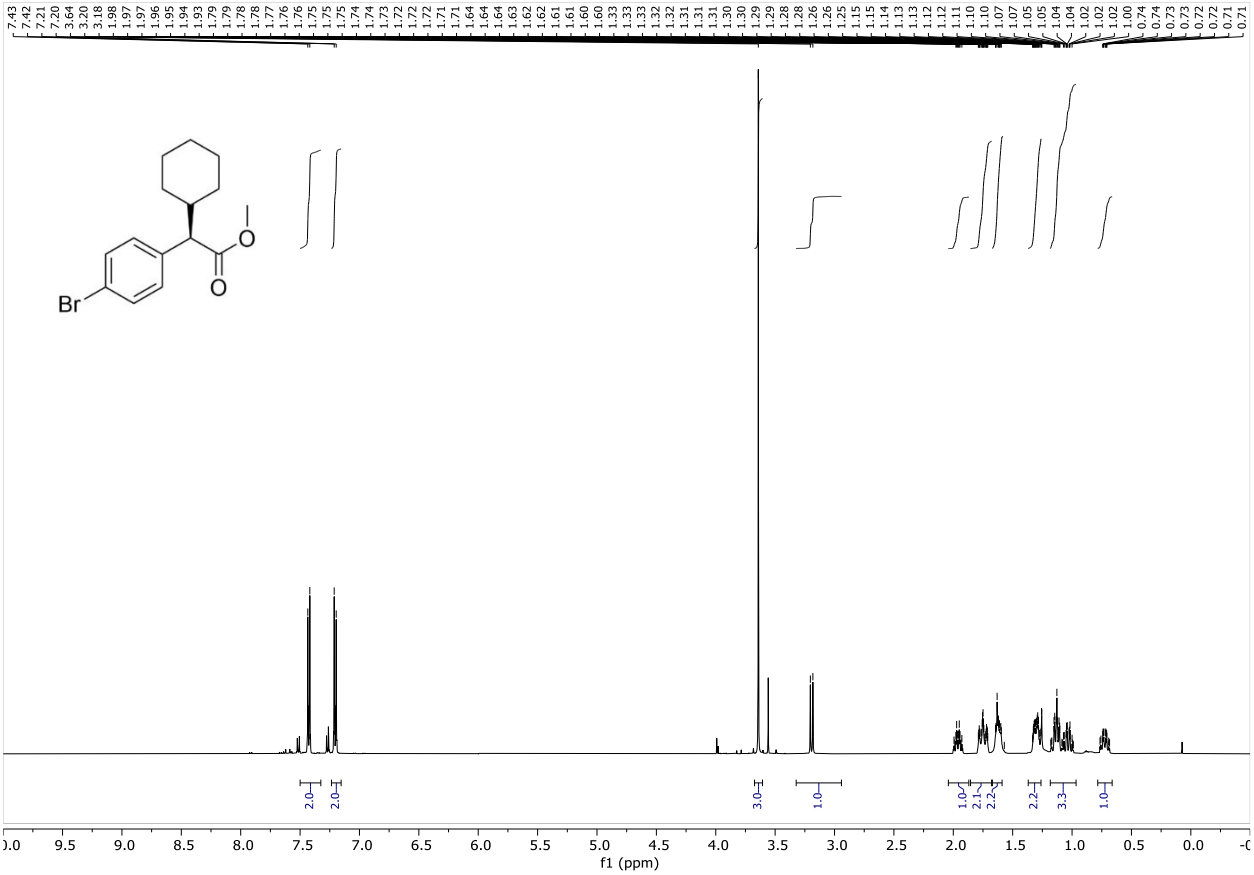


Methyl (R)-2-(4-bromophenyl)-2-(cyclohepta-2,4,6-trien-1-yl) acetate (35): The general procedure for C-H functionalization reactions was employed for the functionalization of 1,3,5-cycloheptatriene (2.5 mmol, 5.0 equiv., 230 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (6.25 mmol, 2.5 equiv., 128 mg) using n-dodecyl (1mol%, 0.01 equiv., 7.9 mg) as catalyst at -50°C. After flash chromatography (SiO_2, 3% Et_2O/Hexane) the title compound (123 mg, 77%) was obtained. HPLC conditions: SS-Whelk, 60 min, 1 mL/min, 0.3% iPrOH/Hexanes, 230 nm. Retention times: 32.6 min and 39 min; 90% e.e.

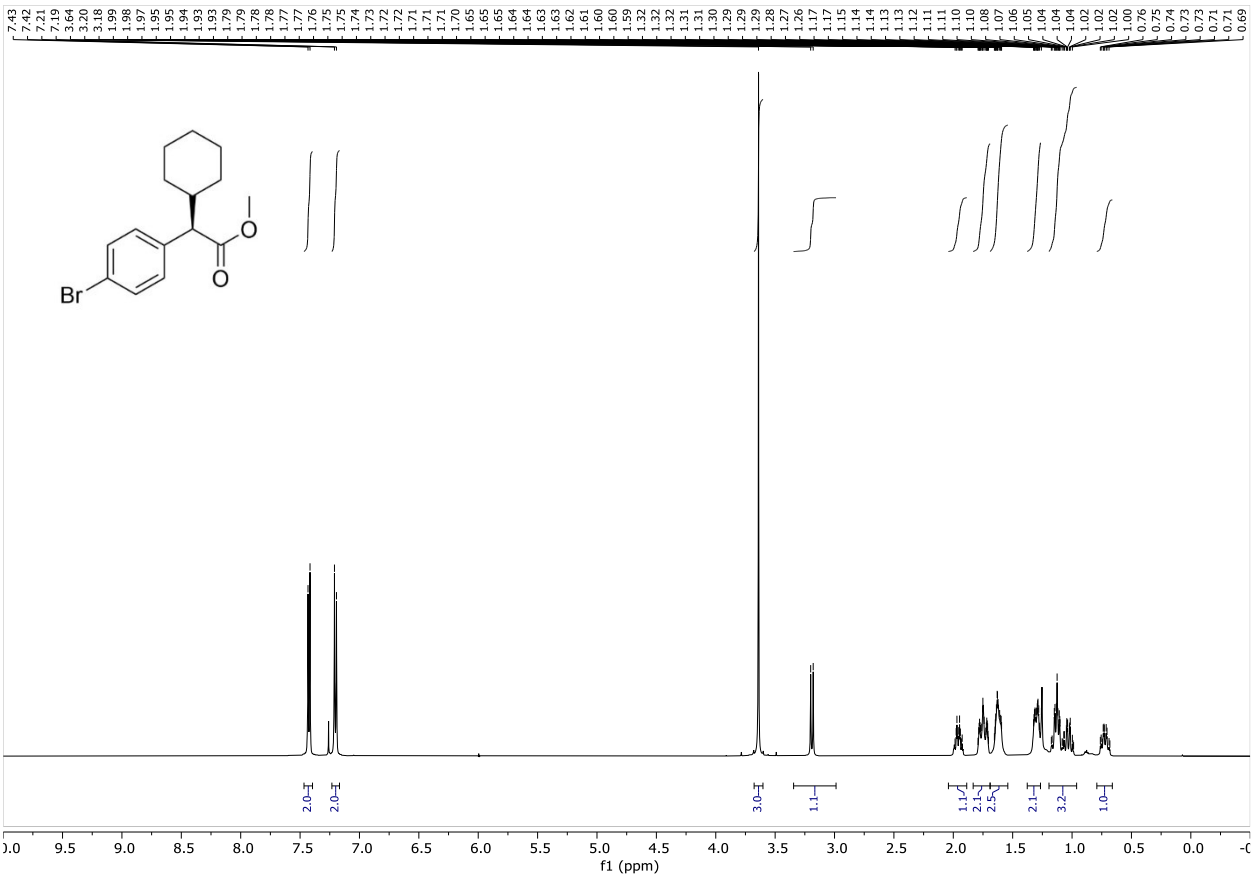
Methyl (R)-2-(4-bromophenyl)-2-(cyclohepta-2,4,6-trien-1-yl) acetate (36): The general procedure for C-H functionalization reactions was employed for the functionalization of 1,3,5-cycloheptatriene (2.5 mmol, 5.0 equiv., 230.4 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (6.25 mmol, 2.5 equiv., 128 mg) using methyl (1mol%, 0.01 equiv., 5.0 mg) as catalyst at -50°C. After flash chromatography (SiO_2, 3% Et_2O/Hexane) the title compound (66 mg, 43%) was obtained. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 8.5 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H), 6.70 (ddd, J = 11.1, 5.6, 0.8 Hz, 1H), 6.65 (ddd, J = 11.1, 5.6, 0.8 Hz, 1H), 6.27 (dd, J = 9.5, 5.6 Hz, 1H), 6.11 (dd, J = 9.6, 5.6 Hz, 1H), 5.36 (dd, J = 9.5, 6.1 Hz, 1H), 4.96 (dd, J = 9.5, 6.4 Hz, 1H), 3.67 (s, 3H), 2.65 (dd, 1H). HPLC conditions: SS-Whelk, 60 min, 1 mL/min, 0.3% iPrOH/Hexanes, 230 nm. Retention times: 32.6 min and 39 min; 60% e.e.



