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Jiaye Hu 09-21-2012

Rhodium(II)-Catalyzed Asymmetric Transformations and Their Applications in The Development of Novel CNS Drug Candidates

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An abstract of

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Abstract

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By Jiaye Hu

Synthetic methodologies using rhodium carbenoids derived from aryldiazoacetates holds the promise of synthesizing new molecules, more cleanly and at higher purity and higher stereoselectivity, than alternative substrates and methodologies. Amino alcohols have applications throughout biology and medicine; however, their functionalization often involves lengthily and inefficient synthetic methodologies. In the first part of this study it was demonstrated that amino alcohols could be stereoselectively functionalized using rhodium carbenoids derived from aryldiazoacetates. To characterize this process the effect of the nature of the protecting group was quantified and a model of the mechanism is proposed.

In the subsequent studies, cyclopropanation with rhodium carbenoids was used to synthesize new biologically active molecules for treating Parkinson's disease and neuropathic pain. Twelve analogs of antidepressant molecules, used in the treatment of depression associated with PD, were synthesized. These analogs were tested for VMAT2 activity. While the molecules studied here did not show the desired biological activity, the synthetic methodology has not been completely exhausted and future studies using combinatorial approaches may yield more promising results.

In the final study, molecules that have high potency toward the neurotransmitter transporters, SERT and NET, with a wide range of relative potencies for the two transporters were generated by computational approaches. In total 30 molecules were hypothesized. Out of those, 12 of the most promising candidates were synthesized and tested *in vitro*.

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Chapter 1. Introduction

The development of novel organometallic reagents for the functionalization of unactivated C-H bonds has been extensively studied over the past few decades.[1,2] Due to the high desirability of a practical C-H functionalization methodology, the reaction has been popularly described as the "Holy Grail" for organometallic chemistry.[3] Recently, emerging applications of the rhodium-carbenoid induced intermolecular C-H functionalization strategy in organic synthesis have been reported.[4]

Donor/acceptor-substituted rhodium carbenoids have proved to be efficient in C-H functionalization at a wide range of positions, including primary, secondary, and tertiary C-H bonds.[43, 46, 47] Moreover, rhodium catalyzed C-H functionalization gives outstanding yield and stereoselectivity at benzylic, allylic, α to oxygen and α to nitrogen positions.[53,54]

In this chapter a background introduction of catalytic C-H activation, catalysts for C-H activation, and rhodium-carbenoid induced C-H functionalization reactions that have been developed in the Davies' group will be described. The reactions described in this chapter serve as the foundation for the thesis work of regioselective C-H functionalization of amino alcohols, which is described in Chapter 2.

1.1 Catalytic C-H Activation

Alkanes represent the most cost effective and abundant starting materials for organic synthesis.[5] However, converting C-C and C-H bonds into more sophisticated value-added complex organic building blocks is a difficult task.[6] The bonds to be broken are thermodynamically strong and kinetically inert. Therefore, hydrocarbons are mainly used as fuels, and the energy content of the bonds is dispensed as heat.[7] Consequently, the efficient and selective activation of C-H bonds, the elementary building block of hydrocarbons, constitutes an interesting alternative with potentially a huge economic impact. The rise of Green Chemistry has increased the emphasis on low-waste transformations. By redirecting the site at which a chemical transformation typically occurs from a traditionally reactive C-X (X: heteroatom) bond to a typically less reactive C-H bond, and by developing methods to functionalize the C-H bond after it is cleaved, we can more easily achieve this goal. The same strategy can also reduces reagent toxicity and cost.

Homogeneous catalysis mediated by transition metal complexes is one of the most efficient ways to achieve both high activity and selectivity in C-H activation. The first reported example of "C-H activation" by a transition metal complex is often attributed to Chatt. Ru(0)$(dmpe)_2$ (**1-1**) was generated, leading to activation of a C-H bond of a ligand phosphinomethyl group or of a C-H bond of naphthalene (**1-2**) (Figure 1).[8]

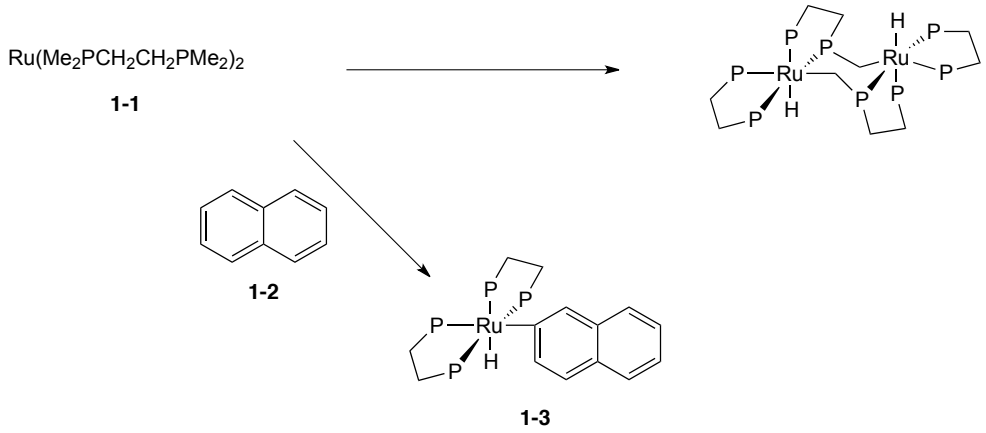


Figure 1 First example of C-H activation

Numerous efforts have been made to achieve high efficiency in organic transformations *via* the metal catalyzed C-H activation process, so much so that it has been studied extensively for the past 30 years.[9] Oxidative addition is the most common mechanism for C-H activation, in which a C-H bond cleaves and an M-C (M: Metal) bond and an M-H bond are formed.[10] It is well accepted that this mechanism starts by coordination of the C-H bond to the metal vacant site (Figure 2). This mechanism is typical for electron-rich, low-valent complexes of the late transition metals (Re, Fe, Ru, Os, Ir, Pt) for which the higher oxidation state of the metal in the product and the necessary change in geometry upon formation of the two new bonds are not energetically penalizing.

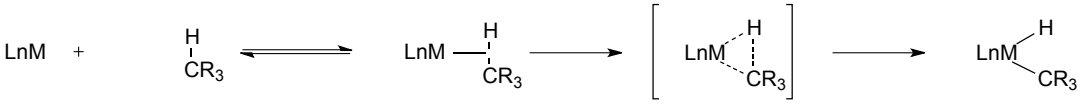


Figure 2 Oxidative addition

Despite seemingly large differences among the various mechanisms of C-H activation, there are only three different fundamental types. The first one is a processes where an

organometallic, i.e. M-C σ-bond is formed as an intermediate or final product. This involves oxidative addition of the C-H bond to low-valent metal center or an electrophilic substitution.[11] This process is usually promoted by a transition metal whose most stable oxidation state differs by two electrons. The second type involves no direct contact between the metal and the C-H bond, (i.e. metal complex cleaves a C-H bond but no **σ**-C-M bond is directly generated at any stage). The metal complex abstracts an electron or a hydrogen atom to form radical ions RH• or R•, which interact with other species such as oxygen.[7] The third type of C-H bond cleavage usually happens when a metal complex promotes the formation of a reactive species which then attacks the C-H bond. The metal complex activates some other reactants (e.g. O_2 or H_2O_2) to form a reactive species usually a radical, such as hydroxyl radical which then attacks the hydrocarbon independent of any participation of the metal complex (e.g. oxidation of alkanes by Fenton's reagent).[12]

Among all the transition metals that are capable of catalyzing C-H activation reactions, palladium and copper are the most studied metals.[13] It is well known that palladium and copper are able to facilitate highly selective C-H bond arylation; C-H bond amination and C-H bond oxidation reactions.[14] Unlike the majority of other transition metal catalysts that are extremely sensitive towards air and moisture, most rhodium catalysts can be handled safely in the air without extra precautions; however, early examples of rhodium catalyzed reactions demonstrated little synthetic application of this reaction due to the lack of selectivity.[15]

1.2 Carbenes and Carbenoids

Carbenes are neutral molecules in which one of the carbon atoms has six valence electrons. Such carbons are divalent; they are directly bonded to only two other atoms and have no multiple bonds. Beginning from Curtius,[16] and Staudinger,[17] carbenes have played an important role as transient intermediates over the last six decades.[18] Introduced by Doering[19] into organic chemistry in the 1950s and by Fischer[20] into organometallic chemistry in 1964, these fascinating species are involved in many exciting reactions of high synthetic utility.

Depending upon their electronic structure, carbenes have two possible electronic structures: triplet and singlet (Figure 3). Triplet carbenes often have radical-like characteristics and are usually more stable. Singlet carbenes resemble carbocations and carbanions that are united on the same carbon, and have either electrophilic or nucleophilic characteristics depending on their electronic environment.[21]

Triplet (two unpaired electrons) **Singlet** (no unpaired electrons)

Figure 3 Triplet and Singlet Carbenes

Due to electron repulsion, there is energy consumption in pairing both electrons in the σ orbital. If a small energy difference between the σ and p orbitals exists, the electrons will remain unpaired (triplet). If a large gap exists between the σ and p orbitals, the electrons will pair in the σ orbital (singlet) (Figure 4). It has been concluded that the best way to stabilize triplet carbenes kinetically is to protect the highly reactive carbene center with bulky substituents, and it has also been found that it is easier to design a substitution pattern to stabilize singlet than triplet carbenes.[19] Back in 1980, Pauling realized that the ideal substituents to stabilize singlet carbenes are ones that retain the neutrality of the carbene center as much as possible.[22]

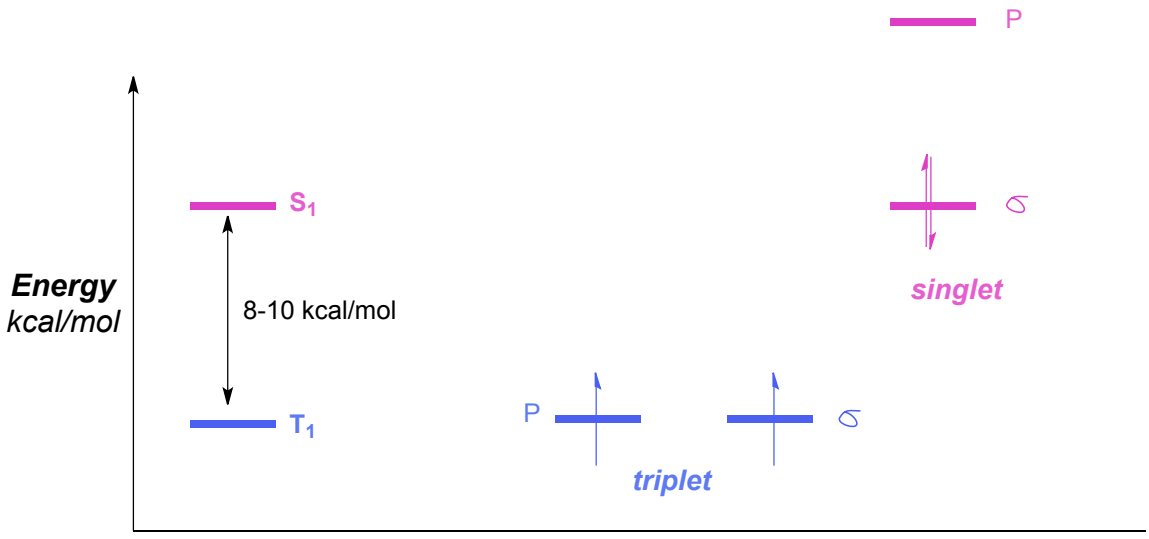


Figure 4 Energy Difference: Triplet *vs* Singlet

Like carbenes, carbenoids are a class of reactive intermediate that can undergo a wide variety of synthetically useful transformations depending on the reaction conditions. Although a vague term, carbenoid is usually used to describe a molecule in which all carbons are tetravalent but still has properties resembling those of a carbene. Carbenoid is structurally related to singlet carbenes and display similar reactivity.[23] The intrinsic reactivity of metal carbenoids is modulated by the transition metal, ligands on the transition metal, and substituents on the carbenoid carbon center.[24] The effects of transition metal and ligands on the metal have been studied extensively, whereas the substituent effect of carbenoid reactivity did not receive substantial research attention until the past decade.[25] Since the substitution pattern has proved to be crucial in controlling carbenoid reactivity, carbenoids have been classified into three types depending upon the substituents on the carbenoid center (Figure 5).[26]

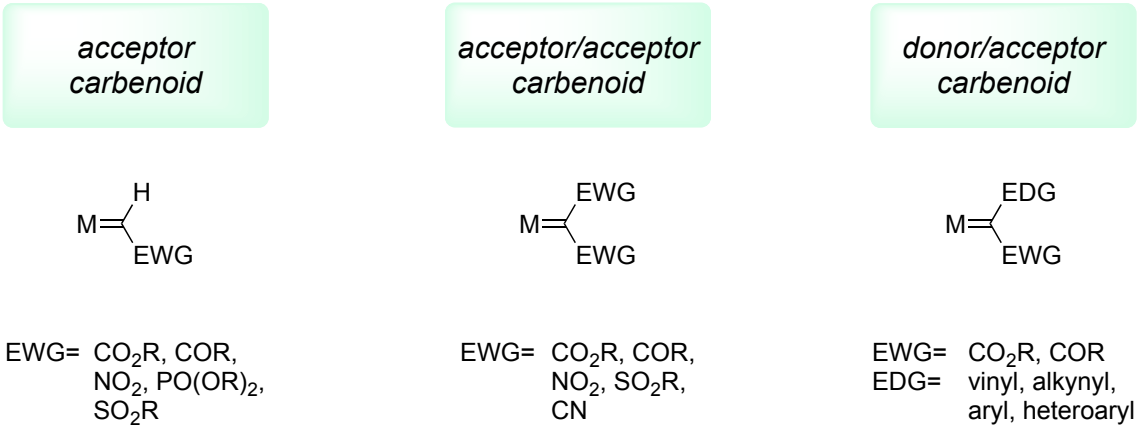


Figure 5 Three Types of Carbenoids

Acceptor carbenoids have one electron-withdrawing group attached to the carbon center; Acceptor/acceptor carbenoids have two electron-withdrawing groups attached to the same carbenoid carbon; Donor/acceptor carbenoids contain an electron-donating group as well as an electron-withdrawing group. The acceptor and acceptor/acceptor carbenoids

have been used in metal carbenoid reactions since early 1950s;[19(a)] whereas the donor/acceptor system did not prove its high synthetic value until the last 20 years when it displayed superior selectivity in intermolecular C-H activation due to the stability conferred by the donor substituent.[27]

1.3 Catalysts for Carbenoid Transformations

Metal catalysis in the decomposition of diazo compounds has been known for more than a century. In 1973 Solomon and Kochi published a benchmark article that has had a great impact on the basic understanding of copper catalysis in carbenoid transformations.[28] It was discovered that copper triflate was a very active catalyst for the cyclopropanation of olefins with diazo compounds. What is more interesting is that they found diazo compounds caused reduction of copper(II) to copper(I). This discovery was consistent with a prior observation by Wittig that copper(II) chloride was reduced to copper(I) chloride by diazo compounds, which supported their conclusion that copper(I), rather than copper(II), was the active catalyst in carbenoid transformations. However, since copper(I) triflate is relatively difficult to handle, copper(II) triflate, conveniently prepared and reduced *in situ* by diazo compounds to the copper(I) catalyst, is preferentially employed for carbenoid transformations of diazo compounds.

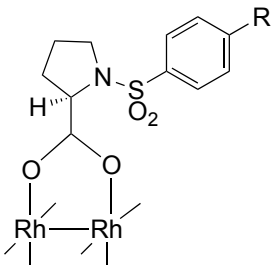
During that time, a number of transition metal compounds were investigated for their effectiveness as catalysts for diazo decomposition, but none showed synthetic potential until the discovery of catalytic activity of rhodium(II) acetate in reactions with diazo compound.[29] After the first discovery of catalytic activity of rhodium(II) acetate, dirhodium(II) complexes have emerged as one of the most robust chiral catalysts for C-H insertion via carbenoid intermediates.[30] Doyle and coworkers developed Rh_2(*S*-MEPY)$_4$ (**1-4**), the first chiral dirhodium(II) carboxamidates catalyst of this type that yielded reasonable enantioselectivity, which then became a model for developing other derivatives.[31] Substitution of the acetate ligands of rhodium acetate with chiral amino

acids or chiral carboxylic acids gave rise to the development of other chiral dirhodium carboxylates. The development of proline-derived dirhodium(II) complexes was sparked by the initial report by McKervey and coworkers (**1-5**) (Figure 6).[32]

1-4, Rh_2(*S*-MEPY)$_4$ **1-5**, McKervey's Catalyst

Figure 6 Rh_2(*S*-MEPY)$_4$ and McKervey's Catalyst

Further development of dirhodium(II) prolinates by Davies and coworkers into more soluble complex, dirhodium(II) tetrakis(*S*)-(N-*p*-*tert*-butylphenyl)sulfonylprolinate, Rh_2(*S*-TBSP)$_4$ (**1-6**) and dirhodium(II) tetrakis(*S*)-(N-*p*-dodecylphenyl)sulfonylprolinate, Rh_2(*S*-DOSP)$_4$ (**1-7**) (Figure 7) led to the discovery that these are excellent catalysts for asymmetric transformations of donor/acceptor carbenoids in nonpolar solvents.[33] Through optimization of the reaction, it was found that these two catalysts gave nearly identical results; however, Rh_2(*S*-DOSP)$_4$ (**1-7**) is completely soluble in hydrocarbon solvents at temperature even as low as -78 °C.



R= ^{t}Bu, **1-6, Rh_2(*S*-TBSP)$_4$**
R= $C_{12}H_{25}$, **1-7, Rh_2(*S*-DOSP)$_4$**

Figure 7 Rh_2(*S*-TBSP)$_4$ and Rh_2(*S*-DOSP)$_4$

Rh_2(*S*-DOSP)$_4$ (**1-7**) has proven to be extremely versatile and is effective with a wide array of substrates.[34,35] Computational studies of Rh_2(*S*-DOSP)$_4$ (**1-7**) in carbenoid C-H activation reactions revealed a predictive model to explain its high stereoselectivity, and a molecular model was proposed for the structure and conformation of Rh_2(*S*-DOSP)$_4$ (**1-7**).[36] The dirhodium(II) paddlewheel carboxylate core is represented in green as a flat disc-like plane (Figure 8).

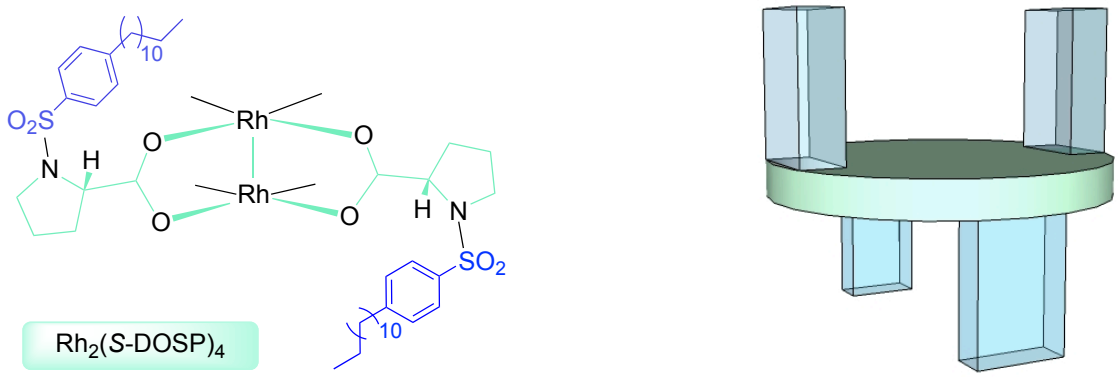
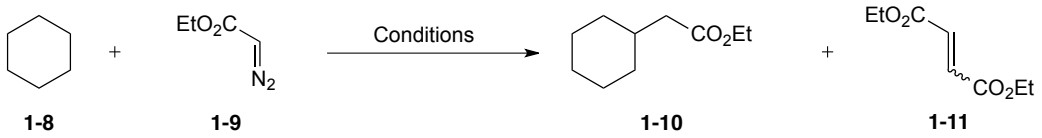


Figure 8 3D Structure of Rh_2(*S*-DOSP)$_4$

The catalyst is thought to adopt a D_2-symmetric conformation, with the dipoles of the polar sulfonyl groups of the nitrogen protecting groups (represented in blue), adopting an up–down–up–down arrangement to minimize the net dipole. Since the ligands in Rh_2(*S*-DOSP)$_4$ (**1-7**) are derived from proline, both enantiomers of the catalyst are readily available. The easy access to the catalyst, stability on the bench, and excellent solubility in hydrocarbon solvents makes Rh_2(*S*-DOSP)$_4$ the prototypical catalyst for donor/acceptor carbenoid C-H activation reactions.