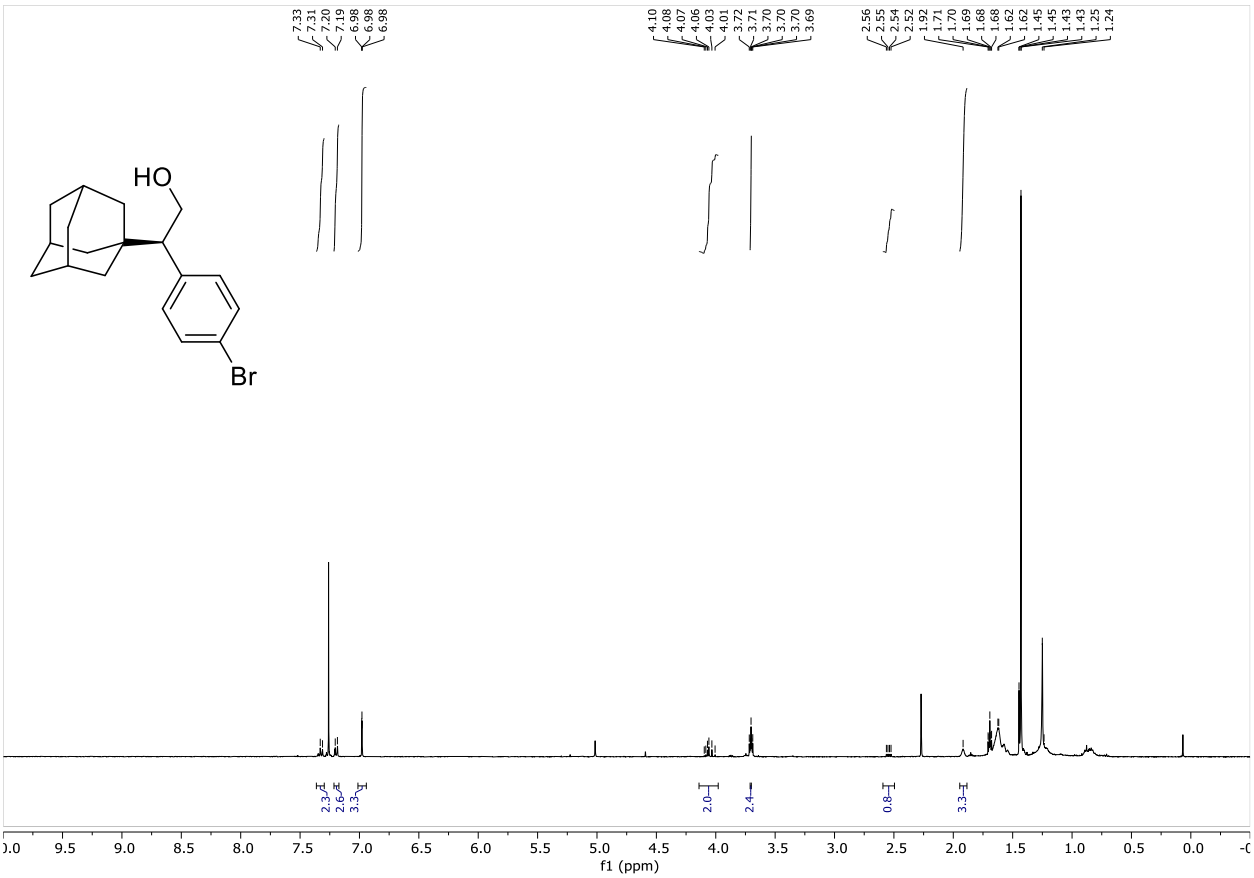
Methyl (R)-2-(4-bromophenyl)-2-cyclohexylacetate (37): The general procedure for C-H functionalization reactions was employed for the functionalization of cyclohexane (10 mL) with methyl 2-(4-bromophenyl)-2-diazoacetate (1.0 mmol, 1 equiv., 268 mg) using n-dodecyl (1mol%, 0.01 equiv., 7.9 mg) as catalyst at 10°C. After flash chromatography (SiO_2, 5% Et_2O/Hexane) the title compound (218 mg, 70%) was obtained. ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 3.64 (s, 3H), 3.19 (d, J = 10.6 Hz, 1H), 2.04 – 1.87 (m, 1H), 1.85 – 1.68 (m, 2H), 1.67 – 1.59 (m, 2H), 1.37 – 1.26 (m, 2H), 1.18 – 0.97 (m, 3H), 0.78 – 0.66 (m, 1H). Consistent with previously reported data[19]. HPLC conditions: Whelk-O, 30 min, 0.5 mL/min, 5% iPrOH/Hexane, 254 nm. Retention times: 9.7 min and 11.3 min; 86% e.e.



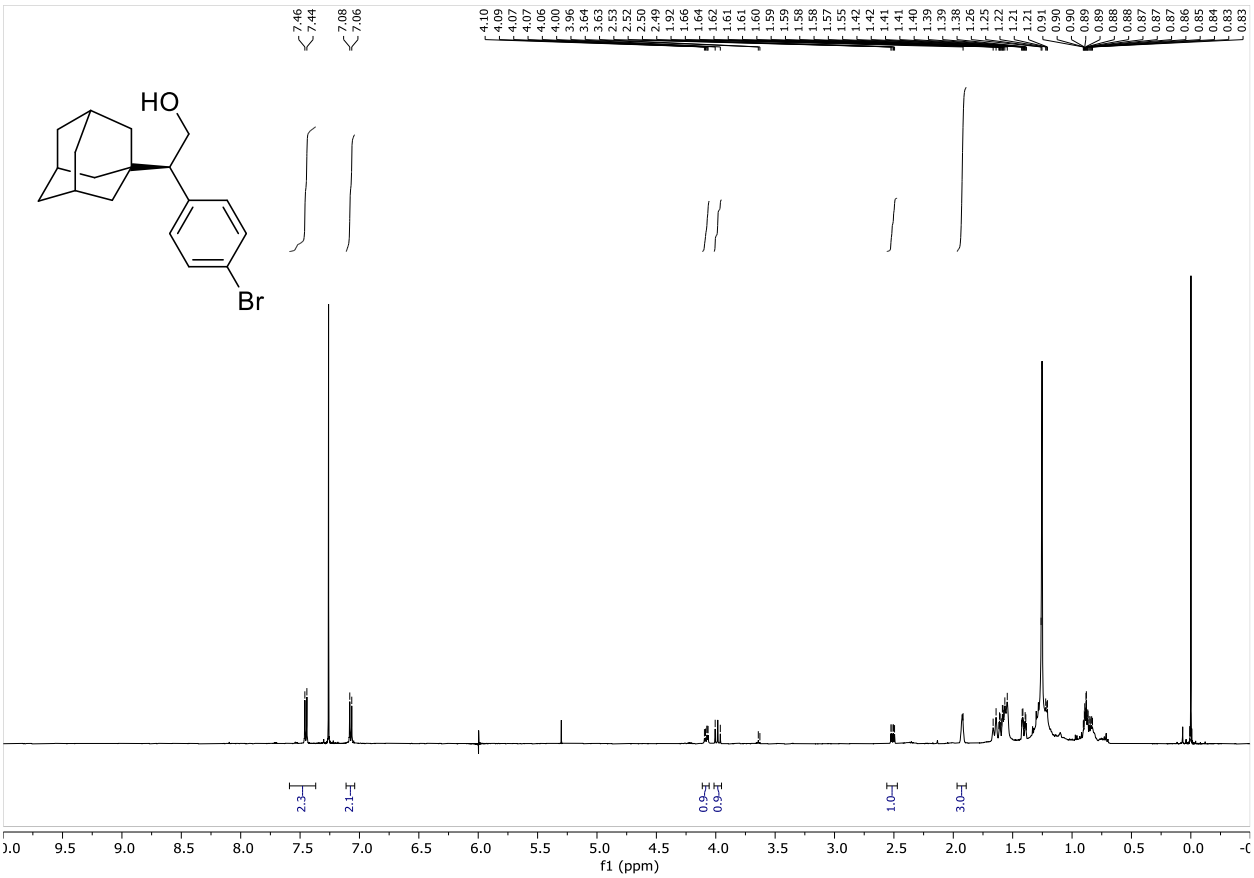
Methyl (R)-2-(4-bromophenyl)-2-cyclohexylacetate (38): The general procedure for C-H functionalization reactions was employed for the functionalization of cyclohexane (10 mL) with methyl 2-(4-bromophenyl)-2-diazoacetate (1.0 mmol, 1 equiv., 268 mg) using methyl (1mol%, 0.01 equiv., 4.9 mg) as catalyst at 10°C. After flash chromatography (SiO_2, 5% Et_2O/Hexane) the title compound (226 mg, 73%) was obtained. ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 3.64 (s, 3H), 3.19 (d, J = 10.6 Hz, 1H), 2.04 – 1.89 (m, 1H), 1.83 – 1.69 (m, 2H), 1.69 – 1.54 (m, 2H), 1.38 – 1.27 (m, 2H), 1.19 – 0.96 (m, 3H), 0.79 – 0.66 (m, 1H).). Consistent with previously reported data[19]. Retention times: 9.7 min and 11.3 min; 68% e.e.



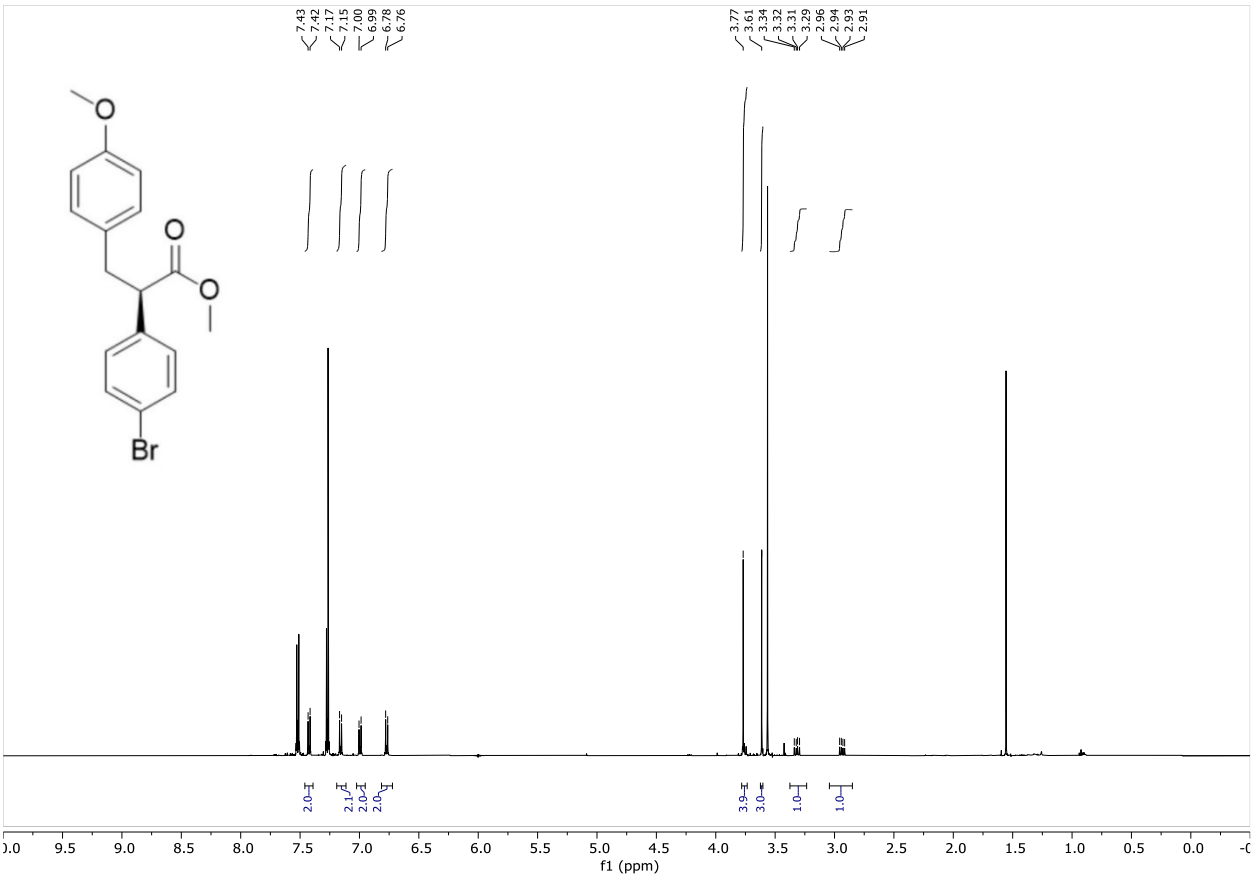
Methyl (R)-2-((3R,5R,7R)-adamantan-1-yl)-2-(4-bromophenyl) acetate (39): The general procedure for C-H functionalization reactions was employed for the functionalization of adamantane (0.75 mmol, 3 equiv., 102 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (0.25 mmol, 1 equiv., 72 mg) using methyl (1mol%, 0.01 equiv., 5.0 mg) as catalyst. After flash chromatography (SiO_2, 5% Et_2O/Hexane) the title compound (35 mg, 39%) was obtained. Compound 39 was reduced with (18 mg, 5 equiv.) of Lithium Aluminum Hydride solution in THF (20 mL) at -78°C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.32 (d, J = 7.6 Hz, 2H), 7.19 (d, J = 7.3 Hz, 3H), 7.01 – 6.94 (m, 3H), 4.11 – 3.99 (m, 2H), 3.71 – 3.70 (m, 2H), 2.54 (dd, J = 10.3, 5.2 Hz, 1H), 1.92 (s, 3H). Consistent with previously reported data[19]. HPLC conditions: Whelk-O, 30 min, 1 mL/min, 6% iPrOH/Hexane, 254nm. Retention times: 12.5 min and 22.1 min; 54% e.e.



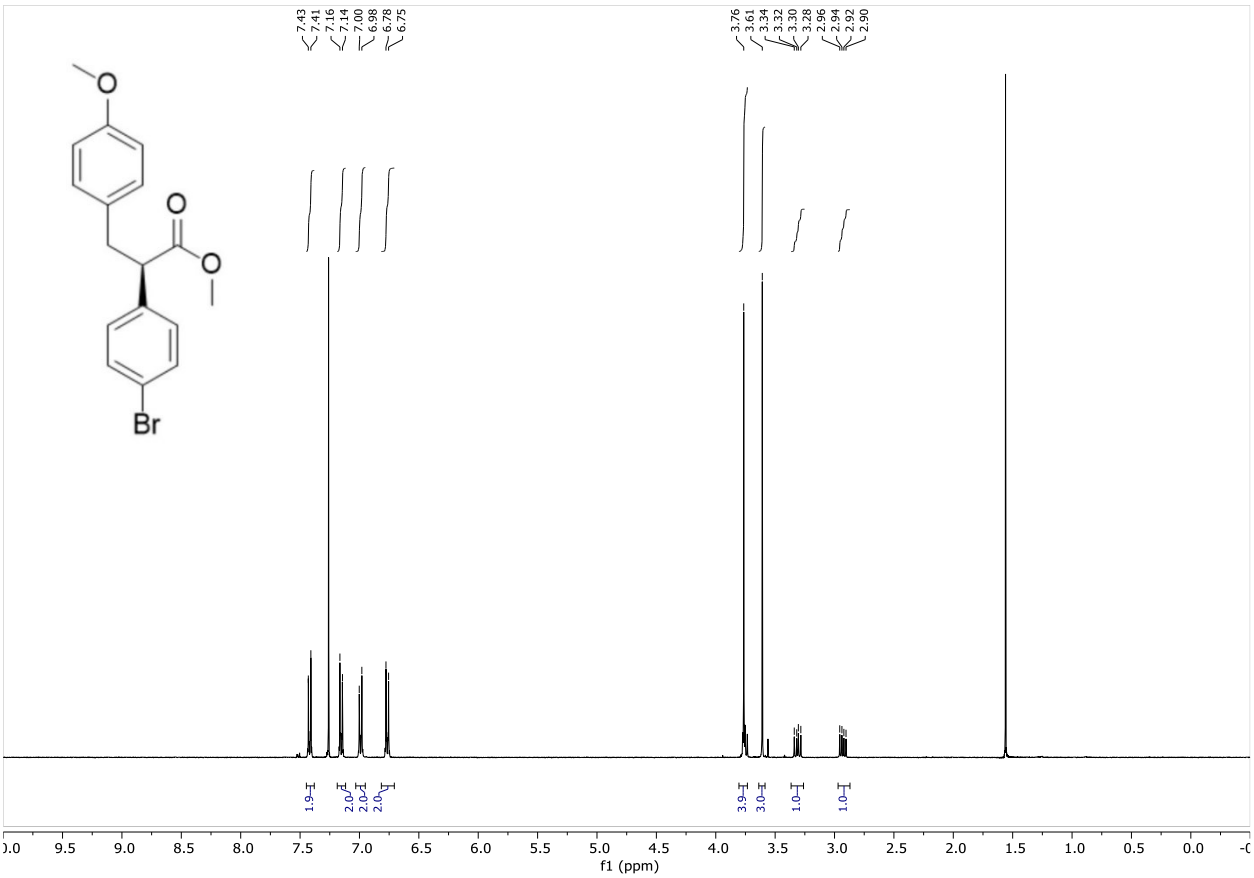
Methyl (R)-2-((3R,5R,7R)-adamantan-1-yl)-2-(4-bromophenyl) acetate (40): The general procedure for C-H functionalization reactions was employed for the functionalization of adamantane (0.75 mmol, 3 equiv., 102 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (0.25 mmol, 1 equiv., 72 mg) using n-dodecyl (1mol%, 0.01 equiv., 8.0 mg) as catalyst. After flash chromatography (SiO_2, 5% Et_2O/Hexane) the title compound (59 mg, 65%) was obtained. Compound 40 was reduced with (31 mg, 5 equiv.) of Lithium Aluminum Hydride solution in THF (20 mL) at -78°C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 4.11 – 4.05 (m, 1H), 4.02 – 3.94 (m, 1H), 2.51 (dd, J = 10.8, 4.5 Hz, 1H), 1.92 (s, 3H). Consistent with previously reported data[19]. HPLC conditions: Whelk-O, 30 min, 1 mL/min, 6% iPrOH/Hexane, 254nm. Retention times: 12.5 min and 22.1 min; 76% e.e.



Methyl (R)-2-(4-bromophenyl)-3-(4-methoxyphenyl) propanoate (41): The general procedure for C-H functionalization reactions was employed for the functionalization of 1-methoxy-4-methylbenzene (0.48 mmol, 1.2 equiv., 58.9 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (0.4 mmol, 1.0 equiv., 102.0 mg) using n-dodecyl (1mol%, 0.01 equiv., 7.9 mg) as catalyst at 36°C in dichloromethane instead of pentane. After flash chromatography (SiO_2, 10% Et_2O/Hexane) the title compound (112 mg, 80%) was obtained. ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 8.5 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 3.77 (s, 4H), 3.61 (s, 3H), 3.32 (dd, J = 13.9, 8.3 Hz, 1H), 2.94 (dd, J = 13.8, 7.2 Hz, 1H). Consistent with previously reported data[20]. HPLC conditions: ADH, 60 min, 0.7 mL/min, 0.5% iPrOH/Hexane, 230nm. Retention times: 47.9 min and 39.6 min; 70% e.e.