1.4 Catalytic C-H Activation by Traditional Alkyldiazoacetate Derived Metal Carbenoids

Before donor/acceptor carbenoids came into play in the C-H activation reactions, the most studied carbenoids were derived from α-diazoacetates.[37] Early work by Scott and coworkers successfully demonstrated an intermolecular C-H insertion of an ethyl diazoacetates (EDA, **1-9**) derived copper carbenoid into cyclohexane (**1-8**) (Scheme 1). [38]



	Conditions	Yield %	Yield %
Scott's work	$CuSO_4$, rt	24	40
Noels' work	$Rh_2(TFA)_4$, reflux	90	-
Callott's work	Rh(porphyrin), reflux	71	-

Scheme 1 Intermolecular C-H Insertion

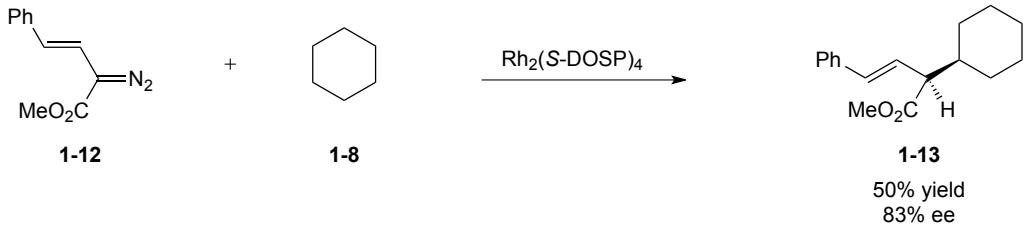
Among various screening reaction conditions, copper sulfate at room temperature gave 24% yield of C-H insertion product (**1-10**) and 40% yield of dimers (**1-11**). The product selectivity was optimized by Noels and coworkers when dirhodium(II) tetra(trifluoroacetate), $Rh_2(TFA)_4$ was used in the reaction under reflux condition.[39] In the presence of $Rh_2(TFA)_4$ under reflux condition, the reaction of cyclohexane (**1-8**) and EDA (**1-9**) resulted in exclusive formation of **1-10**. Callott and coworkers reported the reaction with rhodium porphyrins, which gave an improved yield of 71% of the C-H insertion product **1-10**.[40] Although during that time, the carbenoid intermolecular C-H activation reactions were not considered one of the most powerful synthetic tools for constructing molecules, it laid foundations for the later explosive research interest in the field of intermolecular carbenoid C-H activation reactions. Since the first report of

intermolecular C-H activation, there have been numerous attempts to develop a selective intermolecular C-H activation; however, asymmetric intermolecular C-H activation using the acceptor-substituted carbenoids has resulted in little success.[41]

Acceptor/acceptor substituted carbenoids are relatively less reactive than acceptor carbenoids; therefore, an increase of selectivity in intermolecular C-H activation is expected from this class of carbenoids.[42] Unfortunately, acceptor/acceptor carbenoids still face the challenge of undergoing selective C-H insertion reactions rather than cyclopropanation, dimerization or other possible side reactions.[43] The vast majority of synthetically useful C–H functionalizations with these types of metal carbenes, therefore, have been intramolecular versions.[44]

1.5 Catalytic C-H Activation by Donor/Acceptor Substituted Rhodium Carbenoids

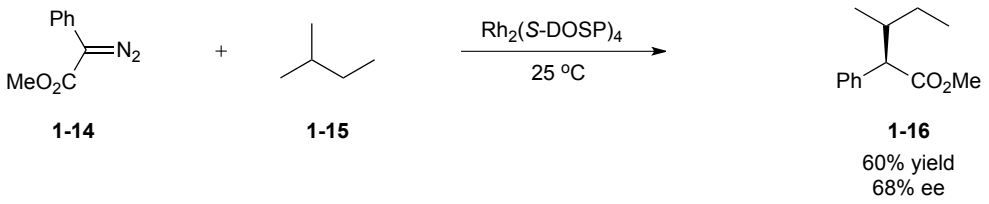
The reactivity of metal carbenoids is modulated by the substituents on the carbene center. The donor/acceptor metal carbenoids are capable of highly selective intermolecular C–H functionalization, especially when rhodium catalysts are employed.[45] In 1997, the Davies group reported the first donor/acceptor carbenoid intermolecular C-H activation using Rh_2(*S*-DOSP)$_4$ as the catalyst (Scheme 2).[46] The C-H insertion reaction between (*E*)-methyl 2-diazo-4-phenylbut-3-enoate (**1-12**) and cyclohexane (**1-8**) gave rise to **1-13** with 50% yield and 83% ee. The reaction demonstrated considerable utility for the asymmetric intermolecular C-H activation and proved to be more promising than any other method available at the time. These studies reconfirmed that the Rh_2(*S*-DOSP)$_4$ with donor/acceptor-substituted carbenoid is an excellent combination for enantioselective carbenoid transformations.



Scheme 2 Intermolecular C-H Insertion of Donor/Acceptor Carbenoid

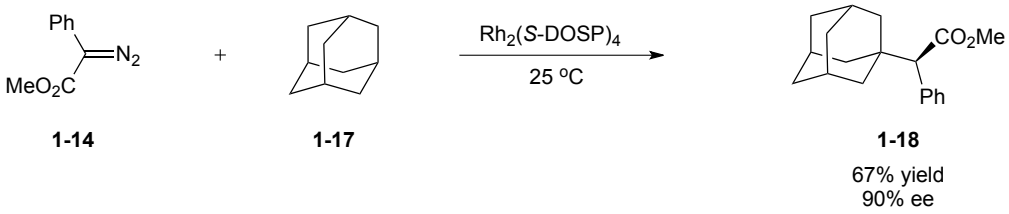
This reaction is applicable not only to vinyldiazoacetates, but also, to a wide range of aryldiazoacetates. Three years after the first report, Davies and coworkers reported an asymmetric C-H activation of alkanes using the chiral dirhodium(II) catalyst and donor/acceptor carbenoid combination.[47] In contrast to earlier studies with EDA (**1-9**), the reaction of phenyldiazoacetate (**1-14**) with 2-methylbutane (**1-15**) resulted in the

highly selective formation of the tertiary C-H insertion product (**1-16**) with respectable yield and enantioselectivity (Scheme 3).



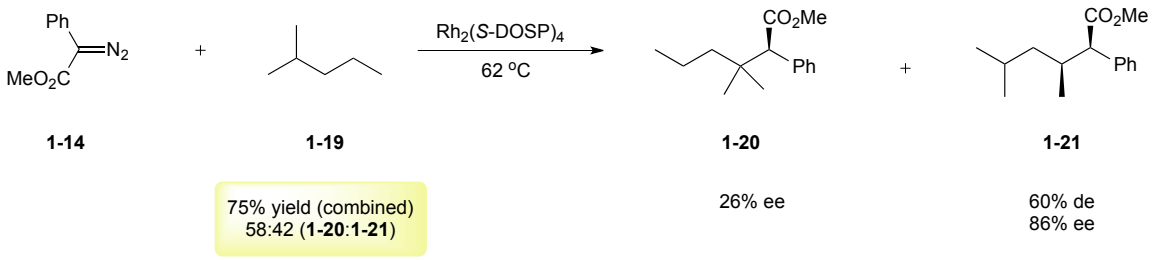
Scheme 3 Tertiary C-H Insertion

A highly regioselective reaction was also obtained in the reaction with adamantine (**1-17**).[43] Decomposition of phenyldiazoacetate (**1-14**) by Rh_2(*S*-DOSP)$_4$ at room temperature gave rise to the tertiary C-H insertion product (**1-18**) with excellent enantioselectivity (Scheme 4).



Scheme 4 Insertion with Adamantane

When the reaction was carried out with 2-methylpentane (**1-19**), two products (**1-20** and **1-21**) were obtained which were the result of insertion into a tertiary C-H bond and a secondary C-H bond (Scheme 5).



Scheme 5 Insertion with 2-Methylpentane

This reaction demonstrated the delicate balance that exists for the regioselectivity in the intermolecular C-H activation reactions. Of the five different sites for C-H insertion in 2-methylpentane (**1-19**), only the methine and one of the methylene sites are functionalized. The almost equal distribution of both products is presumably the end result of competing electronic and steric effects. The methine site is electronically favored; however, it is sterically demanding. The methylene site is more accessible to carbenoid C-H insertion but electronically not favored. Therefore, a mixture of two products was formed in this system.

To further understand the delicate balance between electronic and steric factors, a series of competition experiments between phenyldiazoacetate (**1-14**) and various substrates were examined (Figure 9).

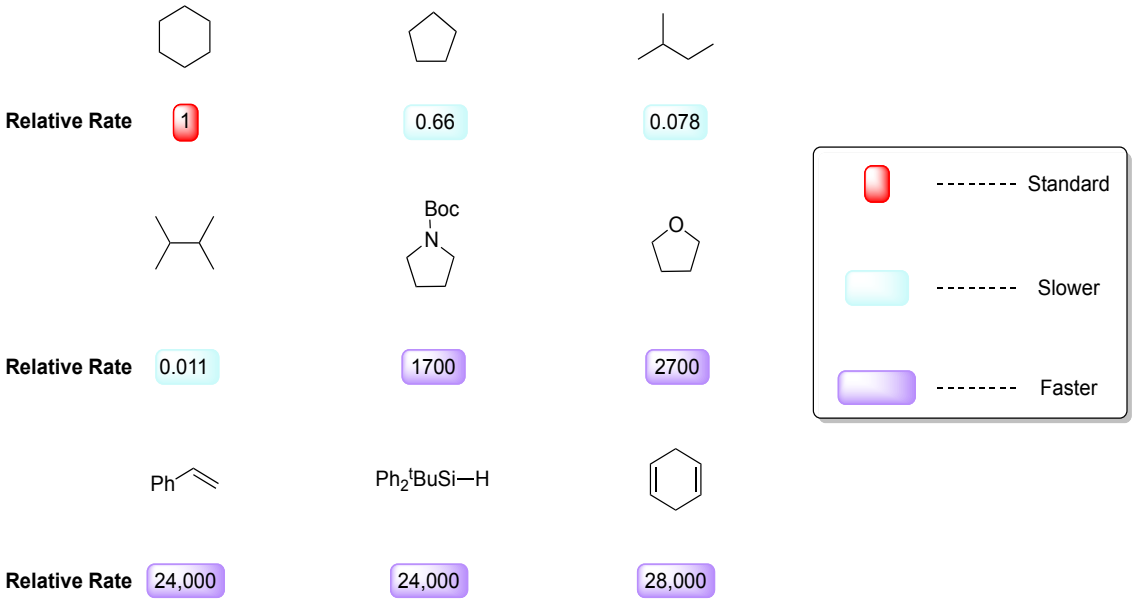
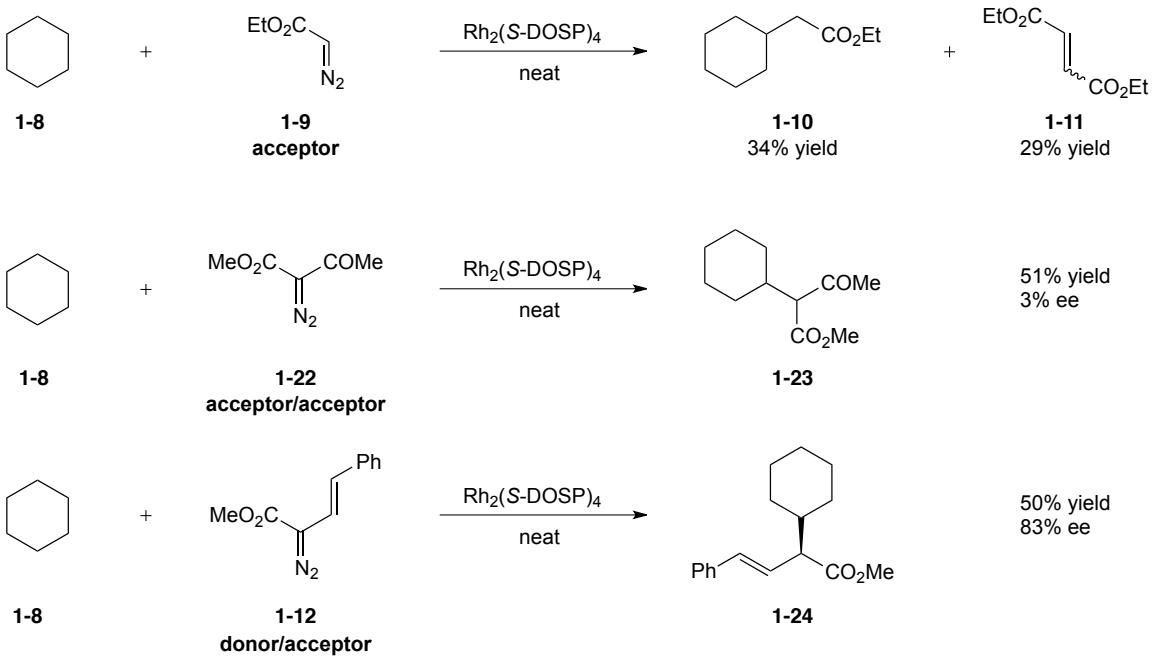


Figure 9 Relative Rates of Reaction

It can be concluded that C-H insertions with phenyldiazoacetate (**1-14**) in the presence of the dirhodium(II) catalyst proceed with remarkable regioselectivity. Substrates with an activating group next to the C-H bond are more favored than unactivated C-H bonds. THF and Boc-protected pyrrole react faster than plain cyclohexane by factors of 1700 and 2700 respectively. Reaction with THF is about 10 times less favorable than Si-H insertion or cyclopropanation of styrene.

To examine the role of the diazo compound in this robust regioselective C-H insertion reaction, Davies and coworkers carried out a series of screening reactions using different diazo compounds in the Rh_2(*S*-DOSP)$_4$ and cyclohexane reaction system (Scheme 6).[23(a)] Ethyl diazoacetates (**1-9**), a representative of an acceptor-substituted diazo compound was decomposed by Rh_2(*S*-DOSP)$_4$ in neat cyclohexane and the reaction gave a 34% yield of the desired C-H insertion product (**1-10**); however, it was accompanied with 29% of dimer side product(**1-11**). Reaction with methyl diazoacetoacetate (**1-22**), an

acceptor/acceptor carbenoid, gave exclusively C-H insertion product **1-23** with 51% yield but the enantioselectivity was only 3% ee. A high level of enantioselectivity was observed with donor/acceptor carbenoid. Under the same reaction conditions, **1-12** gave a 50% yield of the desired C-H insertion product **1-24** with 83% ee.

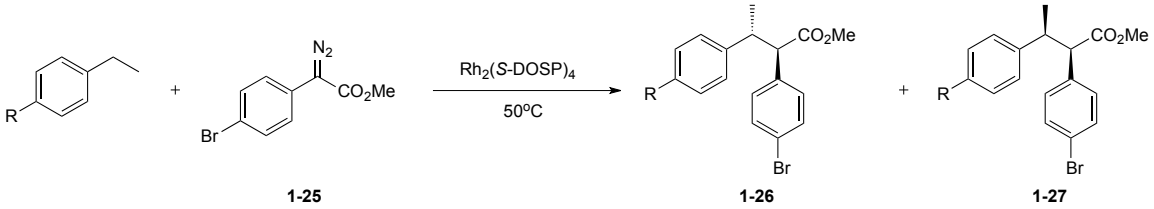


Scheme 6 Regioselectivity with Different Diazo Compounds

1.6 Catalytic C-H Activation at Benzylic and Allylic Positions

The development of general, catalytic and selective functionalizations of unactivated C–H bonds are highly desirable in green chemistry. The aromatic C-H bond activation has been achieved in many transition metal-mediated reactions due to the compensating higher bond strength of the resulting M–C bond for aryl over alkyl groups.[48] Unlike aromatic C-H bond, catalytic activation of benzylic C-H bond is not as well developed. Selectivity for benzylic C-H activation may arise when (a) formation of an aryl–metal product is sufficiently sterically disfavored, [49] (b) the benzylic product is stabilized by $\eta 3$ coordination, [50] or (c) a radical pathway provides kinetic selectivity for the benzylic C–H bond. Most established methods for the activation of benzylic sp^3 C–H bonds involve carbene precursors.[51]

In 2002, Davies and coworkers reported a comprehensive study of asymmetric benzylic C-H activation via donor/acceptor carbenoid insertion. [52] Substrates with different electronic environment were tested in the reaction with *para*-substituted phenyldiazoacetates (**1-25**) in the presence of Rh_2(*S*-DOSP)$_4$ as catalyst (Table 1). All of the screening reactions gave high levels of enantioselectivity with the major diastereomer (**1-26**). Electron-donating substituents increased the amount of the minor diastereomer (**1-27**) formed, which was obtained with moderate enantioselectivity.

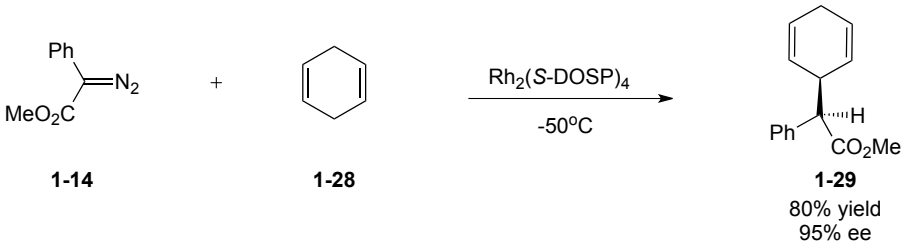


1-25 1-26 1-27

R	Yield(%)	Ratio(1-26/1-27)	ee of 1-26(%)	ee of 1-27(%)
MeO	86	68:32	89	76
Et	71	75:25	89	70
Me	64	82:18	89	74
H	49	84:16	86	-
Br	38	73:27	88	58
OAc	77	78:22	86	53

Table 1 Benzylic C-H Activation

Allylic C-H activation was also shown to be accessible via rhodium carbenoid transformations. Davies and coworkers expanded the scope of rhodium carbenoid chemistry and reported C-H insertion into allylic C-H bonds.[53] Decomposition of methyl phenyldiazoacetate (**1-14**) by Rh_2(*S*-DOSP)$_4$ at -50 °C and trapping of the resulting rhodium carbenoid with 1,4-cyclohexadiene (**1-28**) gave the C-H insertion product (**1-29**) in 80% yield and 95% ee (Scheme 7).



1-14 **1-28** **1-29**
80% yield
95% ee

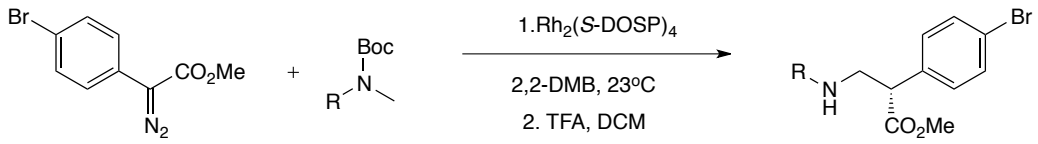
Scheme 7 Allylic C-H Insertion

1.7 Intermolecular C-H Activation Adjacent to Nitrogen

Enantioselective synthesis of β-amino acids was achieved via asymmetric C-H activation α to nitrogen using Rh_2(*S*-DOSP)$_4$ as the catalyst.[54] This methodology provides an easy access to β-amino acids that are useful precursors of biological active molecules. The chemoselective C-H activation occurring at a primary C-H bond instead of the allylic site was first discovered by the Davies group during the investigation of C-H activation of allyl amines (Scheme 8).[62] When **1-30** was subjected to the standard allylic C-H insertion reaction conditions, an unexpected primary C-H insertion product (**1-31**) was obtained as major product in 85% ee.

Scheme 8 C-H Activation of Allyl Amines

The activation at the primary C-H bond was unexpected albeit exciting; therefore, an extensive study was undertaken to broaden the reaction scope. A series of N-butoxycarbonyl (Boc) - protected amine substrates were screened and all of them gave C-H insertion at the methyl site. The best result came from the N-methylbenzylamine (**Compound 1-32 d**) reacting with donor/acceptor carbenoid **1-25** under standard reaction conditions. The reaction gave 62% yield of the primary C-H insertion product (**1-33 d**) in extremely high ee.

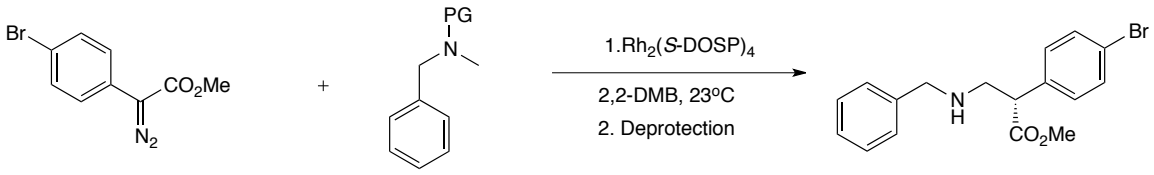


1-25 **1-32** **1-33**

Compound	R	Yield(%)	ee(%)
1-32 a	CH_3	61	31
1-32 b	$CH(CH_3)_2$	57	82
1-32 c	$C(CH_3)_3$	58	54
1-32 d	$C_6H_5CH_2$	62	95
1-32 e	$(CH_3)_2C{=}CHCH_2$	62	87
1-32 f	*trans*-$PhC{=}CHCH_2$	60	87

Table 2 C-H Activation Adjacent to Nitrogen

Prior studies were all focusing on Boc-protected amines as the substrates; a series of screening reactions were carried out to test the compatibility of the reaction with other nitrogen protecting groups. As described in Table 3, the methodology is also compatible with other common nitrogen protecting groups; however, the reaction yields are highly dependent on the protecting groups used. When Boc group was used as the protecting group for nitrogen in substrate **1-32 d**, 95% ee was observed for the product; whereas the observed ee dropped to 90% for Cbz protected N-methylbenzylamine (**1-34 a**). As summarized in Table 3, the size of the nitrogen protecting group has a huge impact on the reaction yield. When larger protecting groups, such as Fmoc (**1-34 b**) and Teoc (**1-34 c**) were present in the molecule, reaction yields dropped dramatically to 21% under the same reaction conditions.

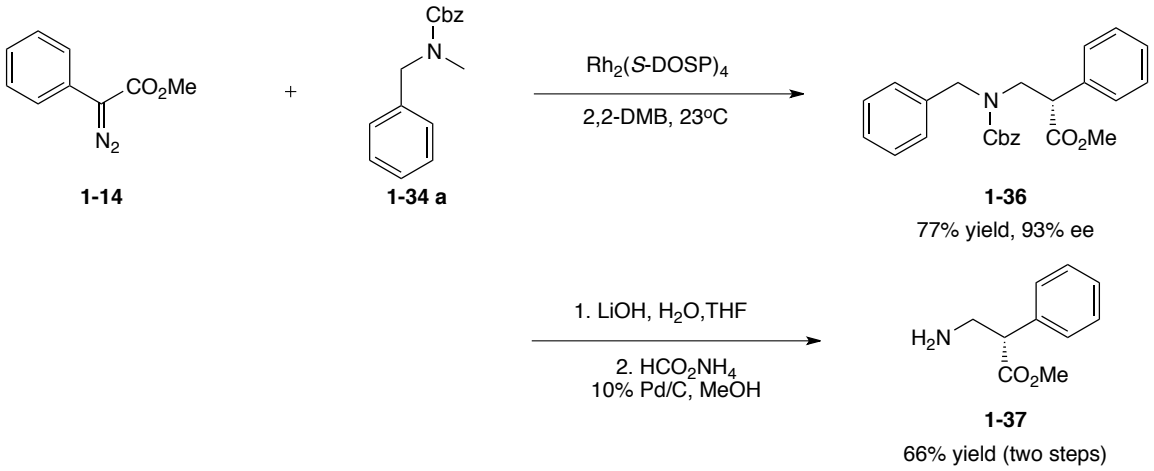


1-25 **1-34** **1-35**

Compound	PG	Yield(%)	ee(%)
1-34 a	Cbz	67	90
1-34 b	Fmoc	21	69
1-34 c	Teoc	26	94

Table 3 Reactions with Different Nitrogen Protecting Groups

The fact that benzylamine is the optimum substrate for this chemistry is very useful as it provides a concise synthetic route to amino acids and peptides. The following example demonstrates this powerful methodology (Scheme 9). The C-H insertion product was obtained in 77% yield and 93% ee. After hydrolysis of the ester and transfer hydrogenation, product was obtained in 66% yield over 2 steps. The absolute stereochemistry of **1-36** was determined to be *S* by comparison of the sign of optical rotation of **1-37** ($[\alpha]^{25}_D$ = -87.6°, *c* =0.13, H_2O) to the known literature value ($[\alpha]^{25}_D$ = +85°, *c* =0.2, H_2O) for the *R* isomer.[55]

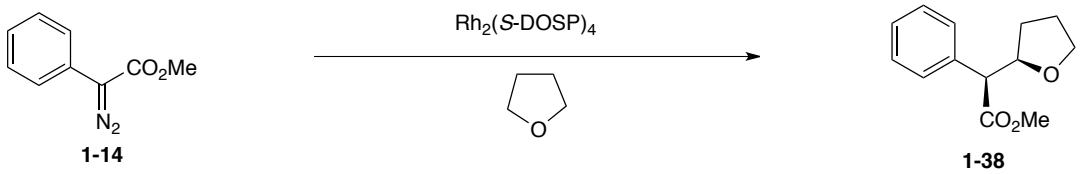


Scheme 9 Application of C-H Insertion with Benzylamine

The broad substrate scope and high reaction yields and enantioselectivities make this methodology very robust. The fact that this methodology can provide an easy access to chiral amino acids and peptides makes this methodology of great utility. The preliminary studies demonstrated that the Rh_2(*S*-DOSP)$_4$ catalyzed intermolecular C-H insertion is a powerful tool for the synthesis of β-amino acids with high yield and chemoselectivity.