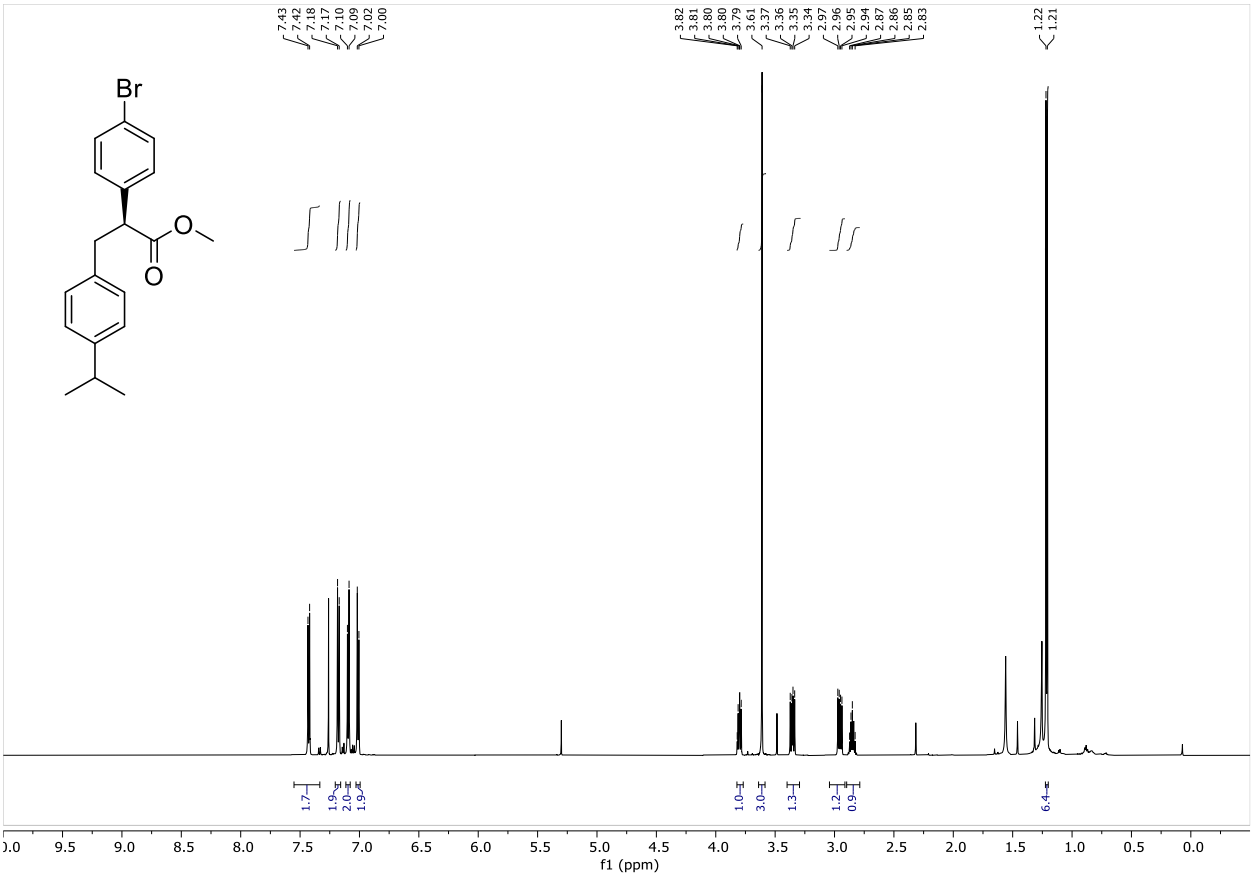


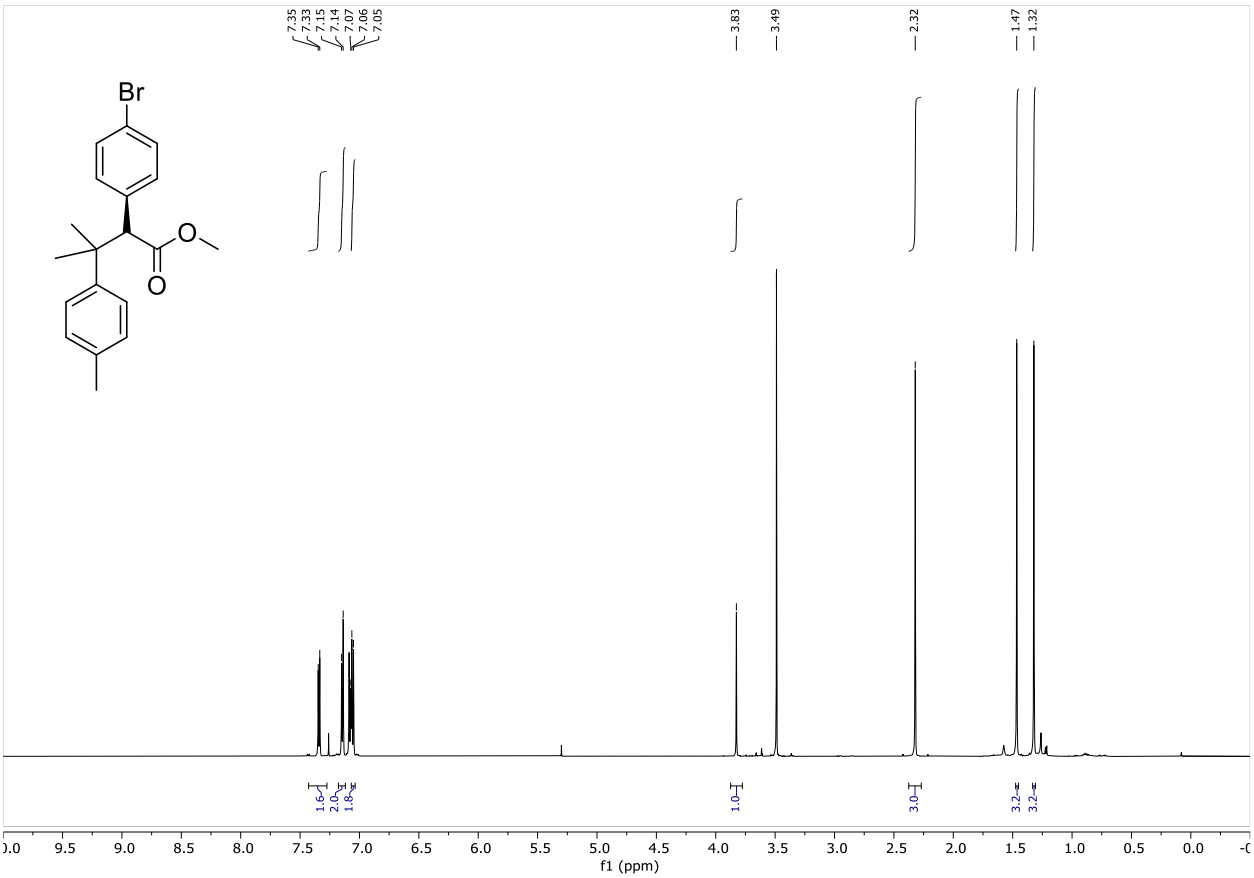
Methyl (R)-2-(4-bromophenyl)-3-(4-methoxyphenyl) propanoate (42): The general procedure for C-H functionalization reactions was employed for the functionalization of 1-methoxy-4-methylbenzene (0.96 mmol, 1.2 equiv., 116 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (0.8 mmol, 1.0 equiv., 204.0 mg) using methyl (1mol%, 0.01 equiv., 4.9 mg) as catalyst at 36°C in dichloromethane instead of pentane. After flash chromatography (SiO_2, 10% Et_2O/Hexane) the title compound (117 mg, 42%) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 3.76 (s, 4H), 3.61 (s, 3H), 3.31 (dd, J = 13.8, 8.3 Hz, 1H), 2.93 (dd, J = 13.8, 7.2 Hz, 1H). Consistent with previously reported data[20]. HPLC conditions: ADH, 60 min, 0.7 mL/min, 0.5% iPrOH/Hexane, 230nm. Retention times: 48.2 min and 36.6 min; 64% e.e.



Methyl (S)-2-(4-bromophenyl)-3-(4-isopropylphenyl) propanoate and Methyl (S)-2-(4-bromophenyl)-3-methyl-3-(p-tolyl)butanoate (43): The general procedure for C-H functionalization reactions was employed for the functionalization of p-cymene (1.2 mmol, 3 equiv., 161 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (0.4 mmol, 1 equiv., 115 mg) using n-dodecyl (1mol%, 0.01 equiv., 5.0 mg) as catalyst. After flash chromatography (SiO_2, 3% Et_2O/Hexane) the title compound (83 mg, 57%) was obtained. Primary insertion: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 7.01 (d, J = 8.2 Hz, 2H), 3.80 (dd, J = 8.5, 6.9 Hz, 1H), 3.61 (s, 3H), 3.35 (dd, J = 13.9, 8.5 Hz, 1H), 2.95 (dd, J = 13.8, 7.0 Hz, 1H), 2.90 – 2.79 (m, 1H), 1.21 (d, J = 6.9 Hz, 6H). Consistent with previously reported data[20]. Tertiary insertion: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, J = 7.8 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 7.06 (t, 3H), 3.83 (s, 1H), 2.32 (s, 3H), 1.47 (s, 3H), 1.32 (s, 3H).

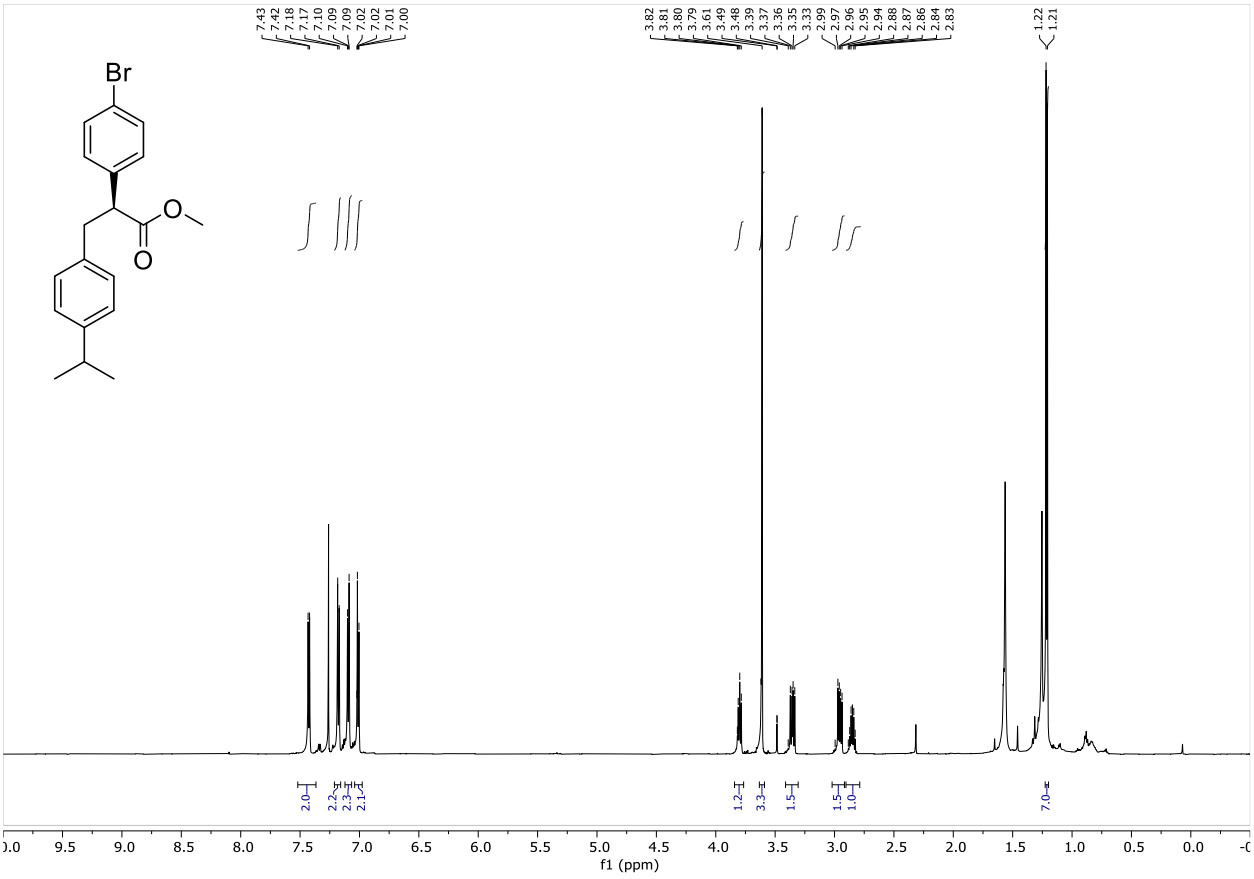
Consistent with previously reported data[20]. Compound 43 was reduced with (23.4 mg, 1 equiv.) of Lithium Aluminum Hydride solution in THF (20 mL) at -78°C. HPLC conditions: AD-H, 1.0 mL/min, 0.5% iPrOH/Hexanes, 254 nm. Retention times for primary insertion: 13.4 min and 15.1 min; 64% e.e. Retention times for tertiary insertion: 21.6 min and 42 min; 19% e.e.

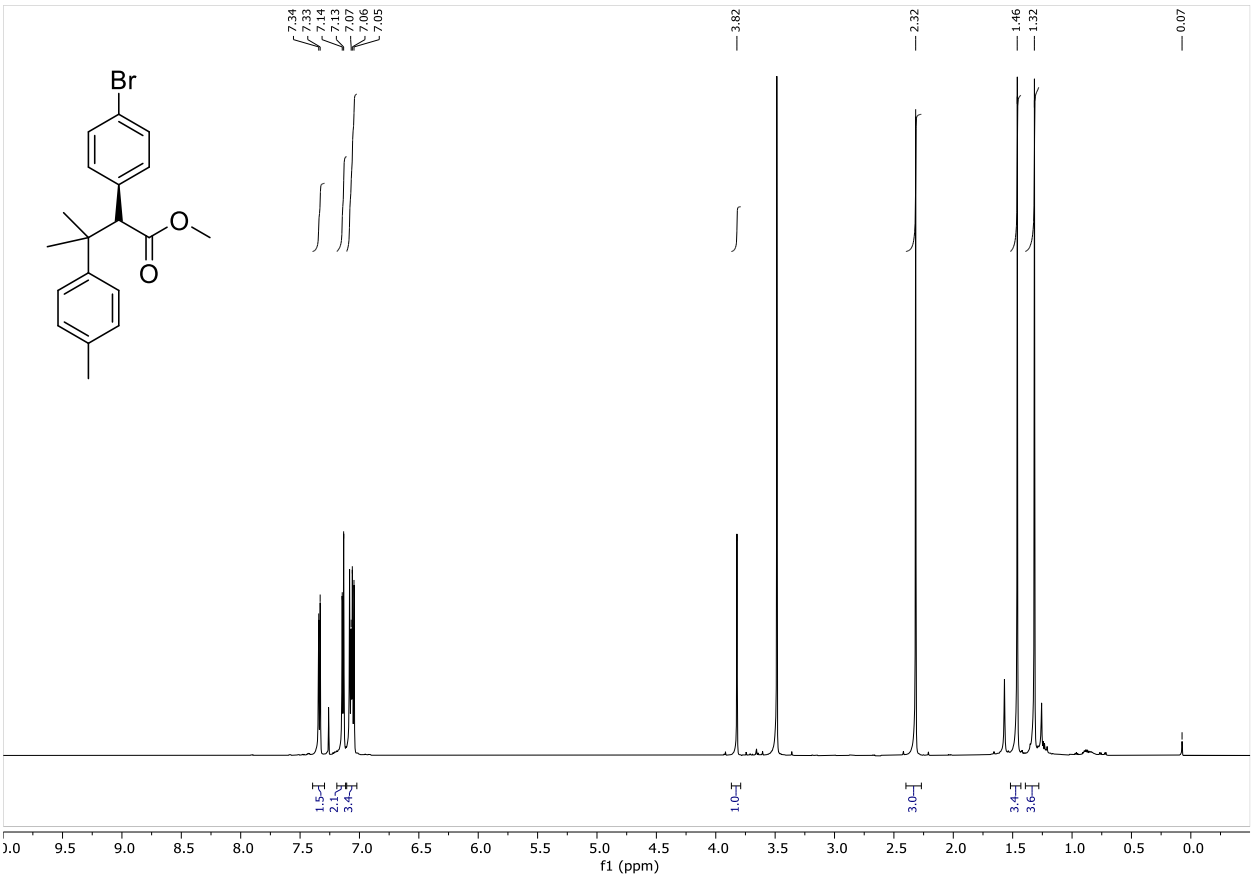




Methyl (S)-2-(4-bromophenyl)-3-(4-isopropylphenyl) propanoate and Methyl (S)-2-(4-bromophenyl)-3-methyl-3-(p-tolyl)butanoate (44): The general procedure for C-H functionalization reactions was employed for the functionalization of p-cymene (1.2 mmol, 3 equiv., 161 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (0.4 mmol, 1 equiv., 115 mg) using methyl (1mol%, 0.01 equiv., 5.0 mg) as catalyst. After flash chromatography (SiO_2, 3% Et_2O/Hexane) the title compound (45 mg, 31%) was obtained. Primary Insertion: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, J = 7.3 Hz, 2H), 7.18 (d, J = 7.4 Hz, 2H), 7.09 (d, J = 7.9 Hz, 2H), 7.01 (d, J = 7.8 Hz, 2H), 3.80 (dd, 1H), 3.61 (s, 3H), 3.35 (dd, J = 13.9, 8.5 Hz, 1H), 2.95 (dd, J = 13.9, 6.9 Hz, 1H), 2.90 – 2.79 (m, 1H), 1.21 (d, J = 6.9 Hz, 6H). Consistent with previously reported data[20]. Tertiary Insertion: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, J = 7.1 Hz, 1H), 7.14 (d, J = 7.0 Hz, 2H), 7.06 (t, 3H), 3.82 (s, 1H), 2.32 (s, 3H), 1.46 (s, 3H), 1.32 (s, 4H). Consistent

with previously reported data[20]. Compound 44 was reduced with (45.1 mg, 1 equiv.) of Lithium Aluminum Hydride solution in THF (20 mL) at -78°C. HPLC conditions: AD-H, 1.0 mL/min, 0.5% iPrOH/Hexanes, 254 nm. Retention times for primary insertion: 13.4 min and 15.1 min; 60% e.e. Retention times for tertiary insertion: 21.6 min and 42 min; 32% e.e.

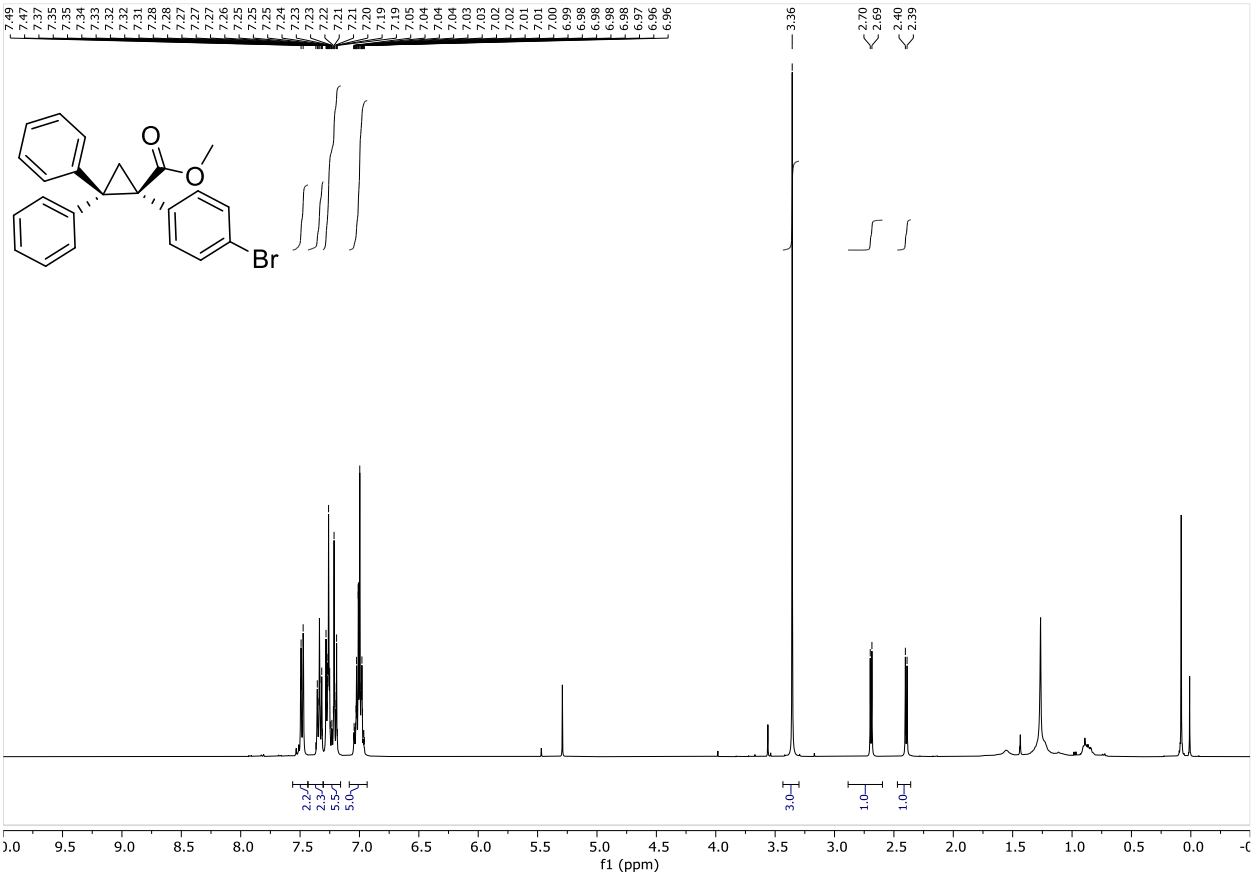




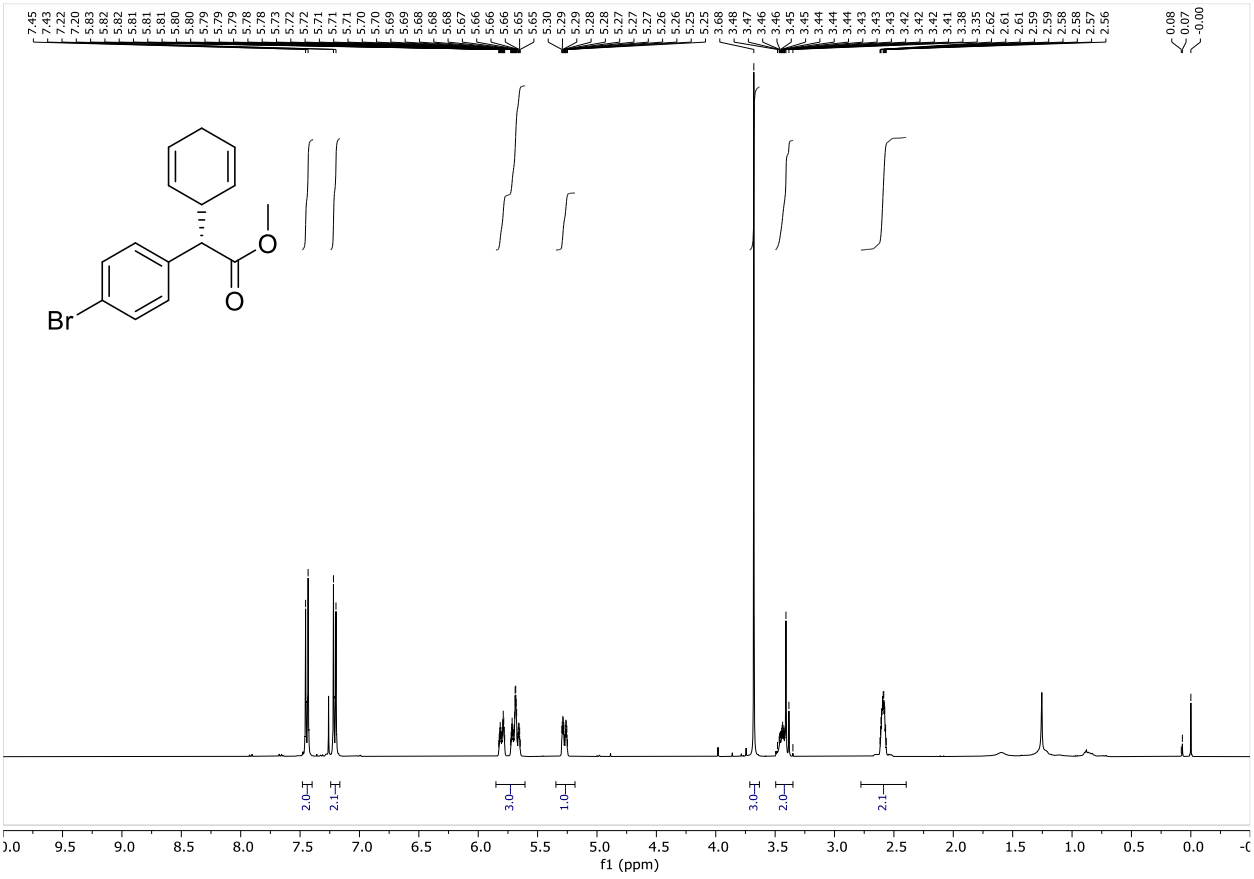
4.7 General Procedure for C-H Functionalization Reactions with R-(DOSP)$_4$