1.8 C-H Insertion Adjacent to Oxygen

Functionalization of C-H bonds has always been an interesting topic. Over the years, the Davies group has developed very powerful methods for C-H activation by rhodium carbenoid induced reactions. Davies and Hansen have demonstrated that intermolecular asymmetric C-H insertions adjacent to oxygen using donor/acceptor rhodium carbenoids are highly enantioselective.[52] In initial studies with tetrahydrofuran acting as both the reactant and solvent, Rh_2(S-DOSP)$_4$ catalyzed decomposition of methyl 2-diazo-2-phenylacetate (**1-14**) gave C-H insertion product (**1-38**) with only 60% ee. The reaction was then optimized under various conditions and it was found that carrying out the reaction at -50 ^oC using 2 equiv of THF in hexane gave the optimum result (Table 4).

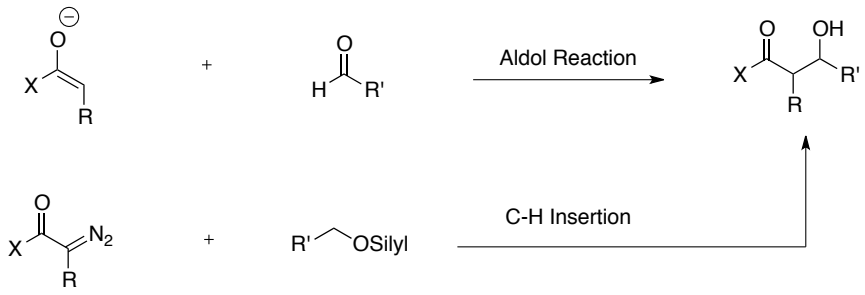


Solvent	Temp (^oC)	Yield (%)	de (%)	ee (%)
THF	60	82	2.3	60
THF	24	68	2.5	82
Hexane/THF	24	78	2.5	85
Hexane/THF	-50	67	4.0	97

Table 4 C-H Insertion with THF

Following Hansen's studies, Davies and Beckwith investigated intermolecular C-H insertion into the methylene site of silyl ethers. A particularly exciting feature of the C-H

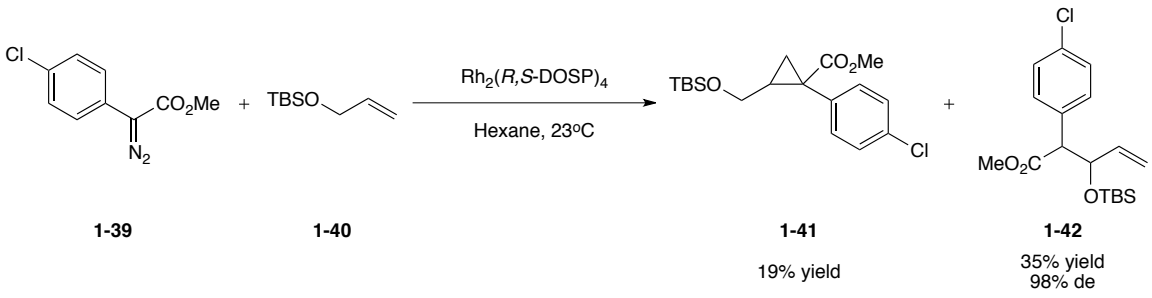
insertion adjacent to silyl ether is the formation of a sily protected β-hydroxy ester, the typical products of an aldol reaction (Scheme 10).[56]



Scheme 10 C-H Activation Adjacent to Oxygen

A thorough exploration of the reaction scope was undertaken, with particular emphasis on the chemoselectivity that can be achieved through modification of the oxygen substituent.[53]

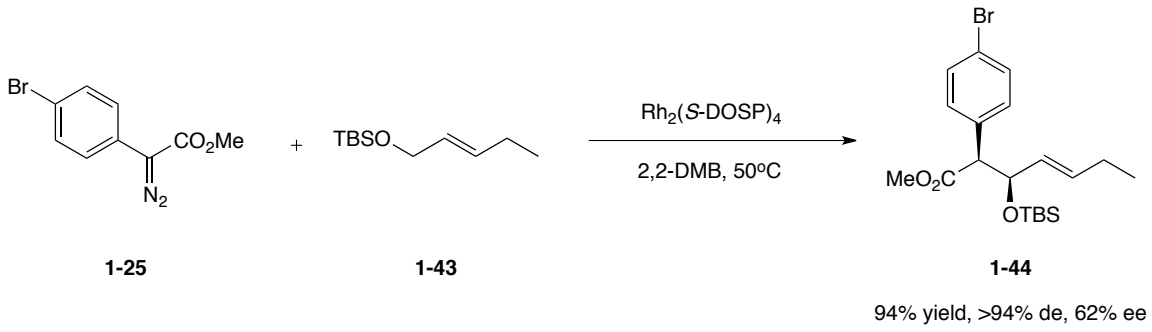
The test reaction of aryldiazoacetate with silyl ether under the typical reaction conditions gave a remarkable result (Scheme 11). The C-H insertion product (**1-42**) was preferred even though the substrate contained a terminal alkene, which is known to undergo cyclopropanation reactions readily.



Scheme 11 C-H Insertion with Silyl Ether

It is widely known that donor/acceptor-substituted carbenoids are ineffective at cyclopropanation of trans double bonds.[53] Protected trans-substituted allyl alcohols were

considered to be ideal substrates because the allylic position would favor insertion, and the competing cyclopropanation would be highly unlikely. Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of methyl *para*-bromoaryldiazoacetate (**1-3**) in the presence of the E-pent-2-enyl silyl ether (**1-43**) is an excellent example of the synthetic potential of this chemistry (Scheme 12). The exploratory reactions were conducted with 1 mol % Rh_2(*S*-DOSP)$_4$ with respect to the aryldiazoacetate (**1-25**), in refluxing 2,2-dimethylbutane, which is a good inert hydrocarbon solvent for this chemistry. When the reaction was conducted with 2 equiv of **1-25**, the C-H insertion product (**1-44**) was obtained in 94% yield and 62% ee. Remarkably, **1-44** is produced with very high diastereoselectivity (>94% de), as the second diastereomer was not observable in the NMR of the crude reaction mixture.



Scheme 12 C-H Insertion with Pentyl Sily Ether

The relative stereochemistry of the C-H insertion products was readily determined to be *syn* by comparing the *J* value for the benzylic proton in the hydrolysis product of the silyl ethers (**1-45**) to those reported in the literature for the *syn*-isomers (**1-46**) (Table 5).[57]

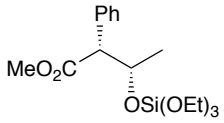
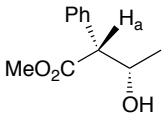
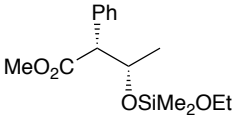
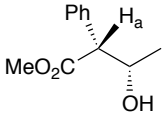
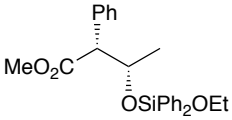
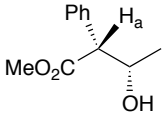
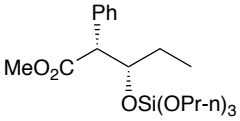
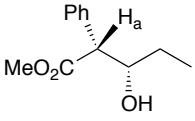
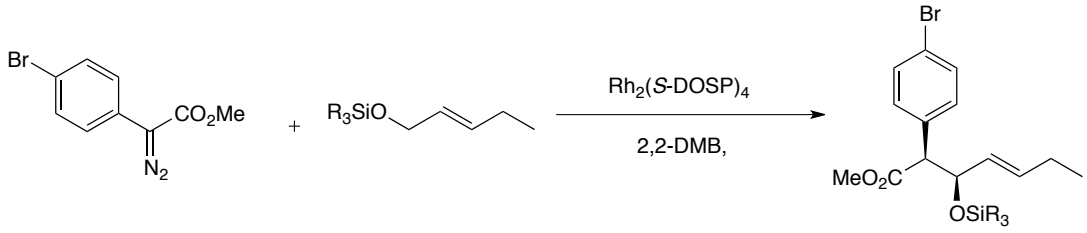
Silyl ether	Corresponding alcohol	Observed *J*	Lit. syn *J*	Lit. anti *J*
 **1-45 a**	 **1-46 a**	6.7 Hz	6.5 Hz	9.0 Hz
 **1-45 b**	 **1-46 a**	6.6 Hz	6.5 Hz	9.0 Hz
 **1-45 c**	 **1-46 a**	6.6 Hz	6.5 Hz	9.0 Hz
 **1-45 c**	 **1-46 c**	6.2 Hz	6.3 Hz	9.1 Hz

Table 5 Determination of Relative Stereochemistry of C-H Insertion Products

Product **1-45 c** was derived from Rh_2(*R*-DOSP)$_4$ catalyzed intermolecular C-H insertion reactions with silyl ethers. The absolute configuration of the C-H insertion product **1-45 c** was determined by hydrolysis to the alcohol **1-46 c**, whose enantiomer had been reported.[57(a)] Absolute configuration of **1-45 c** was determined to be (2*R*, 3*S*) by comparison of the sign of optical rotation of **1-46 c** ($[\alpha]^{24}_D$ = +86.9°, *c* = 0.70, $CHCl_3$), which was the opposite to the literature value ($[\alpha]^{20}_D$ = -84.2°, *c* = 0.87, $CHCl_3$) for the (2*S*, 3*R*) isomer.[57(a)]

1.9 Relative Rates of C-H Activation Adjacent to Oxygen

During the study of the reaction, Davies and Antoulinakis discovered that the reaction yields were very dependent on the size of the silyl groups and reaction temperatures (Table 6).[58]



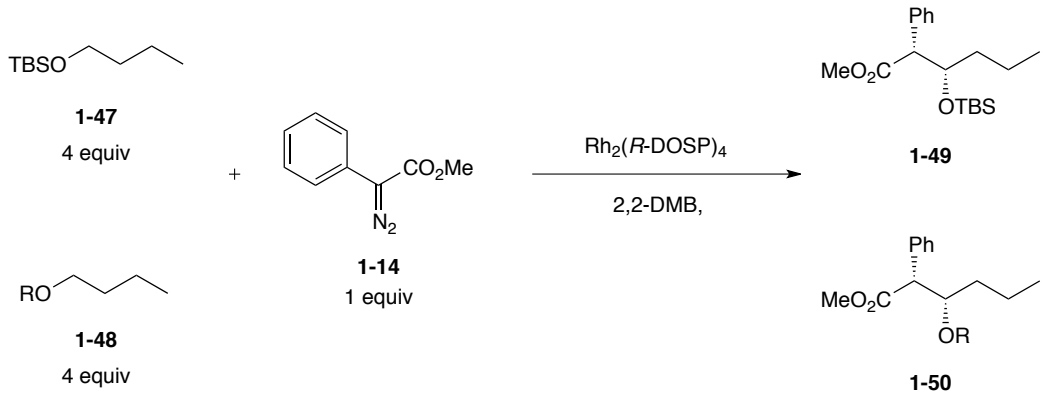
1-25

Entry	R_3	Temp (^oC)	Yield (%)	de (%)	ee (%)
1	Me_3	50	93	>94	65
2	Me_3	23	89	>94	85
3	*t*-$BuMe_2$	50	71	>94	68
4	*t*-$BuMe_2$	23	65	>94	79
5	*t*-$BuPh_2$	50	64	>94	18
6	*t*-$BuPh_2$	23	0	-	-

Table 6 Silyl Group Size Effect

The highest reaction yield was achieved by using trimethylsilyl as the silyl protecting group at 50 ^oC (Entry 1), whereas using tert-butyldiphenylsilyl group at room temperature (Entry 6) lead to no C-H insertion product at all. The fact that different sizes of the silyl groups lead to drastic difference in the reaction yields can be utilized in regioselective C-H activation reactions. Therefore, a series of competition experiments were conducted using *tert*-butyldimethylsilyl ether as the standard (Scheme 13).[52] The competition reaction was carried out with **1-14** as the limiting agent, and equal amount of the standard (**1-47**) and the testing ether (**1-48**) in the reaction mixture. Reaction was run under optimized reaction condition, and the ratio of products formed can be analyzed by

integration of characteristic peaks of **1-49** and **1-50** in the crude ^{1}H-NMR. With the rate of C-H insertion into *tert*-butyldimethylsilyl ether (**1-47**) normalized to 1, relative rates of silyl ethers with different sizes were calculated and summarized in Table 7.



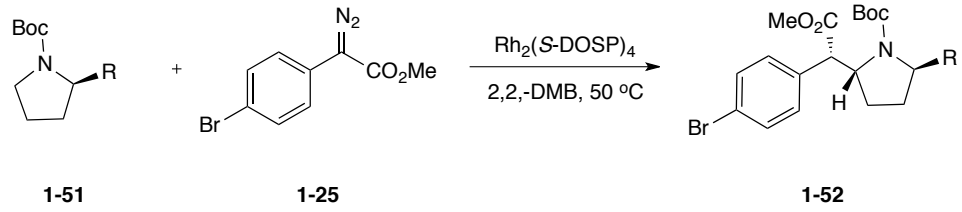
Scheme 13 Competition Study

Compound	R	Relative Rate
1-48 a	TMS	7.3
1-48 b	TES	2.8
1-47	TBS	1
1-48 c	TIPS	0.1
1-48 d	TBDPS	0.07

Table 7 Relative Rate of C-H Insertion Adjacent to Oxygen

1.10 Relative Rates of C-H Insertion into Cyclic Amines

Davies and coworkers have reported excellent region-, diastereo-, and enantioselective intermolecular C-H insertions of methyl aryldiazoacetates into cyclic N-Boc protected amines using Rh_2(*S*-DOSP)$_4$ as catalyst.[59] A few years later, an extensive study of the scope of stereoselective C-H insertion reactions of N-Boc-pyrrolidine was carried out by the Davies group.[60] Regioselectivity of C-H insertions with substrates that contain multiple potential sites, together with matched-mismatched reactions were studied with 2-substituted N-Boc-pyrrolidines (**1-51**) (Scheme 14).



Scheme 14 Matched Regioselective C-H Insertion

The remarkable feature of this reaction was that with two or more different potential active sites within the same molecule, the C-H insertion next to nitrogen prevailed in all cases (Table 8).

Compound	R	Yield, %	de, %
1-51 a	CO_2Me	83	>94
1-51 b	$CO_2{}^tBu$	85	>94
1-51 c	CH_2OAc	92	>94
1-51d	CH_2OTBS	62	>94

Table 8 Regioselective C-H Insertions Next to Nitrogen

Unlike compounds **1-51 a** and **1-51 b**, which have two potential C-H activation sites adjacent to nitrogen; compounds **1-51 c** and **1-51 d** contain one extra potential active site for C-H insertion to occur (Figure 10). Since it has been reported that C-H activation at the methylene site adjacent to silyl ethers reacts at different rates depending on the size of the silyl group,[51] this competition reaction could provide information about the chemoselectivity in a system where methylene sites adjacent to oxygen and nitrogen are both present.

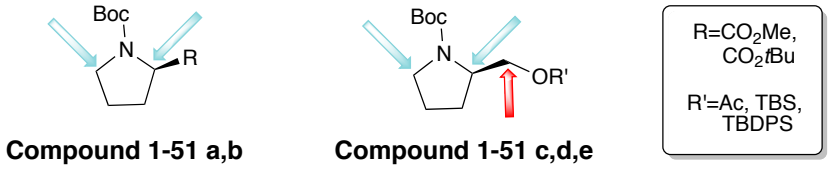
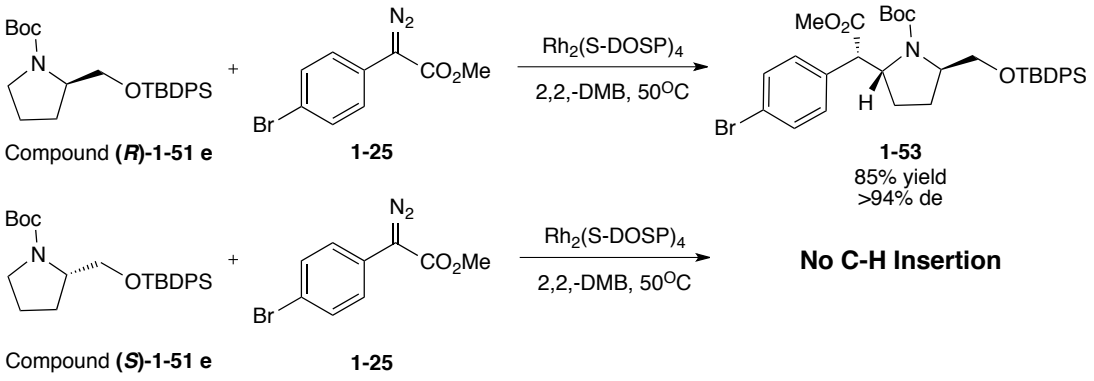


Figure 10 Potential Active Sites for C-H Insertion

From the result of these reactions (Table 8), it can be concluded that the C-H activation occurs more readily at the methylene site adjacent to nitrogen due to steric and electronic effects.



Scheme 15 Matched and Mismatched Reactions with Compound 1-51 e

When Compound **(*R*)-1-51 e** was subjected to the same reaction conditions, the C-H insertion product that originated from the methylene C-H activation adjacent to nitrogen

was obtained in high yield and de. However, when mismatched Compound **(*S*)-1-51 e** was subjected to the same reaction condition, the only observed product was carbene dimer (Scheme 15).[43]

In summary, prior studies demonstrated that the intermolecular C-H insertion of donor/acceptor rhodium carbenoids derived from aryldiazoacetates is an attractive method for the asymmetric synthesis of substituted β-hydroxy ester and β-amino acids. The reaction proceeds with good chemo- and enantioselectivity, and represents an intriguing complement to the classic aldol reaction and Mannich reaction. Although the remarkable steric control in those reactions makes it possible for regioselective C-H insertion reactions with substrates that possess more than one active site, such a study has not been reported where two active sites (ie. α to oxygen and α to nitrogen) coexist within the same molecule.

Chapter 2 Regioselective Intermolecular C-H Functionalization of Protected Amino Alcohols

2.1 Background

The rhodium carbenoid catalyzed C-H functionalization has been shown to achieve high regio-, diastereo- and enantioselective insertion into methylene sites adjacent to oxygen and high regio- and enantioselective insertion into primary C-H bonds adjacent to nitrogen.[52,63] The C-H functionalization adjacent to oxygen and nitrogen are synthetically useful reactions because they can be considered as surrogate to aldol reaction and Mannich reaction.[61,64] To utilize this transformation beyond silyl ether and Boc-protected amines, the regioselectivity of C-H insertion reaction with amino alcohols was studied.

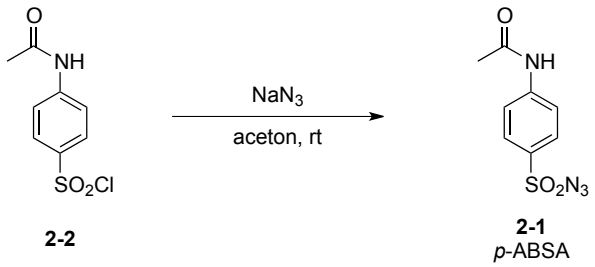
The primary objective of this project is to explore the scope and limitations of the regioselective C-H insertion reaction with protected amino alcohols. A series of protecting groups with different steric and electronic effects were adopted in the investigation to get a general trend of regioselectivity.

The second area of exploration involved a relative rate study to understand the observed regioselectivity in the C-H insertion with protected amino alcohols. Although relative rate studies have been done separately for the C-H insertion of silyl ethers and cyclic amines, there is a lack of direct comparison between the relative rates of those two active sites to explain the observed regioselectivity. Therefore, the relative rate study was carried out to understand the observed regioselectivity in the C-H insertion reactions with protected amino alcohols.

2.2 Preparation of diazo compounds

Davies and coworkers have previously examined the effect of diazo substitution on the enantioselectivity of cyclopropanation and C-H insertion reactions.[26,29,62] Impressive results were obtained when using diazo compounds, which were substituted with an electron withdrawing group (usually a methyl ester), and an electron donating group (usually a vinyl or aryl group) on either side of the diazo moiety. Several of these types of diazo compounds were used in these intermolecular C-H insertion studies. All aryldiazoacetates were synthesized by a modified literature procedure.[63] The key step in the preparation of these donor/acceptor substituted diazo compounds was a diazo transfer reaction to the appropriate arylacetic acid ester using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) in the presence of a non-nucleophilic amine base.