To an oven-dried 25 mL round-bottom flask kept under a dry atmosphere of argon, was added dirhodium tetraprolinate catalyst (1 mol%, 0.01 equiv.) and dry, degassed pentane (2.0 mL) and substrate (0.75 mmol, 3.0 equiv.). A solution of diazo compound (0.25 mmol, 1 equiv.) in dry, degassed pentane (4.0 mL), was then added to the former solution drop-wise over 1.5 h at ambient temperature unless otherwise noted. The mixture was allowed to stir for 1.5h after addition, and then concentrated *in vacuo*. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (Et_2O/Hexane) to afford the pure C-H functionalization product.

Methyl (R)-1-(4-bromophenyl)-2,2-diphenylcyclopropane-1-carboxylate (45): The general procedure for C-H functionalization reactions was employed for the cyclopropanation of 1,1-diphenylethylene (0.75 mmol, 3equiv., 135 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (0.25 mmol, 1 equiv., 72 mg) using R-$(DOSP)_4$ (1mol%, 0.01 equiv., 4.8 mg) as catalyst. After flash chromatography (SiO_2, 3% Et_2O/Hexane) the title compound (62 mg, 61%) was obtained. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.43 (m, 2H), 7.37 – 7.30 (m, 2H), 7.30 – 7.18 (m, 5H), 7.08 – 6.93 (m, 5H), 3.36 (s, 3H), 2.69 (d, J = 5.6 Hz, 1H), 2.40 (d, J = 5.6 Hz, 1H). Consistent with previously reported data[17]. HPLC conditions: RR-Whelk, 1.5% iPrOH/Hexanes, 0.7 mL/min, 30 min, 254 nm. Retention times: 9.6 min and 14 min; 94% e.e.

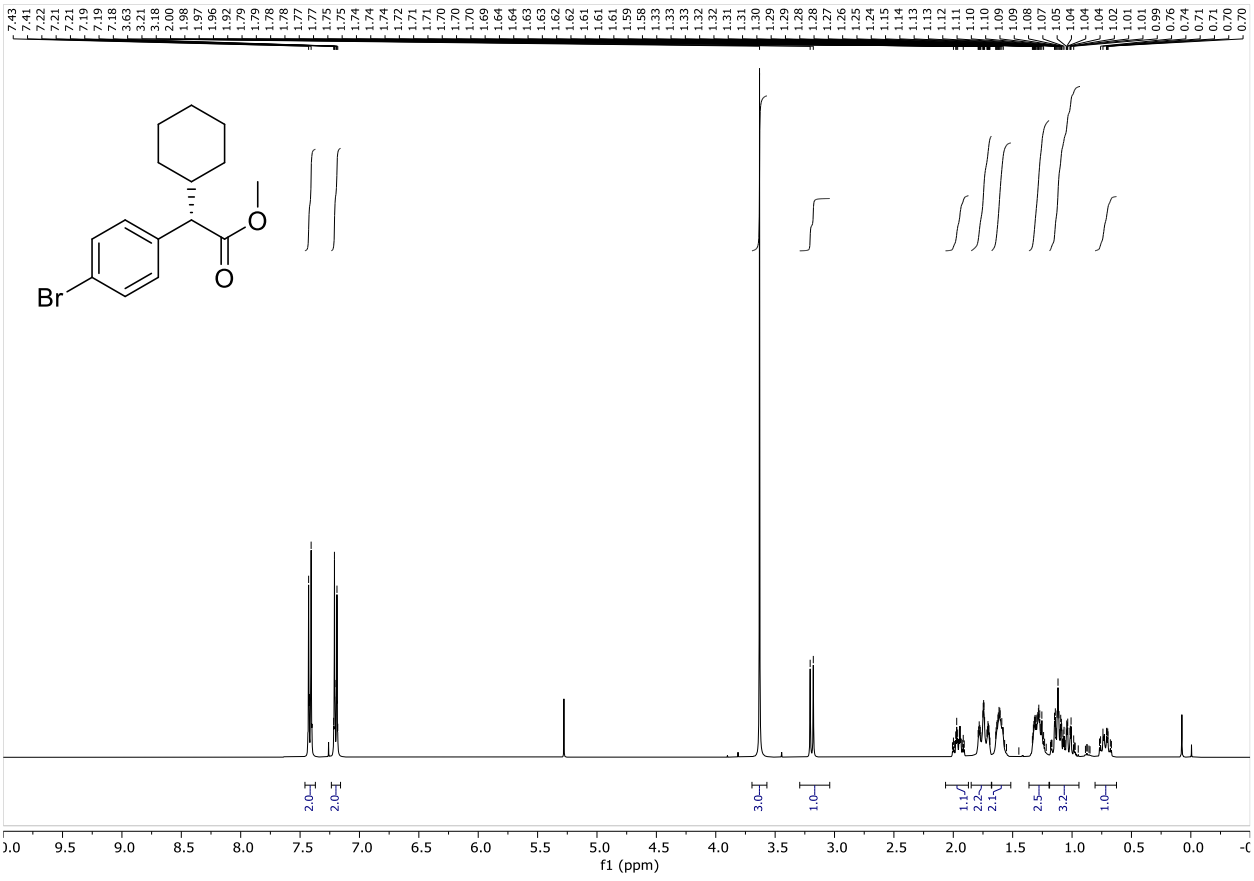


Methyl (R)-2-(4-bromophenyl)-2-(cyclohexa-2,5-dien-1-yl) acetate (46): The general procedure for C-H functionalization reactions was employed for the functionalization of 1,4-cyclohexadiene (0.75 mmol, 3.0 equiv., 60 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (0.25 mmol, 1 equiv., 72 mg) using R-(DOSP)$_4$ (1mol%, 0.01 equiv., 4.9 mg) as catalyst at -50°C. After flash chromatography (SiO_2, 3% Et_2O/Hexane) the title compound (67 mg, 87%) was obtained. ^{1}H NMR (400 MHz, CDCl3) δ 7.44 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 5.85 – 5.61 (m, 3H), 5.35 – 5.19 (m, 1H), 3.68 (s, 3H), 3.50 – 3.35 (m, 2H), 2.64 – 2.54 (m, 2H). Consistent with previously reported data[18]. HPLC conditions: AD-H, 30 min, 1mL/min, 1% iPrOH/Hexanes, 230 nm. Retention times: 6.2 min and 5.8 min; 91% e.e.



Methyl (R)-2-(4-bromophenyl)-2-cyclohexylacetate (47): The general procedure for C-H functionalization reactions was employed for the functionalization of cyclohexane (10 mL) with

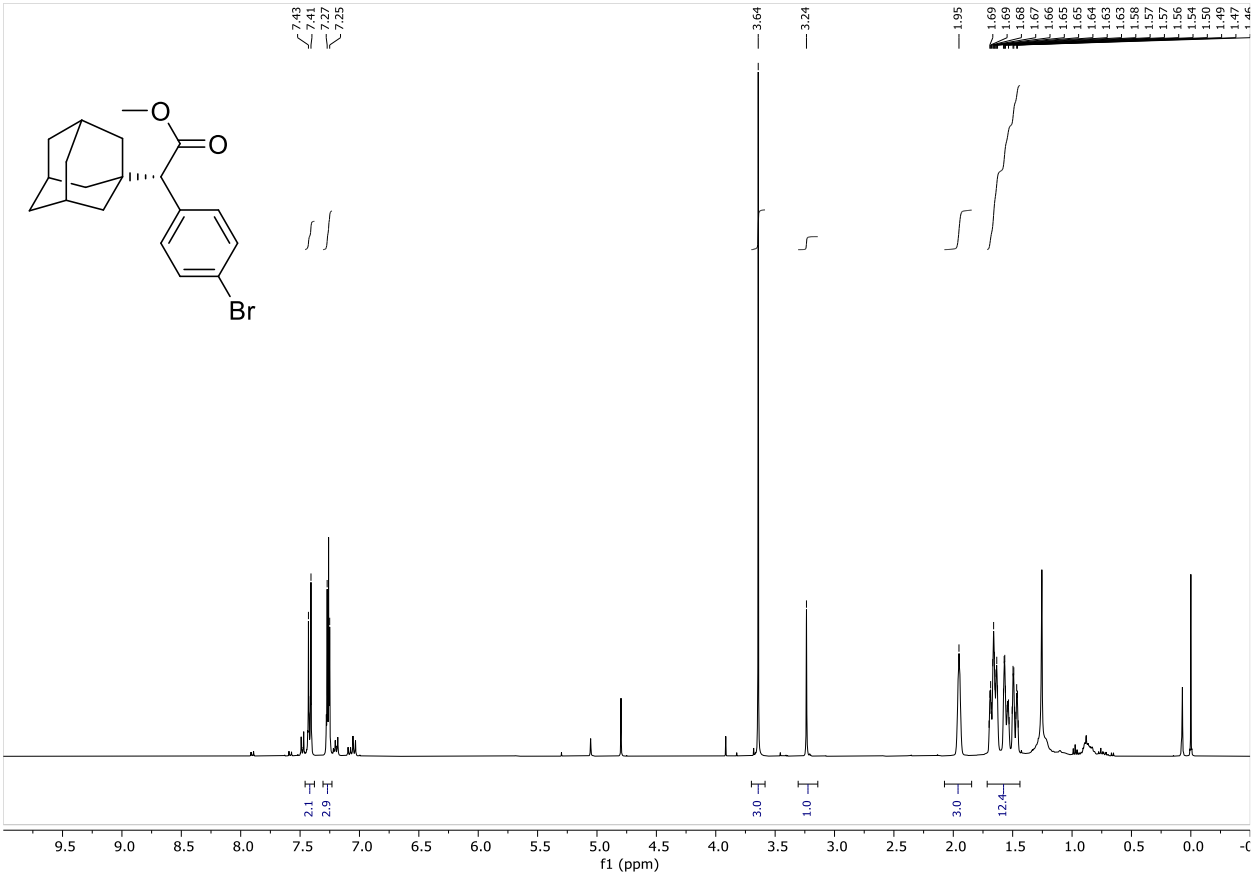
methyl 2-(4-bromophenyl)-2-diazoacetate (1.0 mmol, 1 equiv., 268 mg) using R-$(DOSP)_4$ (1mol%, 0.01 equiv., 19 mg) as catalyst at 10°C. After flash chromatography (SiO_2, 5% Et_2O/Hexane) the title compound (204 mg, 66%) was obtained. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.5 Hz, 2H), 7.24 – 7.16 (m, 2H), 3.63 (s, 3H), 3.19 (d, J = 10.6 Hz, 1H), 2.07 – 1.87 (m, 1H), 1.85 – 1.68 (m, 2H), 1.68 – 1.52 (m, 2H), 1.36 – 1.19 (m, 3H), 1.19 – 0.94 (m, 3H), 0.81 – 0.63 (m, 1H). Consistent with previously reported data[19]. HPLC conditions: RR-Whelk, 30 min, 0.5 mL/min, 5% iPrOH/Hexanes, 254 nm. Retention times: 11.2 min and 9.6 min; 95% e.e.



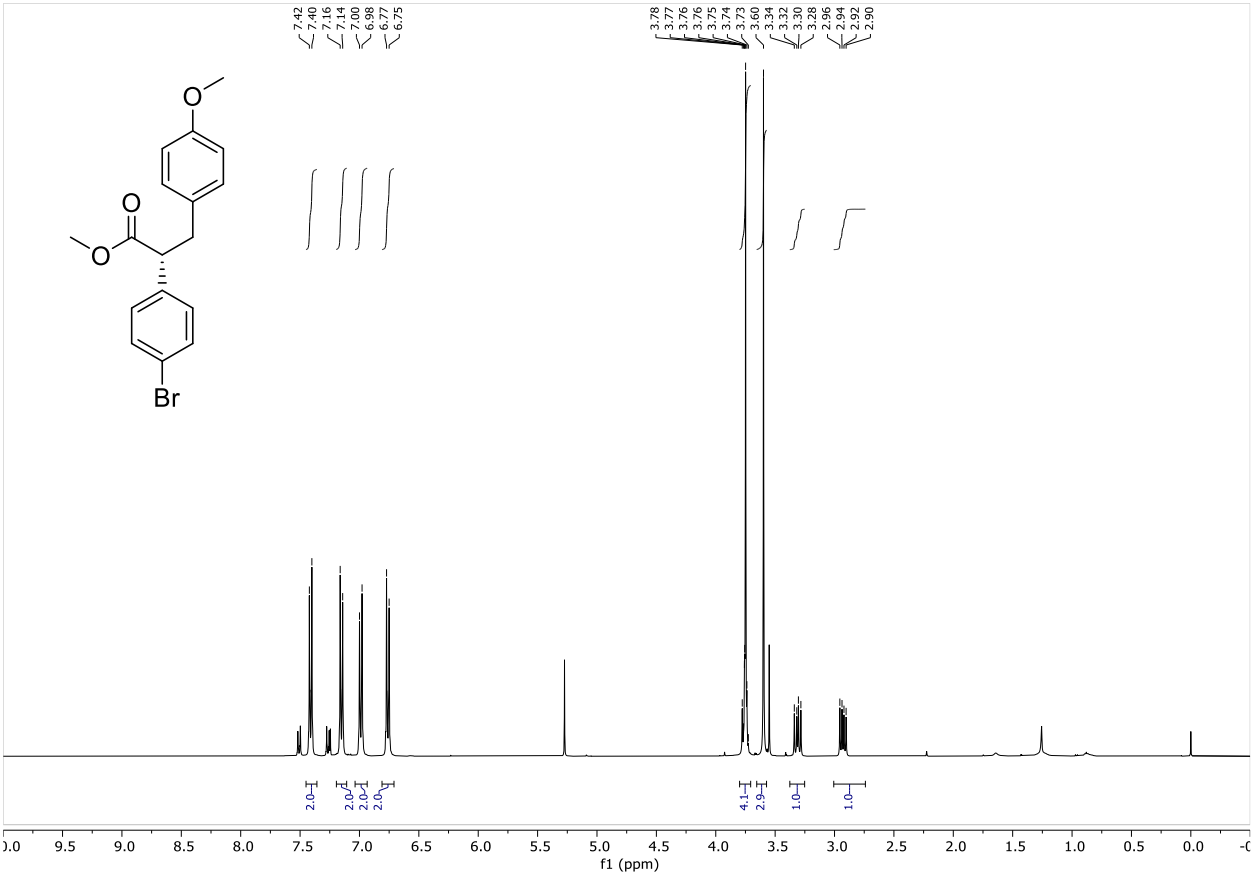
Methyl (R)-2-((3R,5R,7R)-adamantan-1-yl)-2-(4-bromophenyl) acetate (48): The general procedure for C-H functionalization reactions was employed for the functionalization of adamantane (0.75 mmol, 3 equiv., 102 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (0.25

mmol, 1 equiv., 72 mg) using R-$(DOSP)_4$ (1mol%, 0.01 equiv., 4.75 mg) as catalyst. After flash chromatography (SiO_2, 5% Et_2O/Hexane) the title compound (27 mg, 30%) was obtained. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 3.64 (s, 3H), 3.24 (s, 1H), 1.95 (s, 1H), 1.71 – 1.44 (m, 12H). Consistent with previously reported data[19].

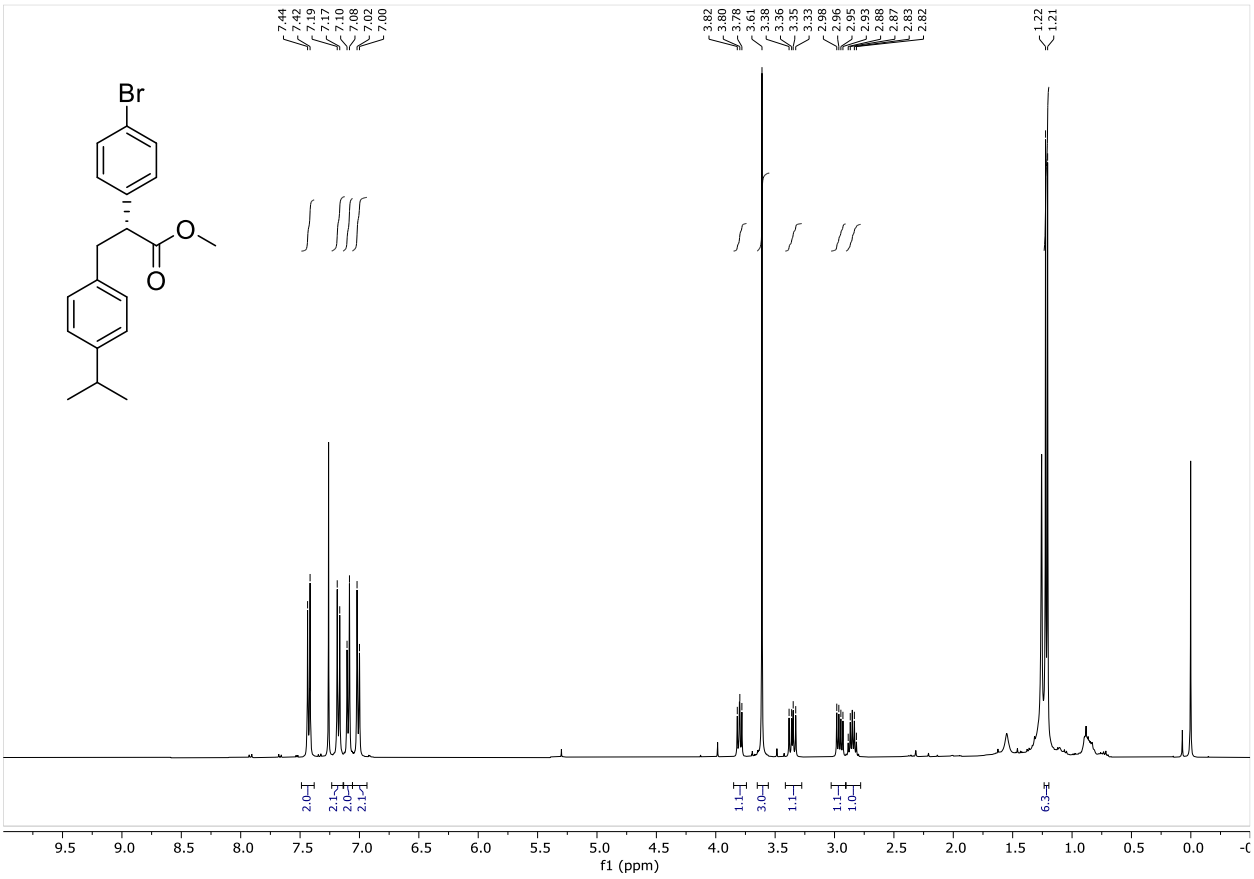
Compound 48 was dissolved in dry THF (10 mL) in 20 mL scintillation vial under argon, and cooled to 0°C using an ice bath. Then LAH (1M in THF, 0.111 mmol, 1.5 equiv., 0.111 mL) was added dropwise via syringe, stirring for 30 min, gradually allowing the solution to come to room temperature. The solution was then quenched with 2 mL water and liquid-liquid extraction was performed. Afterwards, gravity filtration was performed and the filtrate was concentrated *in vacuo* yielding a white solid.



Methyl (R)-2-(4-bromophenyl)-3-(4-methoxyphenyl) propanoate (49): The general procedure for C-H functionalization reactions was employed for the functionalization of 1-methoxy-4-methylbenzene (0.96 mmol, 1.2 equiv., 116 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (0.8 mmol, 1.0 equiv., 230.0 mg) using R-$(DOSP)_4$ (1mol%, 0.01 equiv., 15 mg) as catalyst at 36°C in dichloromethane instead of pentane. After flash chromatography (SiO_2, 3% Et_2O/Hexane) the title compound (201 mg, 72%) was obtained. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 6.76 (d, J = 8.6 Hz, 1H), 3.80 – 3.70 (m, 3H), 3.60 (s, 2H), 3.31 (dd, J = 13.8, 8.3 Hz, 1H), 2.93 (dd, J = 13.8, 7.2 Hz, 1H). Consistent with previously reported data[20]. HPLC conditions: AD-H, 30 min, 0.5% iPrOH/Hexanes, 1.0 mL/min, 254 nm. Retention times: 17.3 min and 19.2 min; 65% e.e.