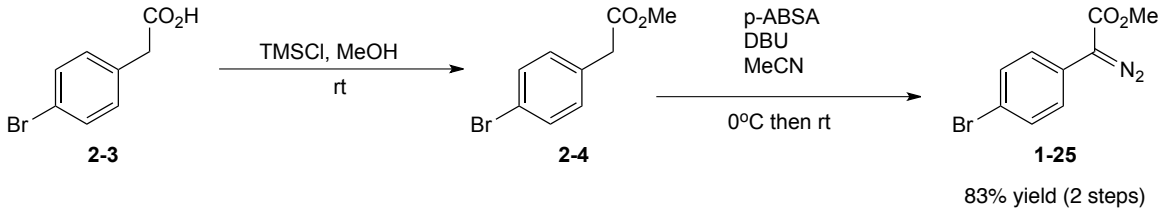
p-ABSA (**2-1**) was prepared on a large scale (~100 g) by reaction of *N*-acetylsulfonyl chloride with sodium azide in acetone according to literature precedent (Scheme 16).[57] The crude product was precipitated out of solution by quenching the reaction mixture in water. The off-white precipitate was washed with water three times and was collected by filtration. The product was dried under high vacuum, and used without further purification.



2-2 **2-1** *p*-ABSA

Scheme 16 Synthesis of *p*-ABSA

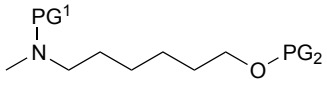
Aside from its bench stable character, *p*-ABSA (**2-1**) is easy to synthesize and the byproduct of the reaction is easily removed by trituration with petroleum ether/diethyl ether.[64] Methyl *para*-bromoaryldiazoacetate (**1-25**) was prepared from esterification of the commercially available 2-(4-bromophenyl)acetic acid (**2-3**) followed by diazo transfer with *p*-ABSA and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base in acetonitrile (Scheme 15). Purification of the desired diazo compound was achieved by flash chromatography on silica gel. These donor/acceptor diazo compounds are adequately stable and phenyldiazoacetate (**1-14**) could be stored at -20 ^{o}C for over a year without any significant decomposition.



Scheme 17 Synthesis of 1-3

2.3 Synthesis of amino alcohols

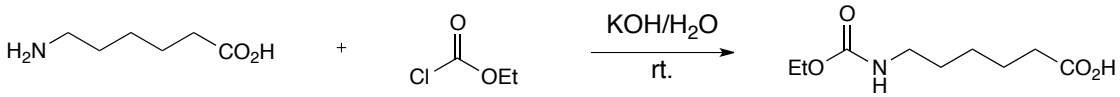
In order to eliminate electronic interference from either oxygen or nitrogen, the model substrate (**2-5**) was chosen to be a 1,5-amino alcohol, which has a methyl amine on one end and an alcohol on the other end of the molecule (Figure 11).



2-5

Figure 11 Model Substrate

In order to synthesize protected amino alcohol precursors, a two-step protocol was followed. Condensation of 6-aminocaproic acid (**2-6**) and ethyl chloroformate (**2-7**) generated 6-(ethoxycarbonyl)amino hexanoic acid (**2-8**) in high yield (Scheme 18).

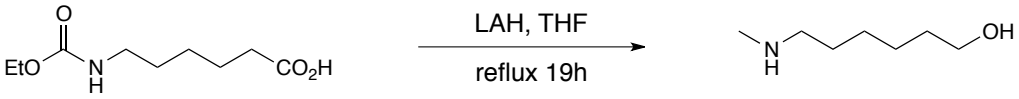


2-6 **2-7** **2-8**

93% yield

Scheme 18 Synthesis of 2-8

Reduction of the 6-((ethoxycarbonyl)amino)hexanoic acid (**2-8**) with lithium aluminum hydride (LAH) gave 6-(methylamino)hexan-1-ol (**2-9**), which is the model substrate for the study of regioselective C-H insertion of protected amino alcohols (Scheme 19).



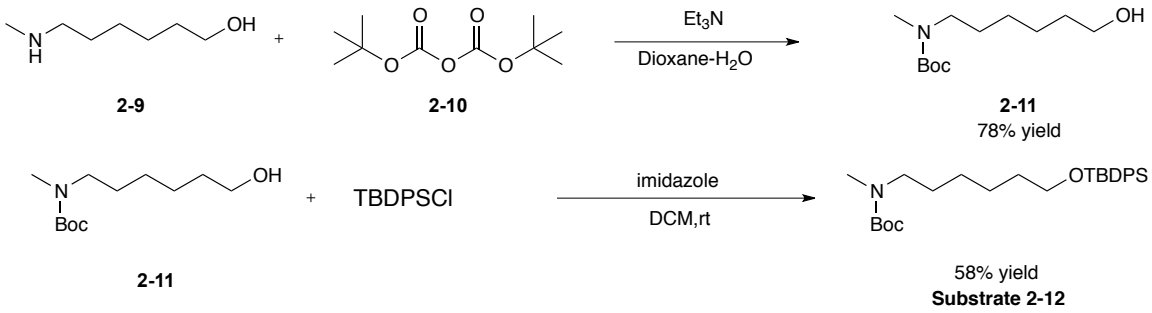
2-8 **2-9**

89% yield

Scheme 19 Synthesis of 2-9

2.4 Synthesis of protected amino alcohols

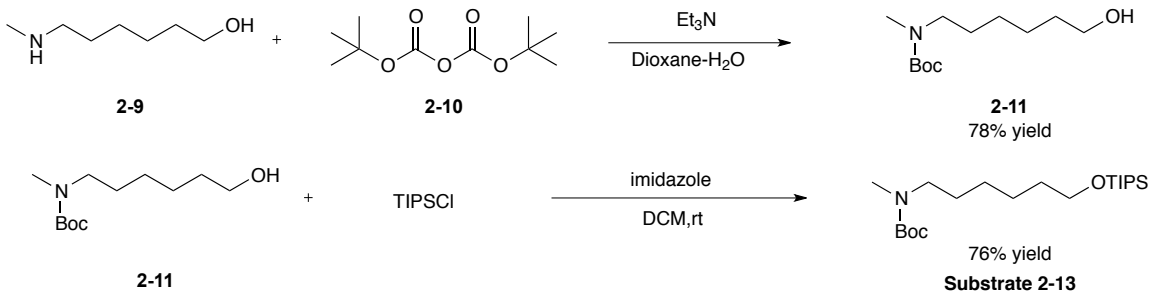
To test the relationship between protecting group size and the regioselectivity of the C-H insertion reaction, 6-(methylamino)hexan-1-ol (**2-9**) was employed as the standard substrate and various protecting groups for oxygen and nitrogen were used. Substrate **2-12** employed *tert*-butyldiphenylsilyl (TBDPS) group as the oxygen protecting group and Boc group was used to protect nitrogen. The synthesis of substrate **2-12** is outlined in Scheme 20.[65]



Scheme 20 Synthesis of Substrate 2-12

Reaction of **2-9** with di-*tert*-butyl dicarbonate (Boc_2O) (**2-10**) gave the Boc-protected **2-11**. Aqueous extraction followed by flash column chromatography on silica gel provided pure Boc-protected **2-11** in 78% yield. Treating Boc-protected **2-11** with TBDPSCl and imidazole in methylene chloride as solvent yielded substrate **2-12**. The TBDPS protecting group is considered a large protecting group, which in turn would prevent rhodium carbenoid from approaching the adjacent methylene site. On the other hand, Boc group is just electron withdrawing enough to keep the nitrogen lone pair from poisoning the catalyst, and yet not sterically demanding enough to encumber the C-H insertion at the adjacent methyl site.

Triisopropylsilyl (TIPS) protecting group is another common silyl ether that is widely used as oxygen protecting group. [66] Due to its steric hindrance, TIPS is known to slow down reactions at silicon compared to trimethylsilyl (TMS); however, this character renders TIPS a selective protecting group for hydroxyl groups. To compare the steric influence between TBDPS and TIPS, substrate **2-13** was synthesized following a similar protocol (Scheme 21).



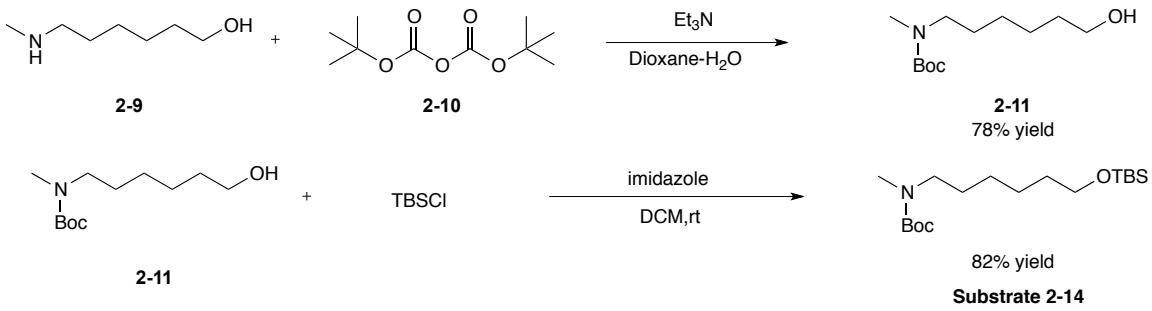
Scheme 21 Synthesis of 2-13

The concept of cone angle[67] was utilized by Imyanitov[68] and by Panek[69] independently to rationalize the steric effect of silyl ethers with different trialkyl substituents. As shown in Table 9,[69] the difference in cone angle between TIPS and *tert*-butyldimethylsilyl (TBDMS) is about 21°; therefore, it will be interesting to see how the size of silyl groups affects regioselectivity in the carbenoid C-H insertion reaction with protected amino alcohols.

R_3Si	Formula	Cone angle θ (°)
TMS	Me_3Si	118
TES	Et_3Si	132
TBDMS	$^tBuMe_2Si$	139
TIPS	$^iPr_3Si$	160

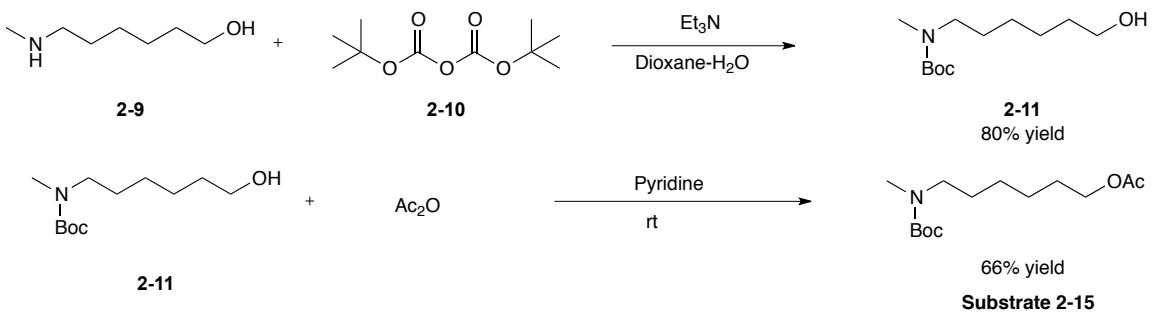
Table 9 Cone Angle for R_3Si

Substrate **2-14** was synthesized by the same protocol in the first step and only varied in the procedure of protecting the hydroxyl group (Scheme 22). With substrate **2-12**, **2-13** and **2-14** sharing the same nitrogen protecting group but different silyl-protecting groups, we can see how the size of the oxygen protecting groups can influence the regioselectivity of the C-H insertion.



Scheme 22 Synthesis of 2-14

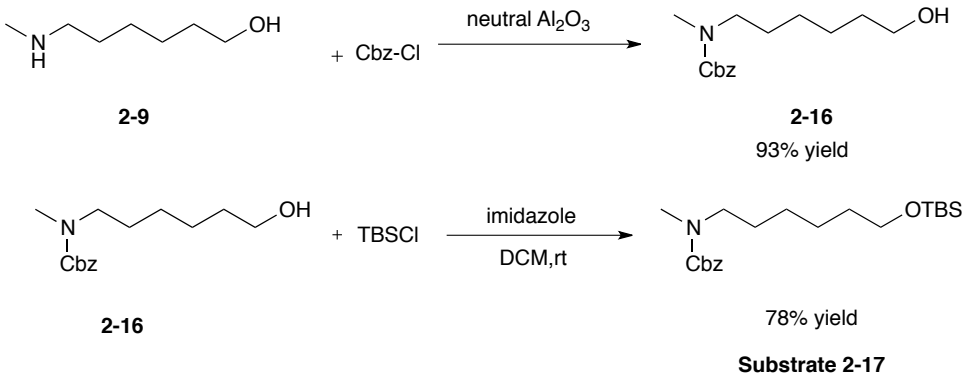
Substrate **2-15** was prepared in a similar manner using Boc_2O in the presence of triethylamine in dichloromethane and then followed by condensation between acetic anhydride and alcohol (**2-11**) (Scheme 23). The acetate group in substrate **2-15** is acting both as a protecting group and a deactivating group for oxygen.[70]



Scheme 23 Synthesis of 2-15

Screening reactions of substrates **2-12** to **2-15** will demonstrate how the size and electronic effect of the protecting groups on oxygen affects the C-H insertion into the methylene site adjacent to oxygen. Since substrate **2-12** to **2-15** share the common nitrogen protecting group, it will be intriguing to see how the size of the nitrogen protecting group influence the outcome of regioselectivity in the reaction of protected amino alcohols.

To get a bigger picture of the regioselectivity of C-H insertion of amino alcohols, a series of common nitrogen protecting groups were introduced into the molecules. Substrate **2-17** bears a benzyloxycarbonyl (Cbz) group on the nitrogen and TBS on the oxygen. The difference between the two protecting groups electronically is minimal; therefore, it will be interesting to see how steric effects plays a role in the regioselectivity of this type of transformation. Substrate **2-17** was prepared in two steps according to literature procedures (Scheme 24).[71]



Scheme 24 Synthesis of 2-17

As one would suspect that substrate **2-12** to **2-17** would give primarily C-H insertion product of the methyl site adjacent to nitrogen, it will be interesting to see if there would be a combination of the protecting groups on the two heteroatoms that will give rise to C-H insertion product derived from the C-H activation at the methylene site adjacent to oxygen. Therefore, substrates **2-18** to **2-20** were synthesized to test the possibility (Figure 12).

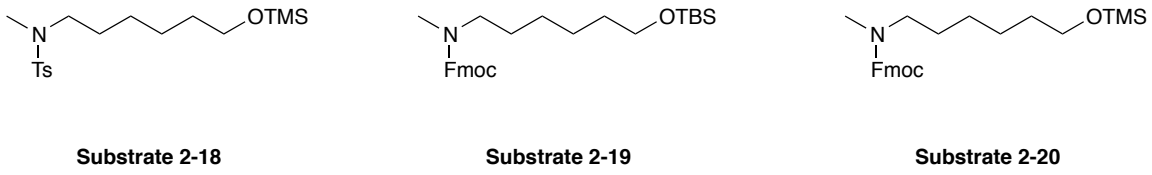
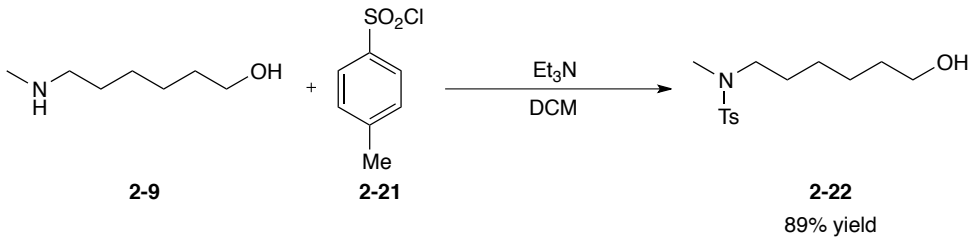


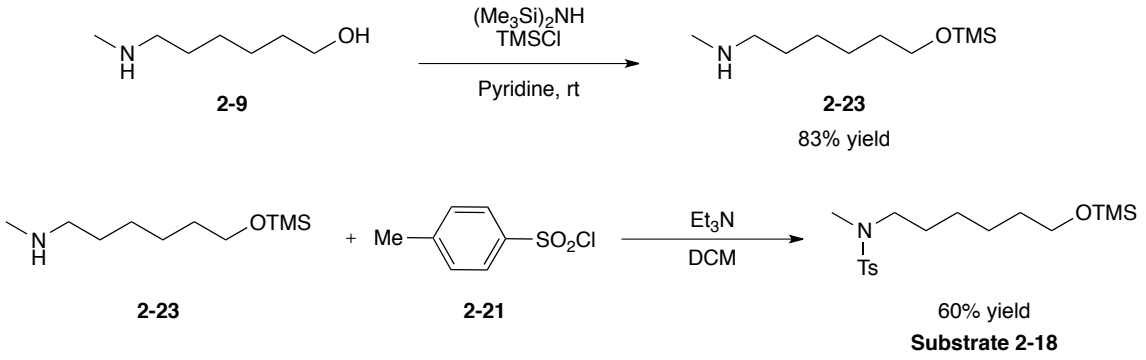
Figure 12 Substrate 2-18 to 2-20

The first synthetic attempt of substrate **2-18** started with protection of **2-9** with tosyl chloride (**2-21**), which gave the advanced intermediate **2-22** in 89% yield (Scheme 25).



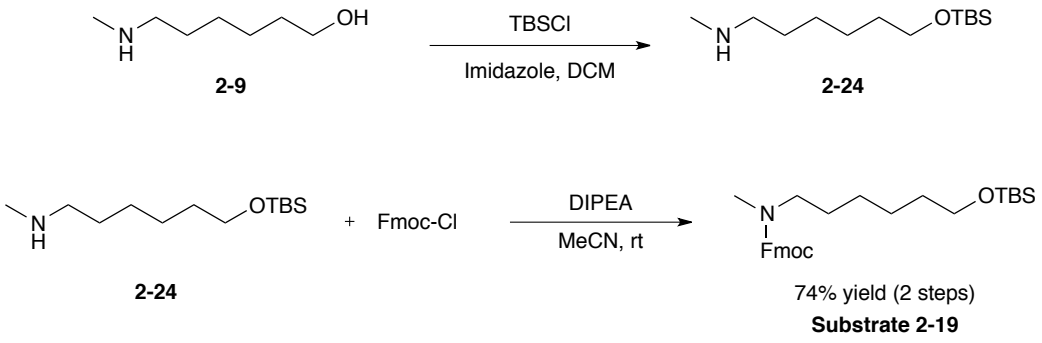
Scheme 25 Synthesis of 2-22

Further treatment of **2-22** with trimethylsilyl chloride (TMSCl); however, did not give the desired silylated product. Therefore, another protocol was followed for the synthesis of substrate **2-18** (Scheme 26). [72]



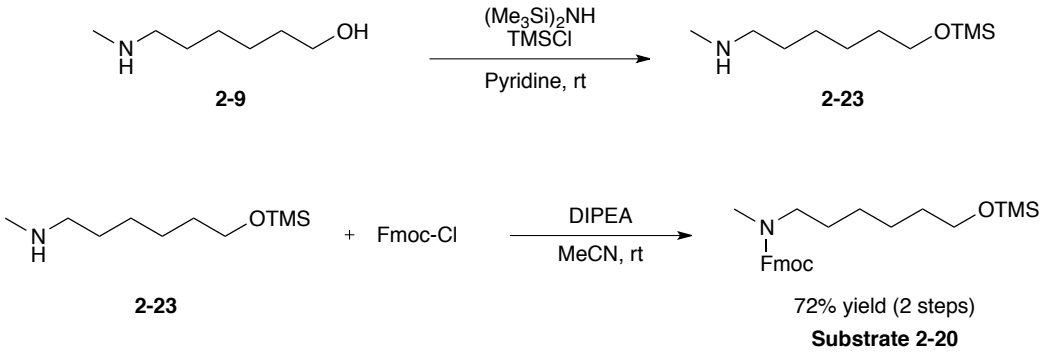
Scheme 26 Synthesis of 2-18

The same reaction sequence was used in the preparation of substrate **2-19** and **2-20** (Scheme 27). Treatment of **2-9** under standard silylation conditions followed by Fmoc protecting with 9-fluorenylmethylchloroformate (Fmoc-Cl) in the presence of DIPEA in acetonitrile gave substrate **2-19** in 74% yield over 2 steps.[73] The reason for installing Fmoc group on the nitrogen is to test the hypothesis if Fmoc is big enough to block the carbenoid approaching the methyl site next to nitrogen and therefore forces the C-H insertion to occur at the methylene next to oxygen.



Scheme 27 Synthesis of 2-19

Substrate **2-20** was synthesized by a similar protocol with an overall yield of 72% (Scheme 28). The difference in the size of two silyl protecting groups of substrate **2-19** and **2-20** will affect the outcome of the C-H insertion; therefore, the relative relationship between the size of the silyl group and the tendency of methylene C-H insertion can be concluded from screening reactions of substrate **2-19** and **2-20**.

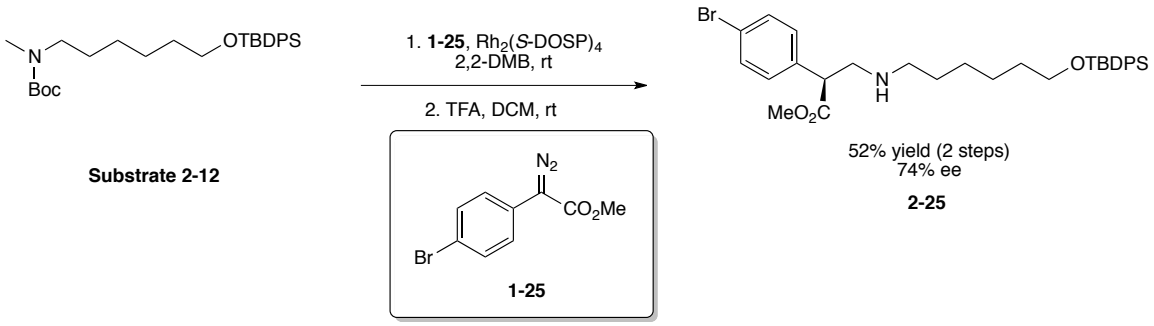


Scheme 28 Synthesis of 2-20

2.5 Regioselective Catalytic Asymmetric C-H Functionalization of Protected Amino Alcohols

During the past decade, the Davies group has done extensive studies on highly stereoselective intermolecular C-H insertion reactions of methyl aryldiazoacetates into cyclic, acyclic amines and silyl ethers using Rh_2(*S*-DOSP)$_4$ as the catalyst.[53,54] However, there have been no studies on the C-H activation into amino alcohols which have two active sites within the molecule. Therefore, the investigation was initiated to determine the scope and limitations of the donor/acceptor carbenoid in regioselective C-H insertion of protected amino alcohols.

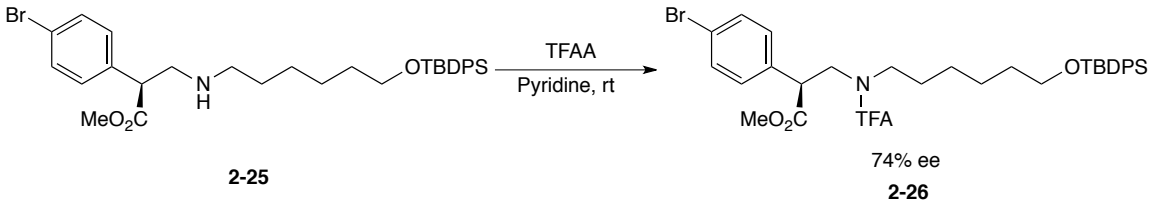
Intermolecular C-H insertions into N-methylbenzylamine using donor/acceptor diazo compounds and Rh_2(*S*-DOSP)$_4$ catalyst has been shown to give excellent results.[64] Hence, the initial evaluation of the intermolecular C-H insertion into protected amino alcohols was attempted with substrate **2-12**, with the hope of primary C-H insertion adjacent to nitrogen (Scheme 29).



Scheme 29 C-H Insertion with 2-12

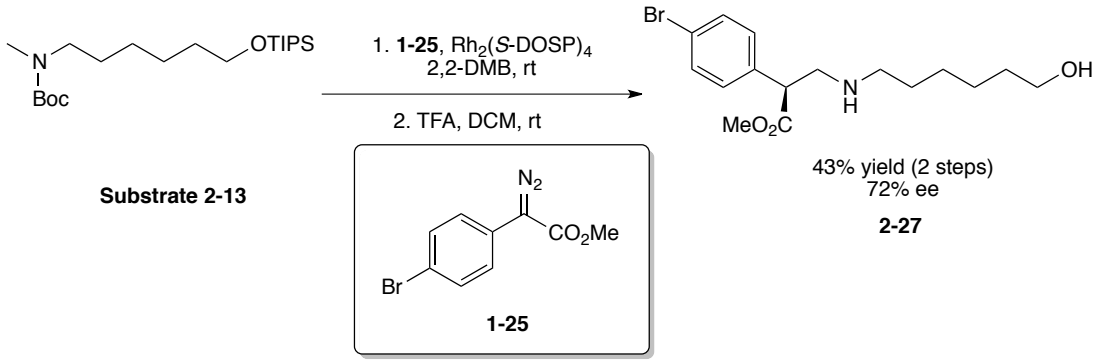
Reaction of substrate **2-12** indeed gave the primary C-H insertion product **2-25**, which is consistent with the fact that rhodium carbenoid derived from aryldiazoacetate behaves as

a sterically demanding reagent.[74,75] The TBDPS group on oxygen proved to be bulky enough to hinder any insertion reaction to occur at the methylene site adjacent to oxygen. After deprotection of Boc group, the β-amino ester **2-25** was formed in 52% combined yield over two steps. No evidence for C-H insertion into the methylene site adjacent to either oxygen or nitrogen was observed. To determine the ee (enantiomeric excess) value of this reaction, nitrogen was protected by trifluoroacetic anhydride and the purified product was analyzed by HPLC to determine the *ee* value (Scheme 30).



Scheme 30 TFA Protection of 2-25

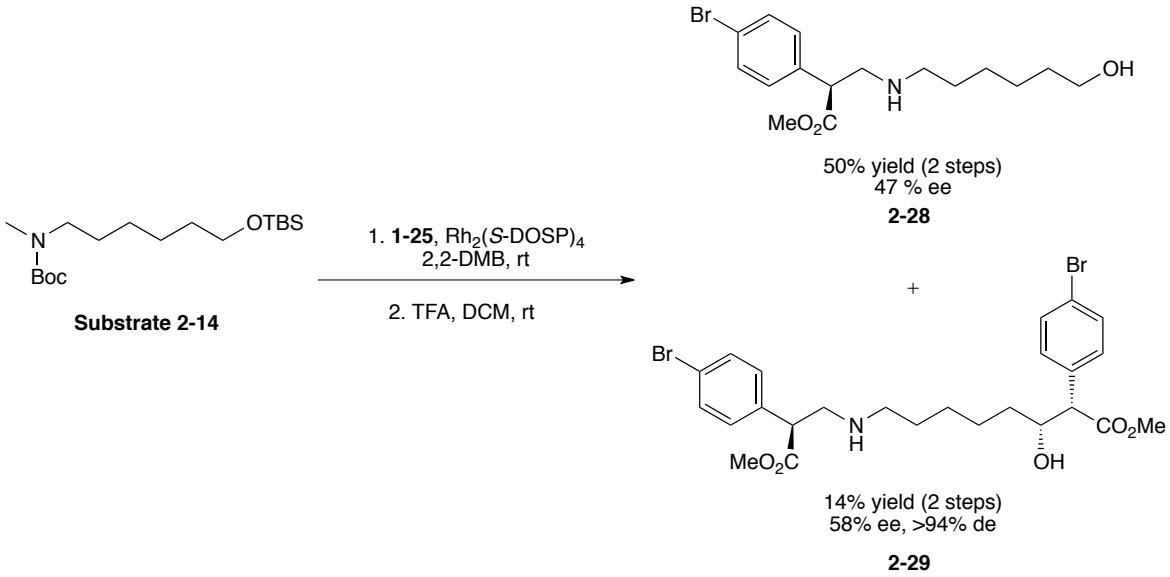
The same reaction condition was used for substrate **2-13** and again due to the size of the TIPS group, the anticipated C-H insertion product was intermolecular C-H activation next to nitrogen. The result of this reaction confirmed our hypothesis and after deprotection, the C-H insertion product **2-27** was obtained in 43% yield and 72% ee (Scheme 31).



Scheme 31 C-H Insertion with 2-7

The stereochemistry of **2-27** was predicted to be *S* since the reaction conditions are the same as the previous work on C-H insertion α to nitrogen (see Chapter 1.7 for reference). Similar absolute configurations were tentatively assigned to the other products derived from primary C-H insertion adjacent to nitrogen, assuming a similar mode of C-H insertion for all the substrates.

When substrate **2-14** was subjected to the standard reaction conditions, an unexpected double C-H insertion product **2-29** was observed together with the mono C-H insertion product **2-28** (Scheme 30).

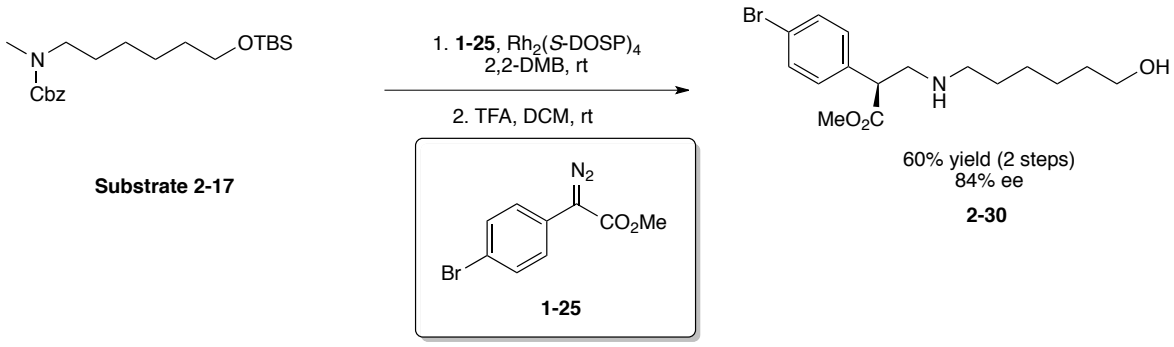


Scheme 32 C-H Insertion with 2-8

Product **2-28** was derived from the primary C-H insertion at the methyl site adjacent to nitrogen; whereas product **2-29** was the product of double C-H insertion of methyl site next to nitrogen and methylene site adjacent to oxygen. This intriguing result is a perfect demonstration of the fine balance in terms of protecting group size in this region-selective C-H insertion of amino alcohols. When bulkier protecting groups (eg. TBDPS,

TIPS) were adopted for oxygen, C-H insertion occurred exclusively at the methyl site adjacent to nitrogen. C-H insertion started to occur at the methylene site when TBS was used for protecting oxygen. The 21° difference in cone angle between TIPS and TBS contributed to this interesting product distribution, which can be utilized in regioselective C-H insertion reactions with Boc protected amino alcohols. Aside from the information about accessibility of donor/acceptor carbenoids towards certain reactive sites, this result also shed a light on relative reaction rate of C-H insertion at methyl site and methylene site. Detailed discussion on this subject will be expanded in Chapter 2.6. The absolute stereochemistry for the second insertion in product **2-29** was tentatively assigned to be (2*S*, 3*R*) by comparison of previous results for C-H insertion adjacent to oxygen (see Chapter 1.8 for reference).

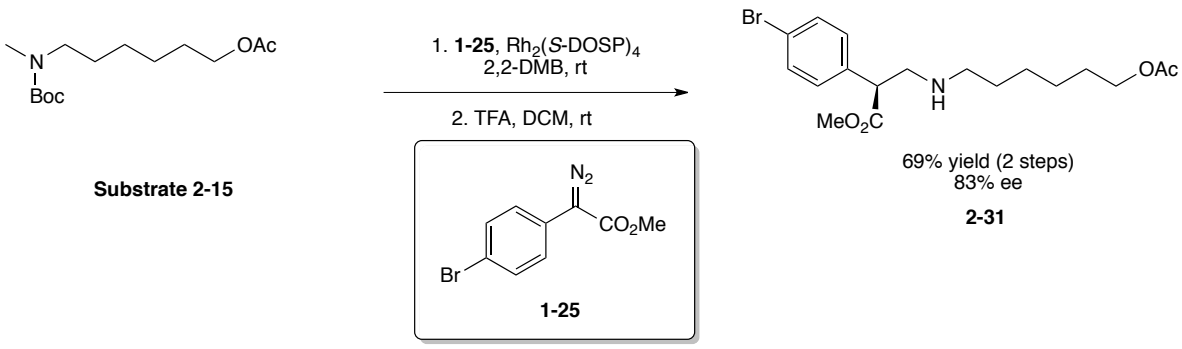
As all of the initial evaluations were carried out with Boc protected amino alcohols, it was intriguing to determine how other nitrogen protecting groups affects the regioselectivity of C-H insertion into amino alcohols. Substrate **2-17** was subjected to the standard reaction condition, and primary C-H insertion product **2-30** was isolated as the sole product from the reaction (Scheme 33).



Scheme 33 C-H Insertion with 2-17

The different outcome of the reaction with **2-17** and **2-14** was very intriguing considering the only difference between these two substrates was in the nitrogen protecting group. Reaction with **2-14** gave rise to two products with moderate enantioselectivity; whereas reaction with **2-17** resulted in C-H insertion product **2-30** with relatively higher enantioselectivity.

After the steric effect on both the oxygen protecting groups and nitrogen protecting groups were examined, electronic effects of the protecting groups were investigated. A screening reaction was carried out with substrate **2-15** (Scheme 34).



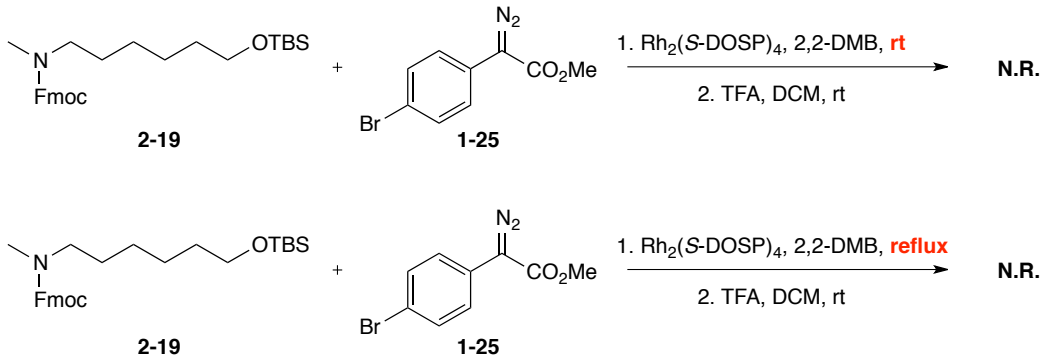
Scheme 34 C-H Insertion with 2-15

Since substrate **2-15** bears an electronically deactivating group for oxygen, C-H activation is postulated to occur exclusively at the methyl site adjacent to nitrogen. Indeed, the result of this screening reaction confirmed the hypothesis. Moreover, the deactivating effect on the methylene site increased the overall performance of C-H insertion next to nitrogen.

The intermolecular C-H insertions with protected amino alcohols have proven to be effective; however, so far all the examples gave predominantly primary C-H insertion

adjacent to nitrogen. Therefore, substrates **2-18** to **2-20** were subjected to the screening reactions to determine if selective C-H insertion at methylene site was feasible.

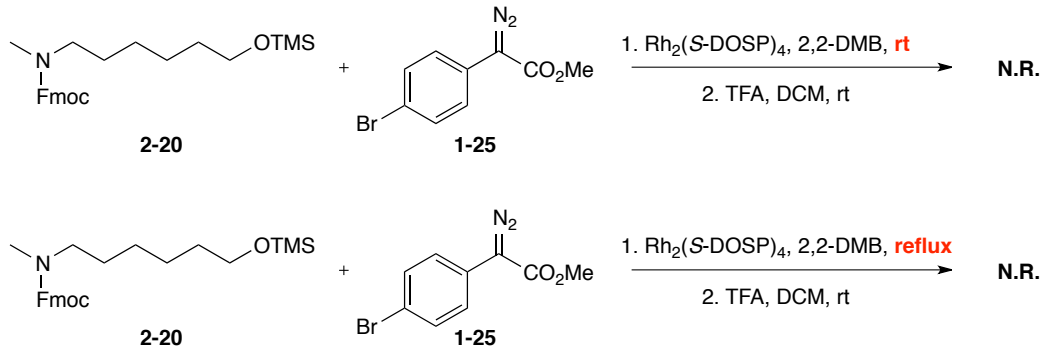
When substrate **2-19** was subjected to the standard reaction condition, no product was observed. The reaction with substrate **2-19** still gave no product even when heated under reflux for overnight (Scheme 35).



Scheme 35 C-H Insertion with 2-19

The fact that substrate **2-19** failed to yield any insertion product may be attributed to the following two factors: (1) the steric hindrance from Fmoc group on the nitrogen prevented rhodium carbenoid approaching the primary site adjacent to nitrogen. (2) the steric hindrance from the combination of Fmoc and TBS groups within the same molecule left little room for the carbenoid to get close enough to the methylene site adjacent to oxygen.

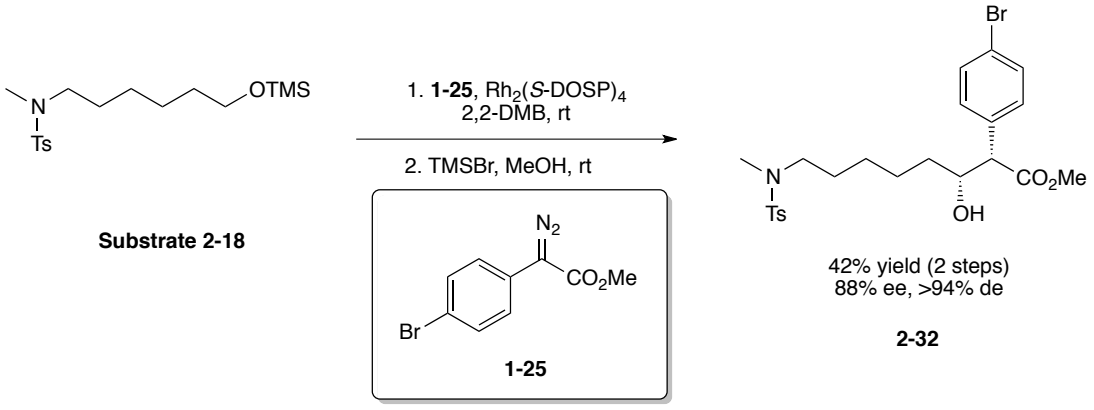
As substrate **2-20** has a less sterically demanding protecting group on oxygen, a test reaction was carried out in the hope of obtaining C-H insertion product derived from methylene site adjacent to oxygen (Scheme 36).



Scheme 36 C-H Insertion with 2-20

Unfortunately, no C-H insertion product was observed even when the reaction was performed at elevated temperature. Diazo dimers were the only products observed from this reaction and the starting material was recovered after reaction.

The electronic effect of the nitrogen protecting groups was examined next. Tosyl group is known to act as an electronically deactivating group in C-H insertion reactions.[64] A test reaction was carried out with substrate **2-18** to determine if selective C-H insertion would occur at the methylene site when the primary position was electronically deactivated (Scheme 37).



Scheme 37 C-H Insertion with 2-18

The discovery that **2-18** gave the product **2-32**, which was derived from C-H insertion adjacent to oxygen, was very exciting because this result demonstrated the possibility of selective deactivation. By using deactivating protecting group on one of the heteroatom, regioselective C-H insertion was achieved with full control of the C-H functionalization site. The overall reactivity profile of the C-H activation of amino alcohols is summarized in Figure 13.

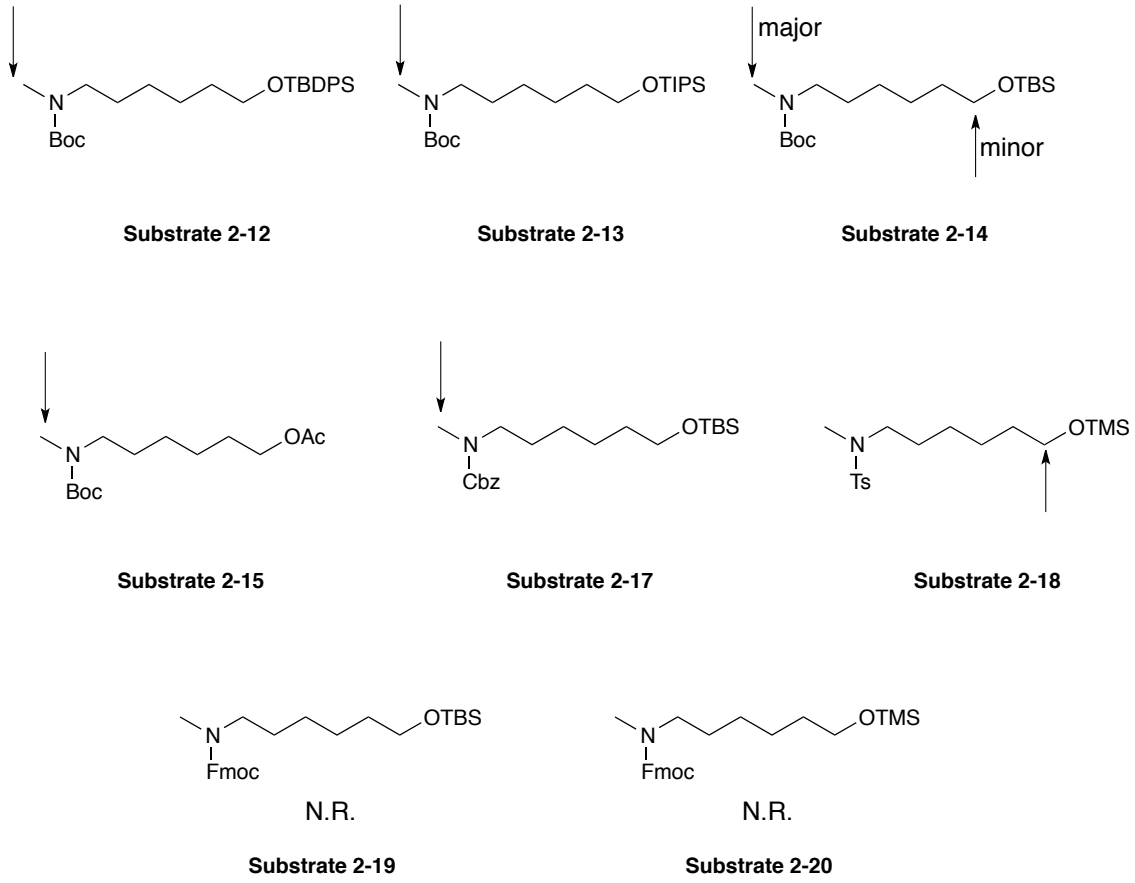


Figure 13 Overall Reactivity Profile

Asymmetric induction in these intermolecular C-H insertion reactions is generated through the use of chiral Rh_2(*S*-DOSP)$_4$ catalyst. Recent computational studies on the

selectivity of donor/acceptor-substituted rhodium carbenoids have revealed a more accurate picture of how the substrates approach the carbenoid complex (Figure 14).[76]

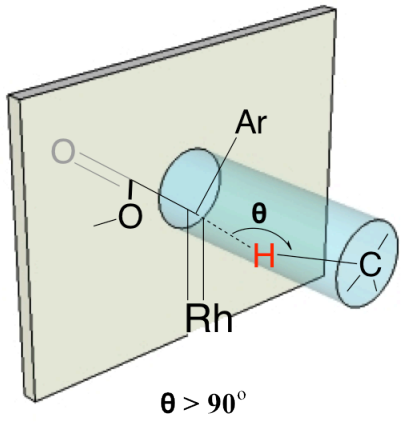


Figure 14 Approach Angle Between Substrates And Carbenoid Complex

The calculation results suggested considerable hydride transfer character during the initial C-H functionalization step. It was found that the C–H bond of the substrate approaches the carbenoid at a vector nearly orthogonal to the rhodium carbene plane (Figure 14).[77] In the case with 1,4-cyclohexadiene as substrate, the C-H-C angle is 165°, while with cyclopetane, it is calculated to be 127°.[77]

The computational result of the approach angle has led to a revised predictive model for the stereoselective intermolecular C-H functionalization with donor/acceptor-substituted carbenoids (Figure 15).[77] The substrate approaches the rhodium carbenoid in a way such that the three substituents adopt a staggered conformation to the three groups around the carbenoid center (Figure 15a). The largest substituent (L) is oriented upwards, which is the furthest from both the blocking groups and the catalyst plane. The second most sterically demanding group (M) is orientated away from the blocking group, while the least sterically demanding of the substituent (S) is located adjacent to the blocking group.