Methyl (S)-2-(4-bromophenyl)-3-(4-isopropylphenyl) propanoate and Methyl (S)-2-(4-bromophenyl)-3-methyl-3-(p-tolyl)butanoate (50): The general procedure for C-H functionalization reactions was employed for the functionalization of p-cymene (1.2 mmol, 3 equiv., 161 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (0.4 mmol, 1 equiv., 115 mg) using R-$(DOSP)_4$ (1mol%, 0.01 equiv., 7.6 mg) as catalyst. After flash chromatography (SiO_2, 3% Et_2O/Hexane) the title compound (65 mg, 45%) was obtained. Primary insertion: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 7.01 (d, *J* = 8.2 Hz, 2H), 3.80 (t, 1H), 3.61 (s, 3H), 3.35 (dd, *J* = 13.8, 8.5 Hz, 1H), 2.96 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.92 – 2.78 (m, 1H), 1.21 (d, *J* = 7.0 Hz, 6H). Consistent with previously reported data[20]. Tertiary insertion: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.07 (t, *J* = 8.5 Hz, 4H), 3.83 (s, 1H), 2.32 (s, 3H), 1.46 (s, 3H), 1.32 (s, 4H). Consistent with previously reported data[20]. Compound 50 was dissolved in dry DCM (10 mL) in 20 mL scintillation vial under argon, and cooled to 0°C using an ice bath. Then LAH (1M in THF, 0.26 mmol, 1.5 equiv., 0.26 mL) was added dropwise via syringe, stirring for 30 min, gradually allowing the solution to come to room temperature. The solution was then quenched with 2 mL water and liquid-liquid extraction was performed. Afterwards, gravity filtration was performed and the filtrate was concentrated *in vacuo* yielding a white solid.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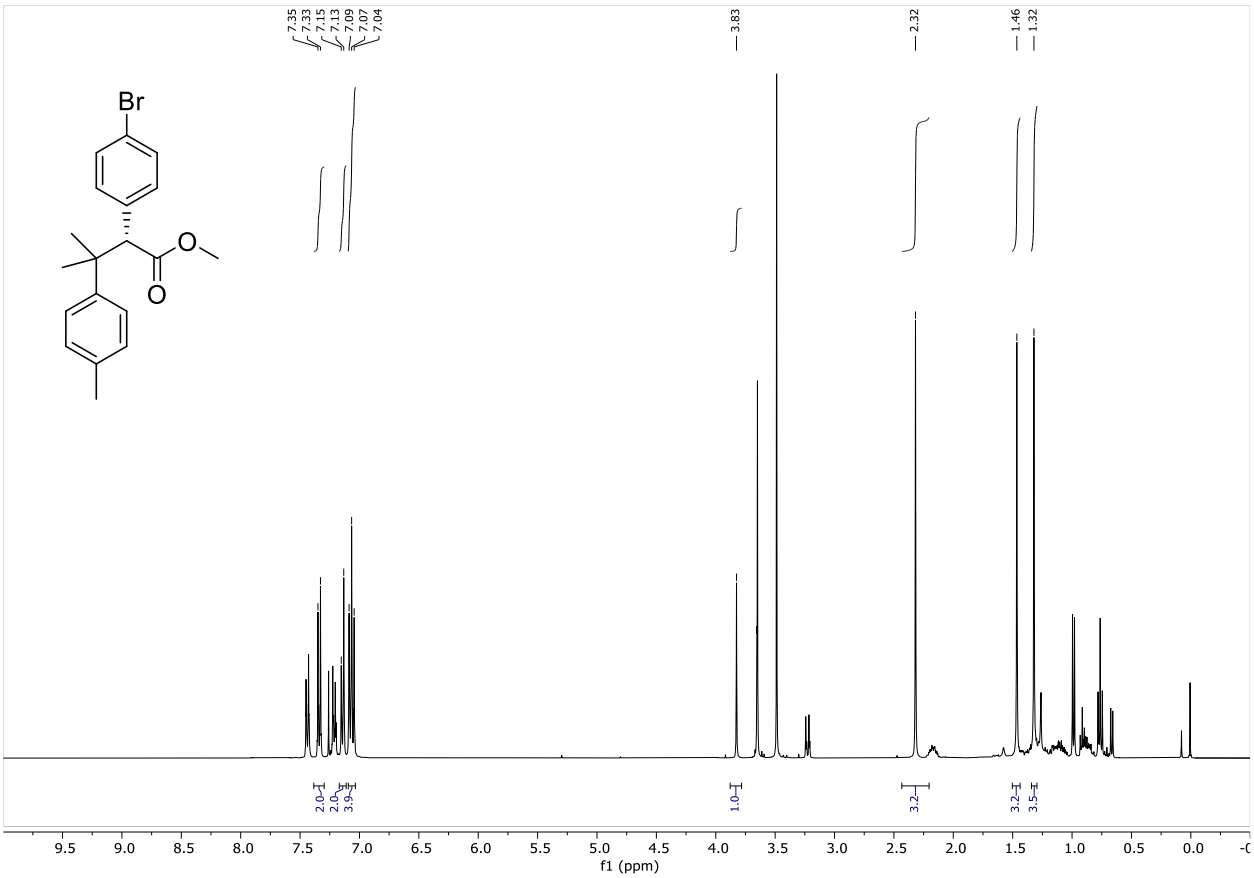
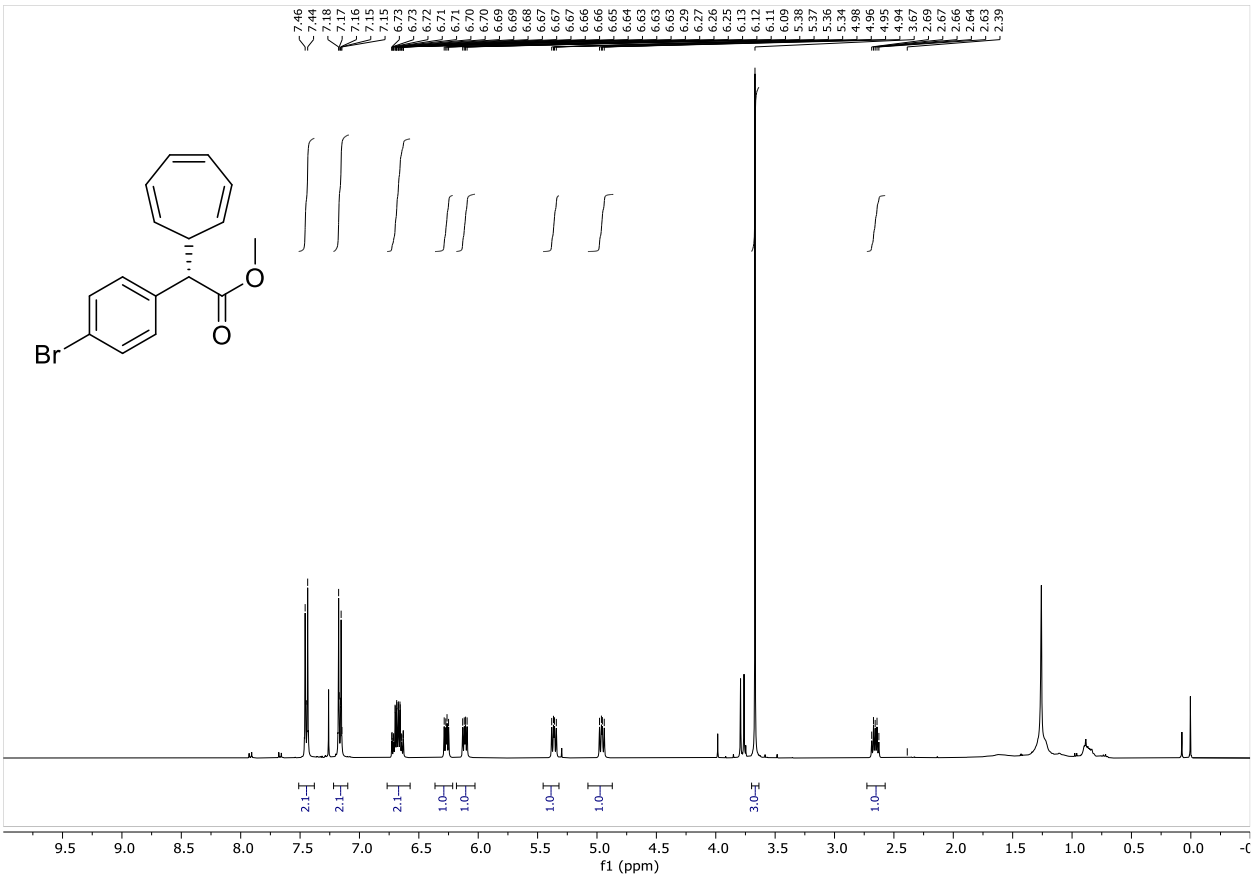
f1 (ppm)



Methyl (R)-2-(4-bromophenyl)-2-(cyclohepta-2,4,6-trien-1-yl) acetate (51): The general procedure for C-H functionalization reactions was employed for the functionalization of 1,3,5-cycloheptatriene (0.75 mmol, 3.0 equiv., 69 mg) with methyl 2-(4-bromophenyl)-2-diazoacetate (0.25 mmol, 1.0 equiv., 72 mg) using R-$(DOSP)_4$ (1mol%, 0.01 equiv., 4.75 mg) as catalyst at -50°C. After flash chromatography (SiO_2, 3% Et_2O/Hexane) the title compound (52 mg, 65%) was obtained. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.5 Hz, 2H), 7.22 – 7.10 (m, 2H), 6.77 – 6.57 (m, 2H), 6.27 (dd, J = 9.4, 5.3 Hz, 1H), 6.11 (dd, J = 9.7, 5.3 Hz, 1H), 5.36 (dd, J = 9.5, 6.0 Hz, 1H), 4.96 (dd, J = 9.6, 6.3 Hz, 1H), 3.67 (s, 3H), 2.66 (dt, J = 12.5, 6.2 Hz, 1H). HPLC conditions: RR-Whelk, 60 min, 1.0 mL/min, 0.3% iPrOH/Hexanes, 230 nm. Retention times: 48 min and 51 min; 98% e.e.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0.0
f1 (ppm)

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