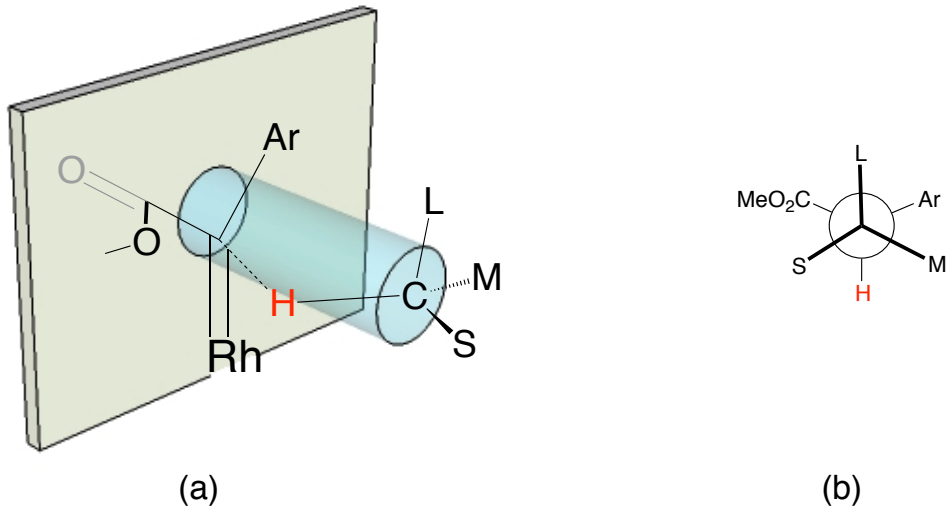


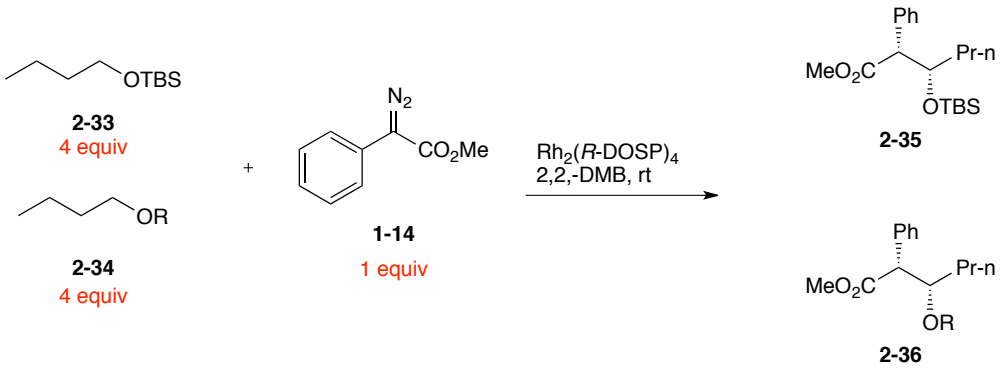
Figure 15 Predictive Model for C-H Insertion

A corresponding Newman projection model (Figure 15b) can be derived from this model, which can be used to predict and rationalize the absolute configuration of the two newly formed stereocenters.[77] Although the trajectory of approach of the substrate has not been determined experimentally, the prediction of this model aligns with the tentative assignment of the stereochemistry in the products of these C-H insertion reactions.

2.6 Relative Rate Study

One of the most notable features of the intermolecular C-H insertion reaction of donor/acceptor-substituted carbenoids is that they are often highly regioselective. Among the 8 substrates studied (Figure 13), 83% of the substrates favor C-H activation at the methyl site adjacent to nitrogen. In an effort to better understand the meaning of these data, competition studies were undertaken to determine the relative rate of reactivity for the regioselective C-H insertion of protected amino alcohols. To get a combined relative reaction rate table with both protected amines and alcohols, two separate series of relative reaction rate must be obtained first (i.e., a table of relative rate of C-H activation with protected alcohols and a table of relative rate of C-H activation with protected amines need to be done as the starting point of making the complete table).

A series of relative rate studies of silyl ethers were carried out prior to this investigation of the regioselectivity of C-H insertion of amino alcohols.[53] Typical procedure for the competition study of various silyl protecting groups is described in Scheme 38.



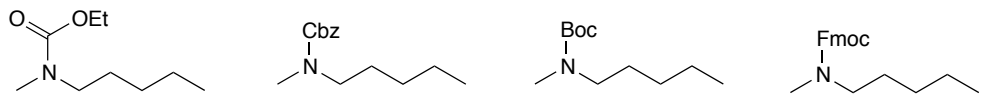
Scheme 38 Competition Study of Silyl Ethers

Phenyldiazoacetate (**1-14**) was the limiting agent, and equal amount of **2-33** and **2-34** were used in the reaction. The product ratio (**2-35 : 2-36**) was determined from the characteristic peaks from both products in the crude ^{1}H-NMR. By changing the protecting groups' sizes, a table of relative reactivity of silyl ethers was obtained (Table 10).

R	Relative Rate
TMS	6.7
TES	2.7
TBS	1.0
TIPS	0.081
TBDPS	0.069

Table 10 Relative Rate of C-H Insertion at Different *O*-silyl Sites

With the literature precedent in hand, the relative rate of C-H insertion at methyl site adjacent to nitrogen can be obtained through the same protocol. Therefore, a series of protected N-methylpentylamines were synthesized according to literature procedures (Figure 16).[55,61,63]

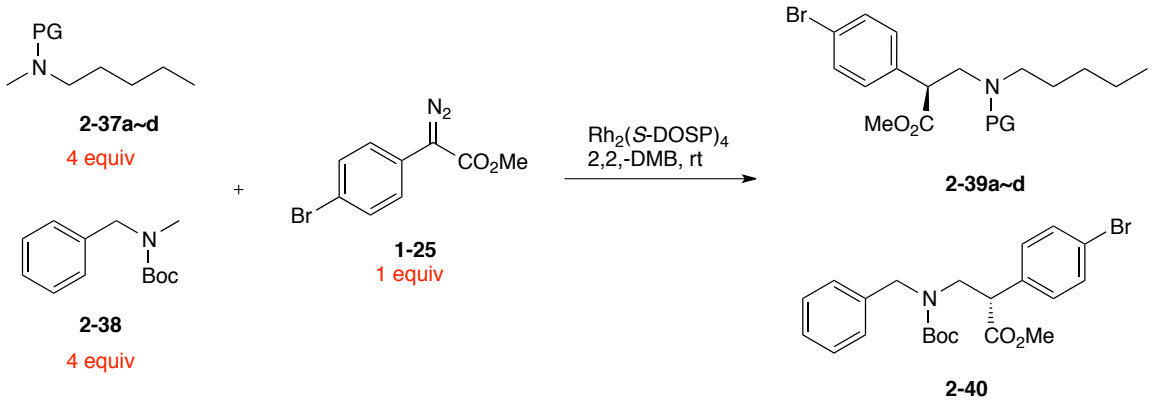


Substrate 2-37a **Substrate 2-37b** **Substrate 2-37c** **Substrate 2-37d**

Figure 16 Substrates for Relative Rate Study

Substrate **2-37c** was used as the internal standard for this series of relative reactivity study. Before conducting competition studies of substrate **2-37a** to **2-37d**, C-H insertion reactions with diazo **1-25** were carried out with all four of the substrates to get clean

spectra of the C-H insertion products. Then a competition study was carried out with equal amount of substrate **2-37a** and **2-37c** using **1-25** as limiting reagent. Unfortunately, the characteristic peaks of products from both substrates were overlapping in the crude ^{1}H-NMR and the ratio of products was not accessible. To circumvent this problem, Boc protected *N*-methylbenzyl amine (**2-38**) was employed as the internal standard substrate for the amine series relative rate study because of its very distinctive proton peak that is easily separable from the C-H insertion product peaks of protected N-methylpentylamines (Scheme 39).



Scheme 39 Competition Study of Protected *N*-methylpentylamines

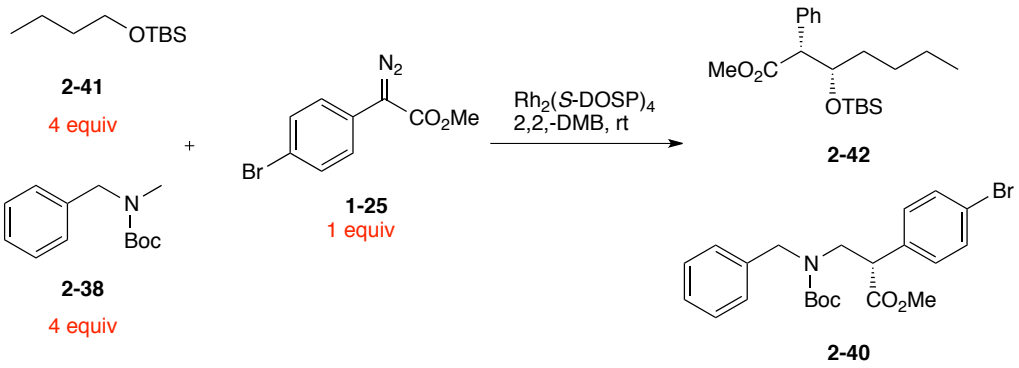
Decomposition of **1-25** by Rh_2(*S*-DOSP)$_4$ in the presence of Boc-protected N-methylbenzyl amine **2-38** and another protected N-methylpentyl amine **2-37a~d** gave C-H insertion products **2-40** and **2-39a~d**, the ratio of which was used to determine the relative rate of reaction for those two substrates. Table 11 summarized the results of these competition experiments, with the relative rate of N-methylbenzyl amine standardized to 1.0. As anticipated, an increase in the size of the nitrogen protecting group decreased the relative rate of C-H insertion reaction. The substrate bearing the smallest nitrogen protecting group, substrate **2-37a** reacted nearly 14 times faster than the most sterically

demanding substrate **2-37d**. Moreover, with the same protecting group, Boc, on substrate **2-37c** and **2-38**, the C-H insertion occurred more readily with substrate **2-38**. This result indicated that the N-methyl alkyl amines are less reactive than N-methylbenzyl amine.

Substrate	Nitrogen Protecting Group	Relative Rate
2-37a	-COOEt	1.34
2-38	Boc-N-methylbenzyl amine	1
2-37b	Boc	0.8
2-37c	Cbz	0.75
2-37d	Fmoc	0.1

Table 11 Relative Rate of C-H Insertion Adjacent to Nitrogen

The data in Table 10 and Table 11 are useful as they provide an insight into the possibility of achieving regioselective C-H insertion when there are two reactive sites available within the same molecule; however, those two sets of data standing alone does not provide enough information. Therefore, to get a logical relationship between those two sets of data, a competition reaction was performed to determine the relative rate of C-H insertion at methyl site of silyl ethers and methylene site adjacent to nitrogen (Scheme 40).



Scheme 40 Relative Rate of 2-41 and 2-38

From the crude ^{1}H-NMR of this reaction, it was concluded that the relative rate of **2-38** is 8 times the rate of **2-41**. Therefore, the reported relative rate of C-H insertion into silyl ethers can be normalized. With all the data in hand, a combined table of relative rate for C-H insertion at either methyl site or methylene site was calculated (Table 12). The result of this rate competition reaction demonstrated that C-H activation at the methyl site adjacent to nitrogen occurs more readily than the C-H activation at the methylene site adjacent to oxygen.

Substrate	Protecting Group	Relative Rate
CH_3-N-PG	COOEt	10.72
CH_2-O-PG	TMS	7.28
CH_3-N-PG	Boc	6.4
CH_3-N-PG	Cbz	6
CH_2-O-PG	TES	2.78
CH_2-O-PG	TBS	1
CH_3-N-PG	Fmoc	0.8
CH_2-O-PG	TIPS	0.12
CH_2-O-PG	TBDPS	0.07

Table 12 Combined Relative Rate

2.7 Conclusion

The catalytic chemoselective asymmetric intermolecular C-H activation of protected amino alcohols has been demonstrated to be a practical reaction. With different protecting groups on either nitrogen or oxygen, one can achieve regio-specific asymmetric C-H insertion with respectable yield and enantioselectivity.

The relative rate study showed a general trend that the C-H insertion occurs more readily adjacent to nitrogen than oxygen, which is consistent with prior studies in the field. With the quantified relative rate, the choice of protecting groups would become an easier task when regio-specific C-H activation of amino alcohols is desired.

Although no specific natural product targets were synthesized using this methodology in the work presented herein, the opportunity for such a synthesis in the future has been made available by these studies on the scope and limitations of the regio-specific catalytic asymmetric C-H insertion with amino alcohols.

Chapter 3. Novel Class of Cyclopropylaminocarboxylic Acid for Parkinson's Disease Treatment

3.1 Introduction of Parkinson's Disease

Idiopathic Parkinson's disease (PD) is the second most common neurodegenerative disorder and is characterized by a preferential loss of dopamine neurons.[77] Typical clinical symptoms of PD include resting tremor, rigidity, bradykinesia, and unsteady gait. The prevalence of PD increases with age and there is a greater than 40-fold increase in prevalence between the ages of 55 and 85.[78] Although the exact cause of PD is unknown, epidemiologic studies indicate that a number of factors may increase the possibility of developing PD. It has been suggested that environmental toxicants, such as pesticides, herbicides, and wood pulp mills contribute to the pathogenesis of PD.[79] Exogenous toxins have also been identified for the onset of parkinsonism, including trace metals, organic solvents, carbon monoxide, etc. Even though no specific toxin has been found in the brain of PD patients, the most compelling evidence for an environmental factor in PD relates to the toxin 1,2,3,6-methyl-phenyl-tetrahydropyridine (MPTP). Exposure of humans to MPTP causes a syndrome that mimics the core neurological symptoms and relatively selective dopaminergic neurodegeneration of PD, and MPTP toxicity in mice is the most commonly studied animal model of PD. So far, studies have focused on three types of cellular dysfunction that may be important in the pathogenesis of PD: oxidative stress, mitochondrial defect, and abnormal protein aggregation (Lewy Body).

3.1.1 Oxidative Stress

Oxidative stress represents the disturbances in the normal redox state of cells (Figure 17, adapted from ref. 74). The imbalance in the cell can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA.[80]

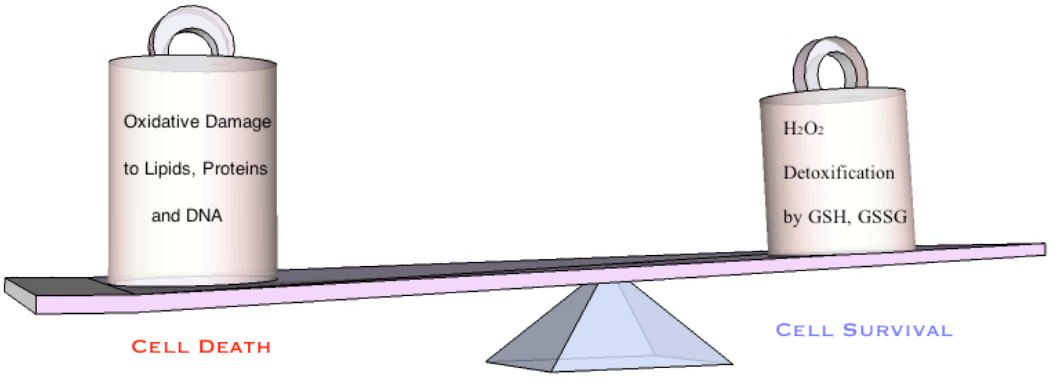
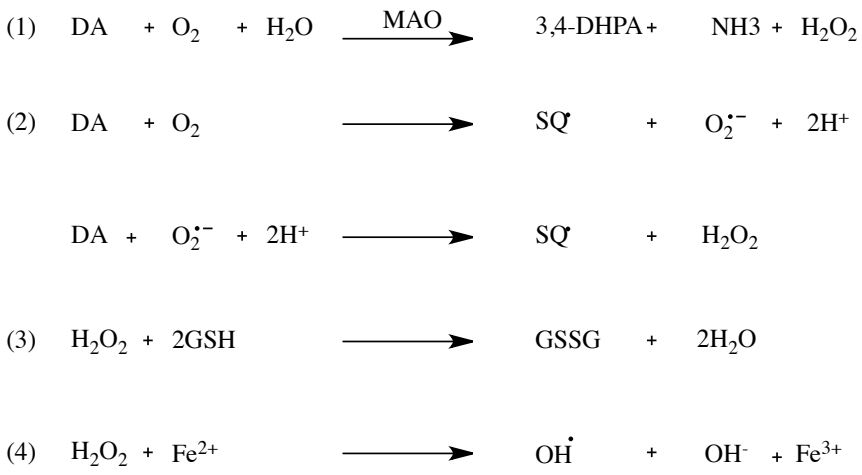


Figure 17 Oxidative Stress

Oxidative stress has been considered as one of the major causes for PD because the oxidative metabolism of dopamine yields hydrogen peroxide and other reactive oxygen species.[81] Scheme 40 demonstrated how oxidative stress forms in a cell. Dopamine breakdown can occur either instantly in the presence of iron, or can be catalyzed by monoamine oxidase (MAO). Both the chemical and the enzymatic metabolism of dopamine (DA) result in the formation of hydrogen peroxide (H_2O_2) (Scheme 41, Equation 1 and 2).[82] Metabolism of DA leads to the formation of several cytotoxic molecules, including superoxide anions ($O^{\bullet -}$), dopamine–quinone species ($SQ^{\bullet}$) and hydroxyl radicals ($OH^{\bullet}$).[83] H_2O_2 is normally cleared by reduced glutathione (GSH) (Scheme 41, Equation 3).[84] However, an increase in the constant concentration of H_2O_2

can lead to the Fenton reaction that generates highly reactive and potentially cytotoxic hydroxyl radical ($OH^{\bullet}$).[85] In normal cells, these cytotoxic species are scavenged through several antioxidant systems. For instance, oxidized glutathione (GSSG) can be reduced by GSSG reductase and therefore, can be reused in the next cycle of H_2O_2 detoxification. Superoxide dismutase converts superoxide to hydrogen peroxide, which in turn is converted to molecular oxygen and water by catalase. In Parkinson's disease, however, an abnormal increase in the production of reactive oxygen species disturbs the balance between production and elimination, leading to enhanced oxidative stress.[86]



Scheme 41 Metabolism of DA

3.1.2 Mitochondrial Defect

There has been an extensive investigation for a mutation in the mitochondrial genome, based on the finding of a defect in mitochondrial complex I in the *Substantia Nigra Pars Compacta* (SNc) of PD patients.[87,88] Complex I is composed of 41 subunits, 7 of which are encoded by mitochondrial DNA (mtDNA).[89] MtDNA is a double-stranded circular genome that is approximately 16.5 kb in length. The rest of the genome is entirely transcribed except for a 1kb noncoding region.[90] MtDNA can be replicated independently of the cell cycle and independent of replication of the nuclear genome. MtDNA contains 37 genes that encode for 13 proteins, 22 tRNAs, and 2 rRNAs, which are required for intramitochondrial protein synthesis.[91] Mitochondrial DNA is much more likely to undergo mutation than nuclear DNA. In a recent study, a complex I defect was found in cybrids carrying mtDNA derived from PD platelets.[71] The result of the study indicates the presence of a defect in the mitochondrial genome, which could be an inherited mutation or the result of a toxic insult, possibly secondary to oxidant stress.

Although no clear evidence has shown that mtDNA mutation is the direct cause of PD, there is some evidence that certain mitochondrial haplogroups influence either prevalence or manifestation of PD.[92] It is proposed that somatic mtDNA mutations occur as a result of oxidative stress within cells and, once formed, these often clonally expand.[93] If this is the case, then cells that are affected by PD are more likely to have mtDNA mutations as a result of the ongoing oxidative stress within these cells. Thus, the mtDNA mutations are secondary to the primary disease process but, once clonally expanded to high levels, can contribute to neuronal cell death similar to that seen in primary mitochondrial diseases.

Figure 18 (Adapted from ref. 88) demonstrated how mtDNA deletions from patients with mitochondrial disease and patients with PD could lead to mitochondrial dysfunction and ultimately neurodegeneration, especially within the substantia nigra.[94]

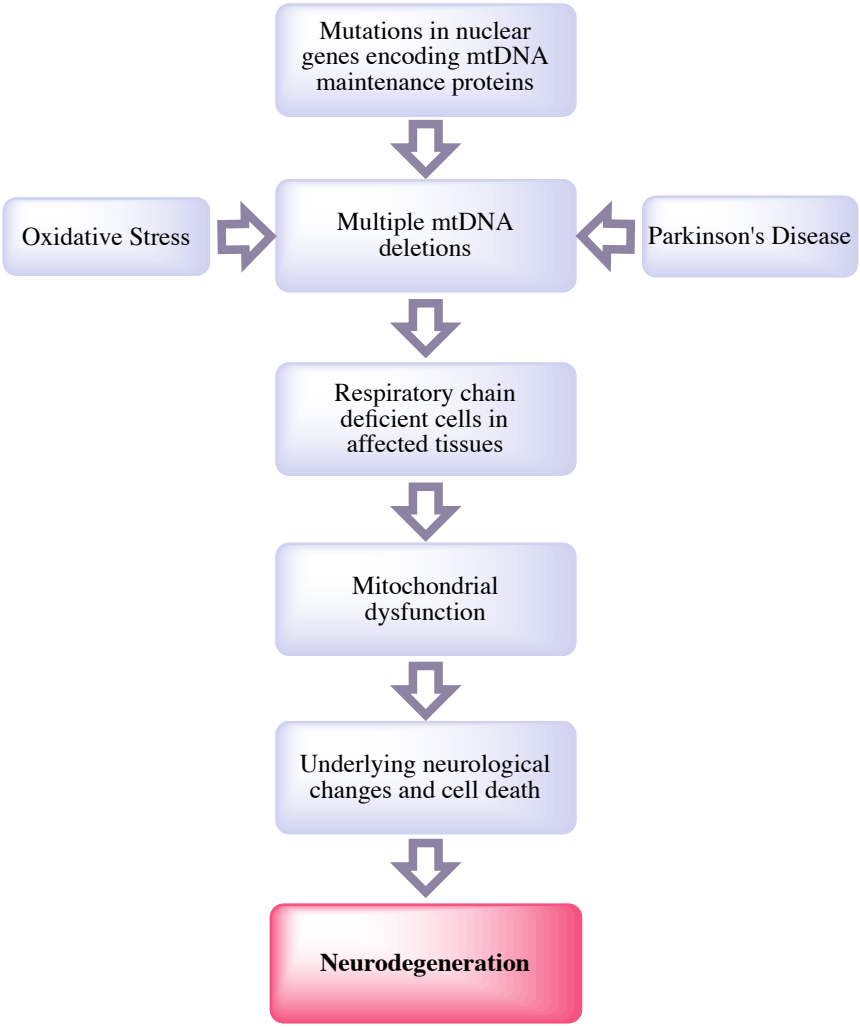


Figure 18 Mitochondrial Deletion Leading to Neurodegeneration

3.1.3 Abnormal Protein Aggregation (Lewy Body)

A common pathological stamp of Parkinson's disease is the Lewy body, a rounded intracytoplasmic neuronal inclusion that is found in the brain cell, most notably in the substantia nigra.[95] Lewy bodies can also be found in the normal ageing brain and the in the brains of patients with other neurodegenerative diseases. A classical Lewy body consists of an electron-dense core surrounded by a halo of 10-nm wide radiating fibrils, the primary structural component of which is α-synuclein. [96]

In PD patients, it is possible that various factors can trigger a cascade of events that lead to an elevated dopamine level in cytoplasm. Misfolding or loss of normal function of α-synuclein in dopaminergic neurons promotes an elevation of cytoplasmic dopamine, which in turn gives rise to reactive oxygen species and causes oxidative stress.[97] As illustrated in Figure 19 (Adapted from ref. 91), mutations in α-synuclein promote a positive feedback loop that eventually leads to neurodegeneration. The terms highlighted in green represent deleterious processes that are part of this vicious cycle leading to cell death (red arrows).

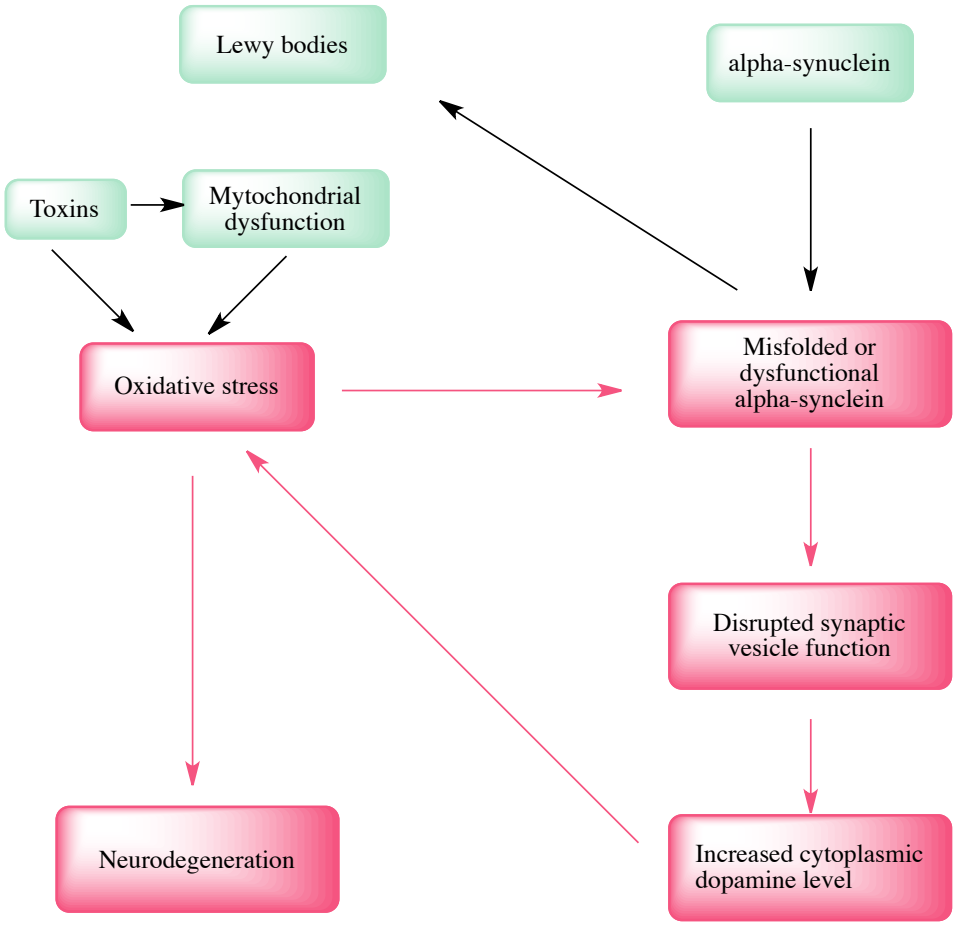


Figure 19 Neurodegeneration Vicious Cycle

Even though different factors might underlie sporadic and familial forms of Parkinson's disease, these different pathways might all result in the accumulation of dopamine in the cytoplasm. Given the high tendency of dopamine to oxidize when not stored in synaptic vesicles, elevations in cytoplasmic dopamine could lead to enhanced oxidative stress and neurodegeneration.[98]Although it is hard to pin point one single cause for the idiopathic PD, it provides numerous opportunities for developing new drugs that target different stages of the cycle, with a common goal of suppressing oxidative stress, which directly leads to neurodegeneration.

3.2 VMAT2 and PD

Monoamine neurotransmission constitutes several critical steps in the synaptic area of the neuron including (1) biosynthesis of transmitters from precursors in the cytosol and active accumulation into synaptic vesicles through a proton gradient driven uptake system; [99] (2) continued biosynthetic transformations within the synaptic vesicles depending on the nature of the transmitter followed by exocytotic release from the synaptic vesicles into the synaptic cleft in response to physiological stimuli;[100] (3) interaction of the transmitter with their target receptor or protein on the postsynaptic membrane, thereby mediating signal transduction; (4) dissociation from the receptor or protein followed by reuptake into the presynaptic terminal or surrounding glia cells through Na^+ and Cl^- driven plasma membrane transporters or inactivation by specific monoamine metabolizing enzymes.[101] Thus, efficient reuptake of the transmitter from the synaptic cleft through plasma membrane monoamine transporters, followed by reaccumulation into synaptic vesicles through the vesicular monoamine transporters (VMATs), constitutes crucial steps of monoamine neurotransmission.[102,103]

Two closely related vesicular monoamine transporters, VMAT1 and VMAT2, have been cloned, expressed, and characterized. [104, 105] In humans, VMAT1 is preferentially expressed in large dense core vesicles of various neuroendocrine cells.[106] VMAT2 is primarily expressed in multiple monoaminergic cells in the brain, sympathetic nervous system, mast cells, and histamine containing cells in the gut. [107] Although the crystallographic structures are not resolved, the sequence analyses of these and related proteins suggest that they are transmembrane proteins with 12 transmembrane domains (TMDs) similar to plasma membrane monoamine transporters.[108]

VMAT is solely responsible for the transport of cytoplasmic monoamines into synaptic vesicles for storage and subsequent exocytotic release in the central nervous system.[109] The cytosolic accumulation of catecholamines could cause increased oxidative stress and oxidative damage to the catecholaminegic system, potentially leading to neurodegenerative diseases. [110] Therefore, pharmacological enhancement of catecholamine sequestration into synaptic vesicles by VMAT2 could be a possible strategy for treating and/or preventing neurodegenerative diseases, such as PD.[111] Agents that reduced the dopaminergic neurotransmission have been shown to lessen chorea associated with Huntington disease patients.[112] Neuroleptics, such as haloperidol, have long been used for this purpose, but are associated with extrapyramidal side effects. Tetrabenazine (TBZ) has also been long used for the treatment of chorea associated with Huntington disease in the United Kingdom, Canada, and Australia1,[113] and has been recently approved in the United States.[114] Although the precise mechanism of the antichorea effects of TBZ is not clear, its ability to inhibit the VMAT2 resulting in the depletion of monoamines in the nerve terminals have been considered as a possibility.[115]

A recent positron emission tomography (PET) study of low-dose MPTP non-human primate model of PD revealed that the loss of VMAT2 function is associated with an accumulation of cytosolic monoamines, reduction in vesicular sequestration of monoamines, and depletion of striatal monoamines.[116] It is hypothesized that VMAT2, together with the dopamine transporter (DAT), may be able to modulate susceptibility to neurodegeneration.[117] There has been much speculation about the role of VMAT2 in mediating efficient clearance of DA in those populations vulnerable to neurodegeneration.[118]

α-synuclein, the key component of Lewy bodies has been found to bind and penetrate vesicles, which is the potential cause of leakage of monoamines into the cytosol.[119] It was reported that overexpression of α-synuclein can cause the downregulation of VMAT2 protein *in vitro,* which in turn will upregulate cytosolic DA and ROS.[120] Therefore, it can be concluded that the perturbation of VMAT2 can create an environment conducive to PD-related neurodegeneration. A schematic diagram of DA synthesis and proposed function of VMAT2 is shown in figure 20.[121] Cytoplasmic dopamine is synthesized in the nerve terminals of DA neurons. Tyrosine is first converted to l-3,4-dihydroxyphenylalanine (L-DOPA) by tyrosine hydroxylase (TH), which is then decarboxylated by aromatic amino acid decarboxylase (AADC) to generate DA within the cytoplasm.[122] Right after DA is synthesized, VMAT2 transports the synthesized DA into the pre-synaptic vesicles, which later delivers DA to synaptic junction by exocytosis.[123] Following the release of DA into the synaptic cleft, DA then interacts with pre- and post-synaptic DA receptors. Termination of neurotransmission is accomplished via the metabolism of extracellular DA by catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) to homovanillic acid (HVA). The extracellular DA is also transported back into the pre-synaptic terminal by the DA transporter (DAT). DA is then recycled into the pre-synaptic vesicles, or undergoes metabolism by intracellular MAO to 3,4-dihydroxyphenylacetic acid (DOPAC). The latter diffuses out of the cell and is further metabolized by COMT to HVA.

3.3 Current Treatment for PD

L-DOPA is a chemical that is made inside our human bodies via biosynthesis through tyrosine.[124] Since its discovery in the 1960s, dopamine replacement therapy with L-DOPA has long been the first treatment for PD. For many patients, L-DOPA therapy successfully relieves symptoms for several years following the initial diagnosis.[125] However, prolonged use of L-DOPA leads to debilitating condition called L-DOPA-induced dyskinesia (LID), which occurs in nearly 90% of patients with PD within a decade.[126] Furthermore, current dopaminergic therapies do not seem to alter the underlying progression of PD such that disease-modifying therapies are still a major medical unmet need.[127] This is also true for effective therapies to treat the many nonmotor symptoms of PD for which there are currently only few interventions with established efficacy through randomized controlled trials.[128]

Converging evidence from experimental and clinical studies suggests that discontinuous drug delivery is a major factor for the development of LID.[129] Several new approaches to improve dopaminergic drug delivery have reached an advanced stage of clinical development. A novel formulation of infusible L-DOPA (Trade name: Duodopa®) has been developed in which the drug is embedded in a carboxymethylcellulose gel providing a concentration of L-DOPA/carbidopa of 2/0.5 g in only 100 ml.[130] Several clinical studies have consistently reported remarkable reductions in severity of preexisting LID when such infusion systems were used in PD patients.[131,132] Currently available extended-release formulations of L-DPOA use pharmacokinetic principles have limited efficacy. IPX066 is a novel levodopa/carbidopa extended-release oral formulation.[133] A phase II

trial in 27 patients with fluctuating PD showed significantly longer duration of action from a single dose of IPX066 as compared with standard levodopa/carbidopa.[134]

Apomorphine is the only dopamine agonist with similar effect size on the motor symptoms of Parkinson's disease as the gold standard drug L-DOPA. It is also the first of its class for which a dry powder formulation has been developed that can be delivered via oral inhalation. Drug inhalation provides ultrarapid access to the systemic circulation via the lung's large alveolar surface. This novel drug delivery approach proved a practically important therapeutic advance provided long-term pulmonary safety.[135]

Tianeptine (Figure 20) is a new effective antidepressant drug. However, its neurochemical profile in animals differs from that of tricyclic antidepressants. Until recently, it has been assumed that Tianeptine is a selective serotonin reuptake enhancer (SSRE), opposite to the action of SSRIs.[136] Tianeptine has also been found to be effective in depression in Parkinson's disease.[137] Therefore, it will be interesting to make a series of Tianeptine analogs and test them in the treatment in Parkinson's disease.

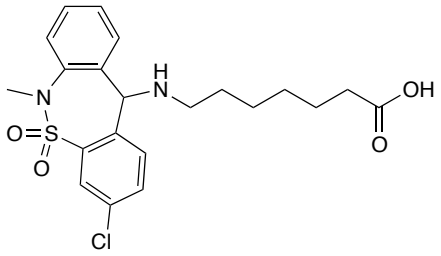
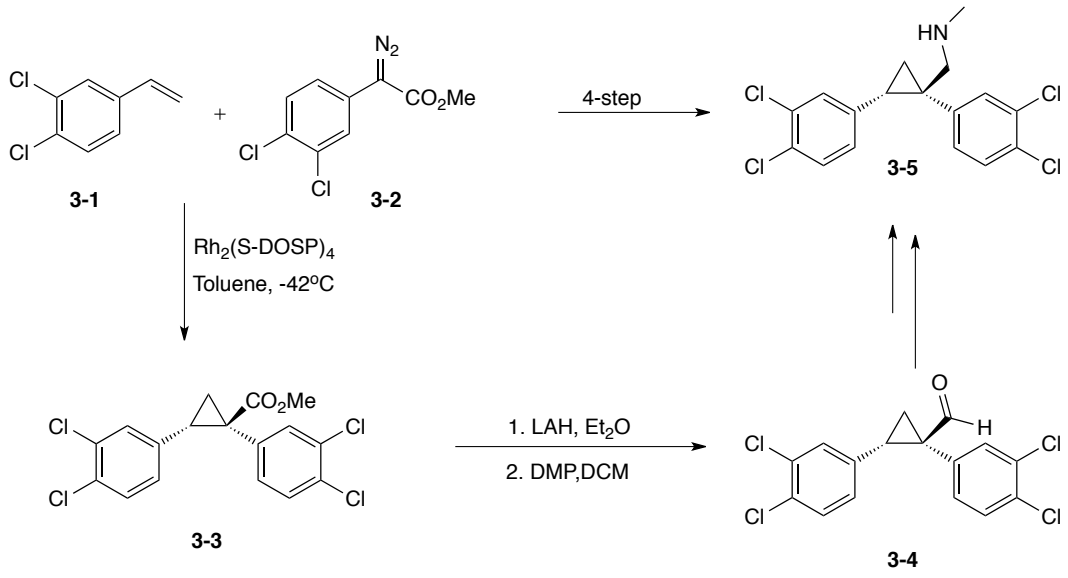


Figure 20 Tianeptine

3.4 Drug Development for Treating PD

Previously the Davies group had developed a concise synthetic route for making diaryl cyclopropylamines and the biological evaluation of diaryl cyclopropylamines targeting the serotonin 5-HT_{2A} receptor was carried out (Scheme 42, Dr. Spandan Chennamadhavuni's thesis work).



Scheme 42 Synthesis of Diaryl Cyclopropylamines

These compounds were then tested through the NIDA Addiction Treatment Discovery Program and it was discovered that these compounds were active at the neurotransmitters (SET, NET, and DAT) and at the 5-HT_{2A} receptor. Two compounds in particular showed very promising results at the 5-HT_{2A} receptor (Figure 21).

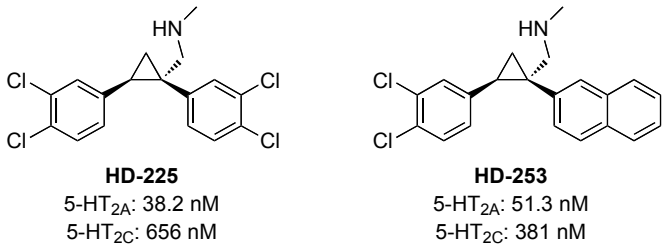


Figure 21 Potent 5HT Compounds

Inspired by the potency of HD-225 and the structural similarity of the diaryl cyclopropylamine to the pharmacophore of Tianaptine, the design, synthesis, and biological evaluation of novel diaryl cyclopropylamino carboxylate derivatives targeting the VMAT2 reactivity were carried out.

The initial design of this array of analogs was to synthesize cyclopropylaminocarboxylic acids with different numbers of the carbon chain. At the same time, monoaryl cyclopropylamino carboxylic acids were also set as targets since the number of the aryl groups in the molecule plays a role as well. Therefore, to see how the number of the carbon chain and aryl groups influences the biological activity, the following targets were set (Figure 22). As the stereochemistry of the analog has an important role in the biological activity, both enantiomers of the two different series need to be synthesized.

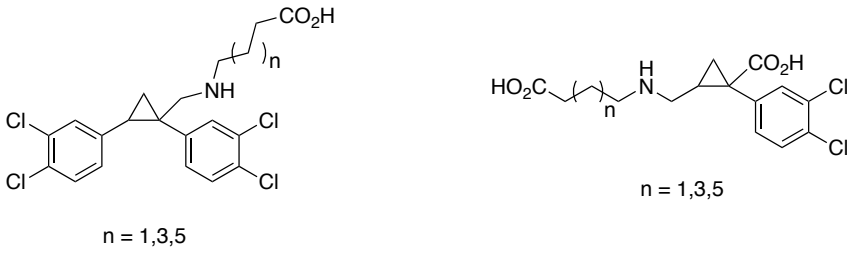
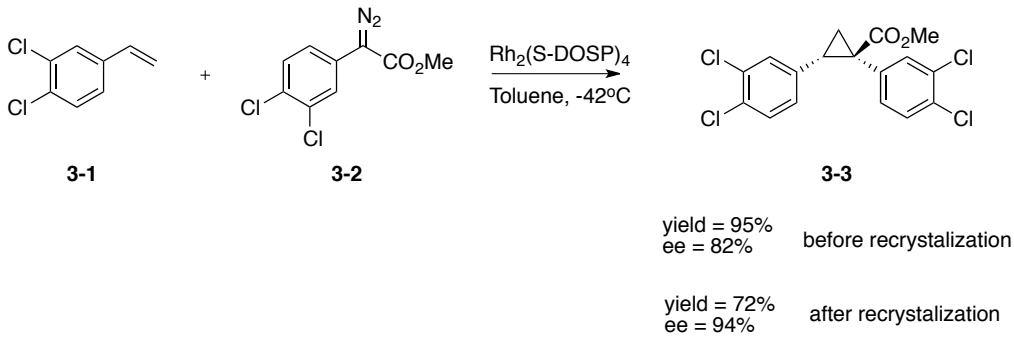


Figure 22 Targets for The Synthesis

The synthesis started with the protocol that was developed in the Davies group. The cyclopropanation between 3,4-dichlorostyrene (**3-1**) and 3,4-dichlorophenyldiazoacetate

(**3-2**) gave desired product (**3-3**) in 95% yield and 89% ee. After recrystallization, the ee value was increased to 94% (Scheme 43).

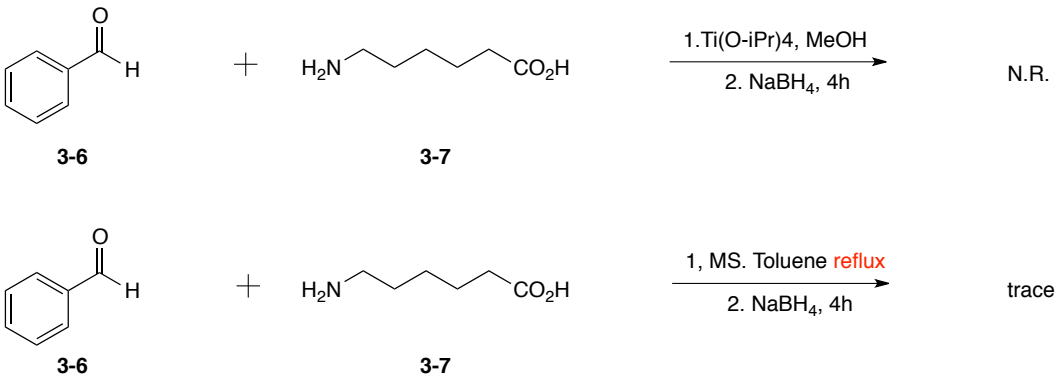


Scheme 43 Cyclopropanation As The First Step

Reduction with LAH in dry ether, followed by oxidation using DMP gave the aldehyde (**3-4**) smoothly in 74 % yield over 2 steps (Scheme 44).

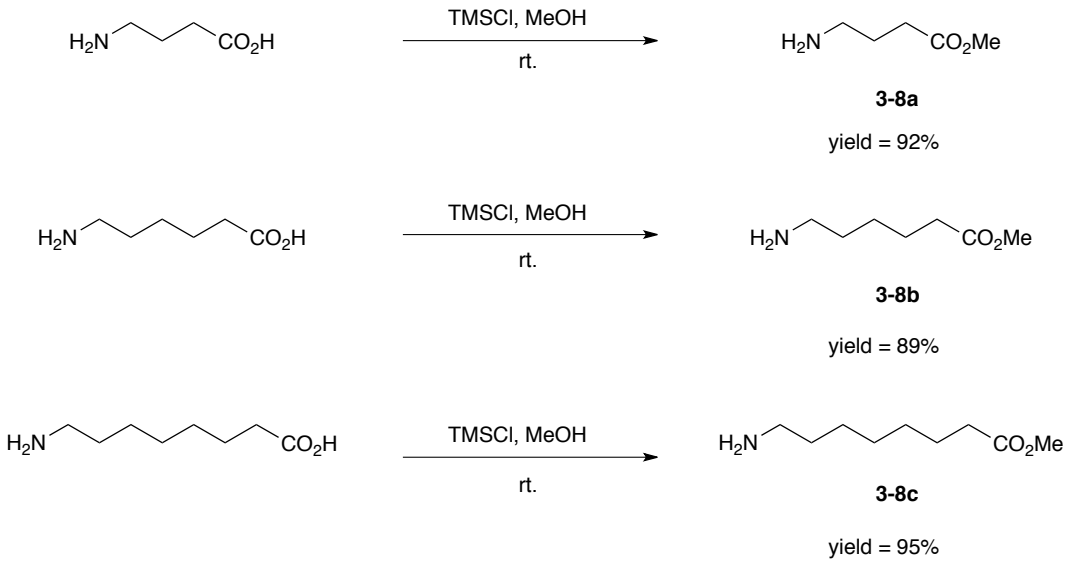
Scheme 44 Reduction Followed by Oxidation

According to the standard protocol, the next step is the reductive amination. Unfortunately, first attempt with the aldehyde and the amino alcohol was unsuccessful and the reaction did not proceed. To understand the issue in this transformation, a series of test reactions were carried out with benzaldehyde (**3-6**) and **3-7** under various conditions (Scheme 45).



Scheme 45 Test Reactions

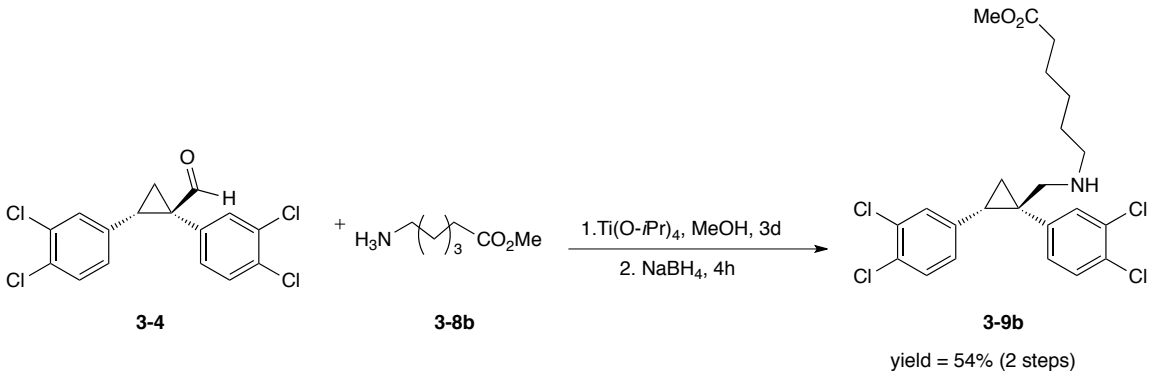
Neither test reactions gave the desired product because the aminocaproic acid (**3-7**) was not soluble in either solvent. Therefore, to circumvent the solubility issue, amino alcohols were converted to their amino ester counterparts (Scheme 46).



Scheme 46 Converting Amino Acids to Amino Esters

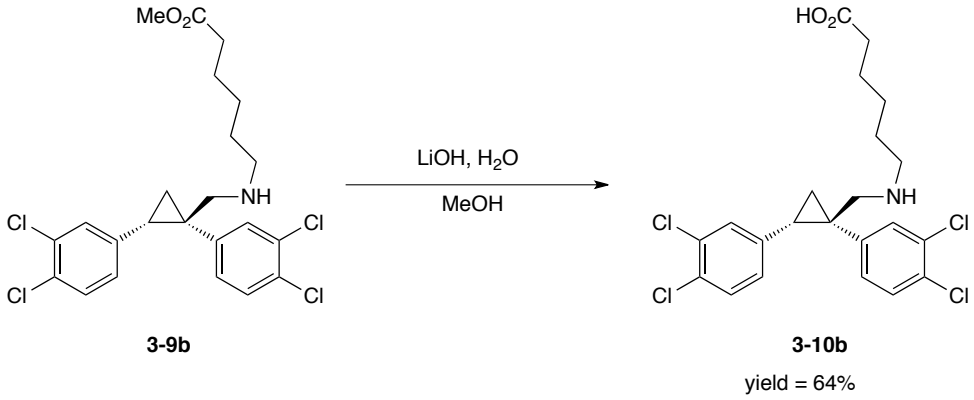
After the amino alcohols were converted to the amino ester, reductive amination was attempted again. The ester group increased the solubility of the molecule, and; therefore, the desired imine was formed after 3 days of reaction time according to the crude ^{1}H-

NMR. Reduction with $NaBH_4$ afforded the desired amino carboxylic ester **3-12** (Scheme 47).



Scheme 47 Synthesis of 3-9b

Since the biological screening of these samples occurs in the cell, carboxylic ester **3-9b** was then hydrolyzed, following a literature precedent, to its acid form to increase solubility (Scheme 48).[138]



Scheme 48 Hydrolysis of 3-9b

With the success of the synthesis of **3-10b**, this reaction sequence was used as the protocol for the synthesis of all other candidates in the series. **3-10a** to **3-10c** together with their enantiomers ***ent*-3-10a** to ***ent* 3-10c** were all obtained in moderate to good yields and were submitted for biological testing (Figure 23).

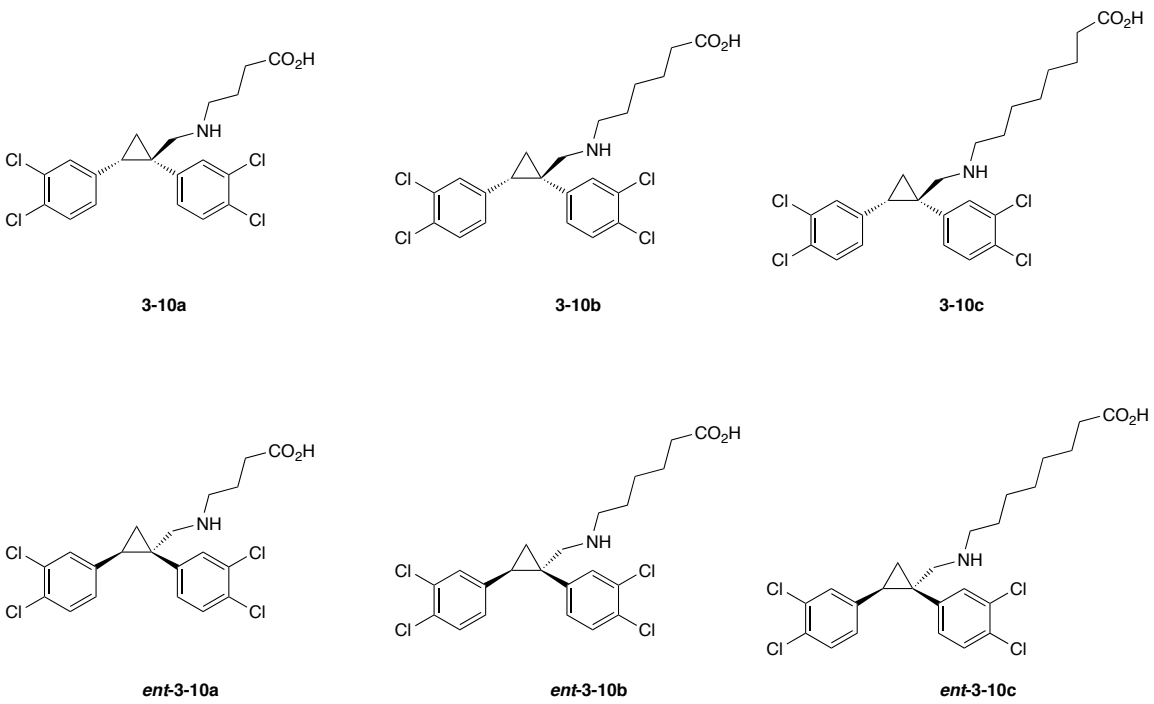
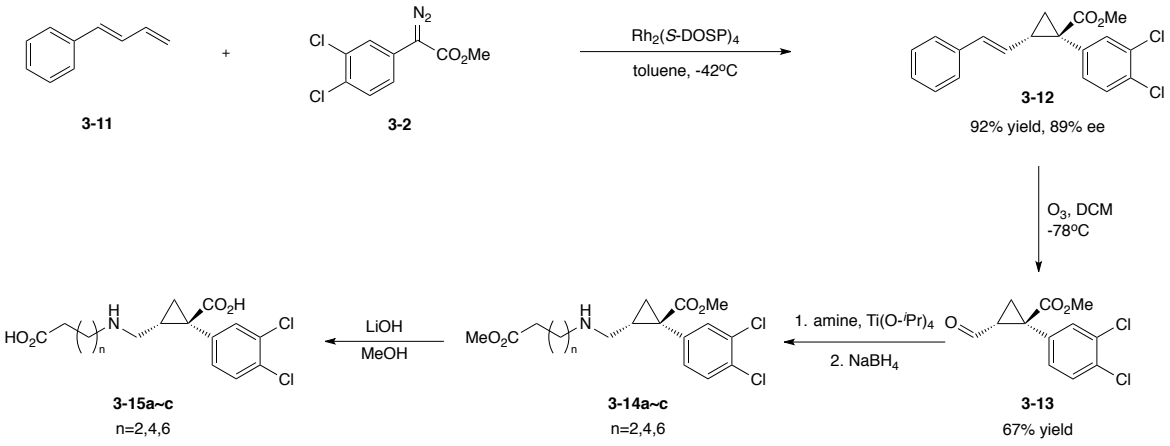


Figure 23 List of Final Compounds

To test the hypothesis that the presence of aromatic rings in the molecule affects the potency of the drug, the synthesis of a series of mono-aryl cyclopropylamines was pursued. Scheme 49 demonstrated the typical sequence of the synthesis of mono-arylcyclopropylamines **3-15a~c**.



Scheme 49 Synthesis of Monoarylcyclopropylamines

Cyclopropanation of phenyl butadiene with 3,4-dichlorophenyl diazoacetates (**3-2**) using Rh_2(*S*-DOSP)$_4$ proceeded smoothly under standard condition to give cyclopropanated product (**3-12**) in high yield and ee. Ozonolysis of the vinyl cyclopropane (**3-12**) gave rise to the cyclopropyl aldehyde (**3-13**), which is unstable at room temperature, and was purified and subjected to the following reaction immediately. Treating the cyclopropyl aldehyde with the corresponding amino ester (**3-8a~c**) yielded the desired aminated product after reduction with $NaBH_4$. After hydrolysis with LiOH in methanol, amino carboxylic acids **3-15a~c** were obtained as off-white solid. The enantiomers of **3-15a~c** were prepared by the same protocol, and compound **3-15a~c** together with their enantiomers ***ent*-3-15a~c** were submitted to Gary Miller's laboratory for *in vitro* screening (Figure 24).

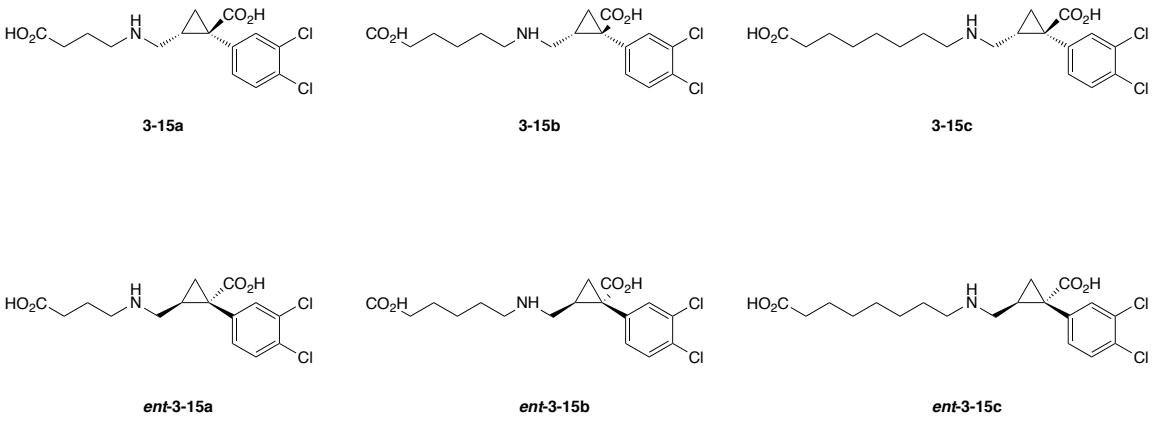


Figure 24 Monoaryl Cyclopropyl Carboxylic Acids

3.5 *In Vitro* Data from Dr. Gary Miller's Laboratory

The *in vitro* data was provided by Kristen Stout from Gary Miller's laboratory. Each compound was screened first via a whole cell radioactive uptake assay. This assay is relatively medium throughput, allowing 8 to 16 chemicals to be screened in a day. From the data this assay provides, compounds that are likely acting on the dopamine transporter were then eliminated from further screening. Compounds that are potentially acting on VMAT2 were further analyzed by vesicular uptake to determine the potency.

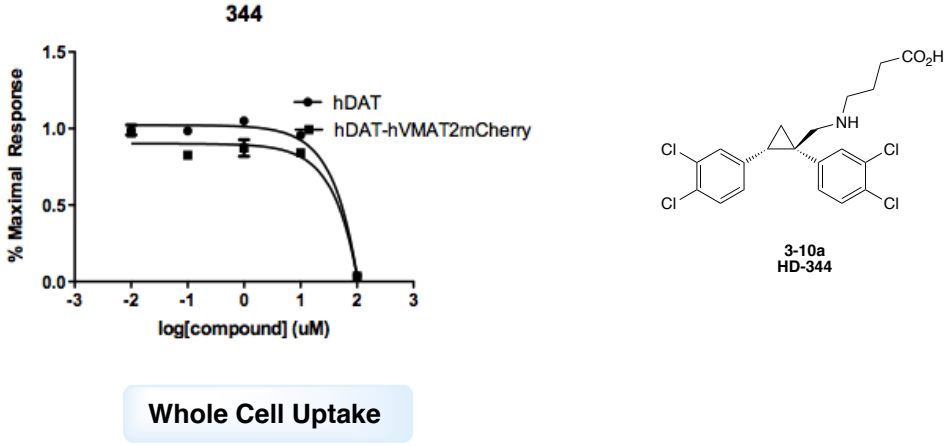
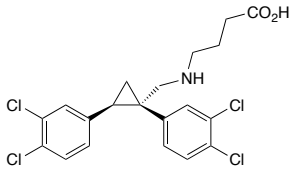


Figure 25 *In Vitro* Data for 3-10a

	IC_{50} Whole Cell	r^2	IC_{50} DAT	r^2
Whole Cell Uptake	~177704	0.9734	~429243	0.9916
Whole Cell Uptake-EC20	21.01	0.9258	6.341	0.9711

According to the model presented in Figure 25, **3-10a** behaves as an inhibitor on DAT and has no effect on VMAT2. As can be seen from the diagram, the curve of hDAT-hVMAT2 matches well with the curve generated from hDAT experimental data. Therefore, compound **3-10a** is not of interest in this study.



ent-3-10a
HD-347

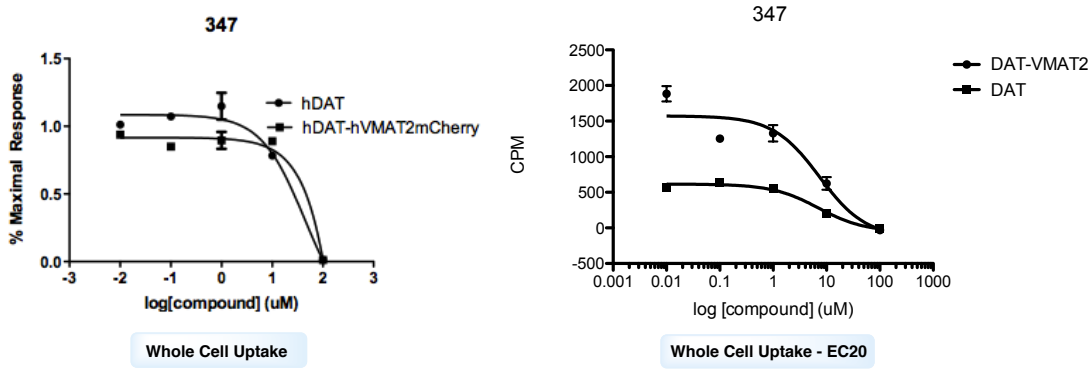


Figure 26 *In Vitro* Data for *ent*-3-10a

	IC_{50} Whole Cell	r^2	IC_{50} DAT	r^2
Whole Cell Uptake	~479213	0.9782	43.82	0.9705
Whole Cell Uptake-EC20	7.372	0.899	7.074	0.9887

The Whole Cell Uptake data obtained with the original method gave curves with two different patterns. With the hope of ***ent*-3-10a** could be VMAT2 enhancer, the experiment was repeated with a different analysis method, the Whole Cell Uptake - EC20 method (Figure 26). Unfortunately, the result of this experiment showed that ***ent*-3-10a** was an inhibitor for both DAT and VMAT2.

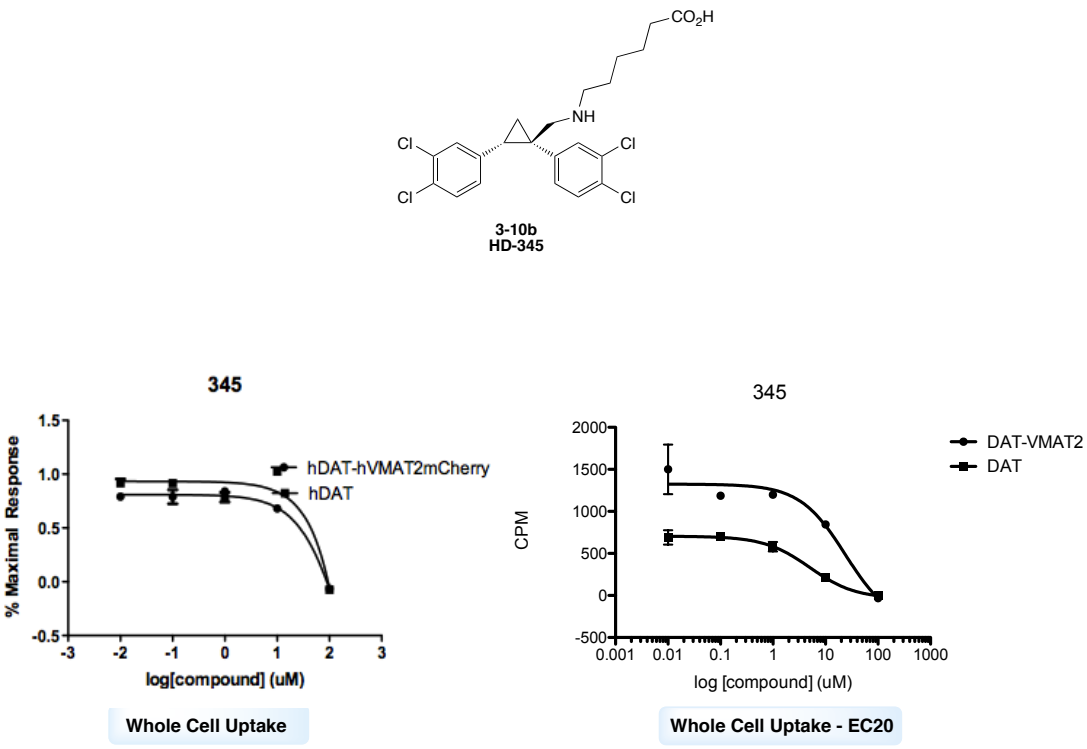


Figure 27 *In Vitro* Data for 3-10b

	IC_{50} Whole Cell	r^2	IC_{50} DAT	r^2
Whole Cell Uptake	210.3	0.9871	Ambiguous	-
Whole Cell Uptake-EC20	23.99	0.9046	5.025	0.9716

From the data, it can be concluded that compound **3-10b** behaves as a DAT, VMAT2 inhibitor just like **3-10a**. Therefore, at this point, it was not particularly interesting towards the goal of the project. The *in vitro* data of all the compounds that were submitted for testing is shown below. Unfortunately, none of the compounds stood out as being potentially useful in enhancing VMAT2 function (Figure 27 to Figure 29).

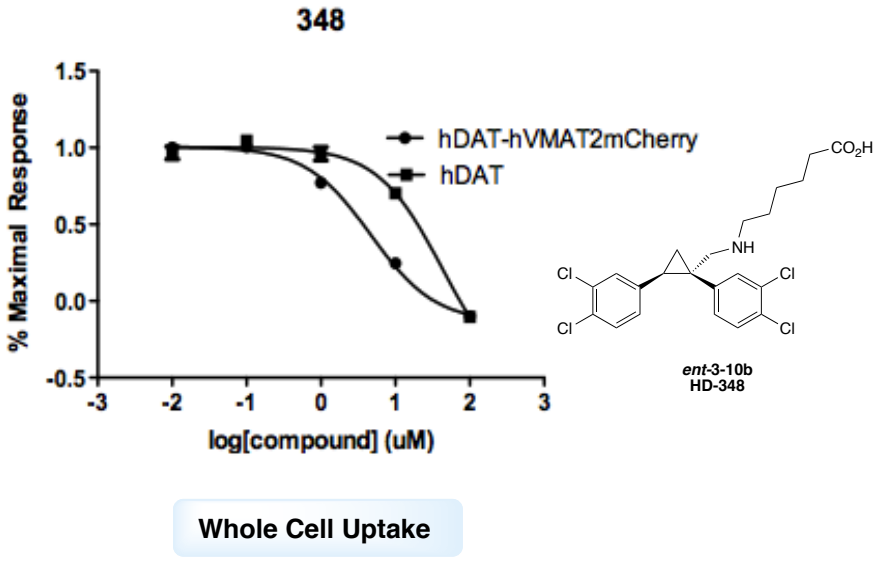


Figure 28 *In Vitro* Data for *ent*-3-10b

	IC_{50} Whole Cell	r^2	IC_{50} DAT	r^2
Whole Cell Uptake	4.644	0.996	43.32	0.9918

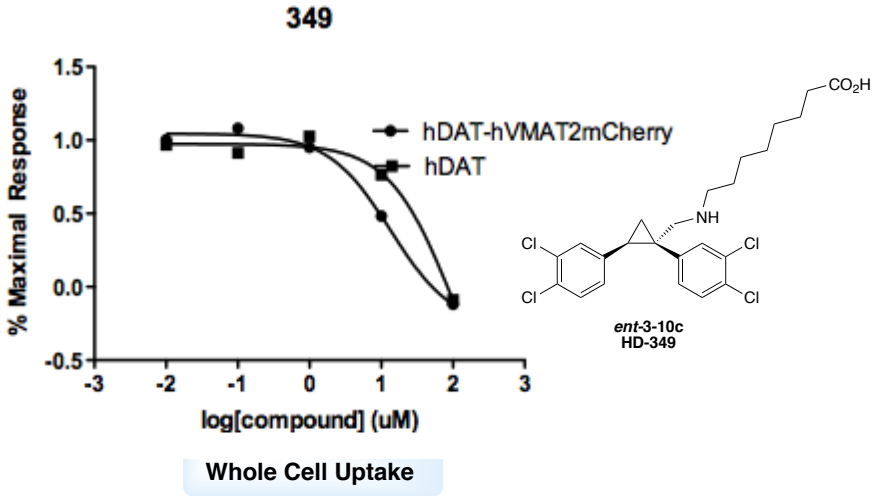
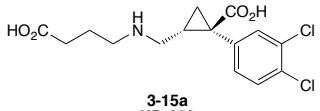


Figure 29 *In Vitro* Data for *ent*-3-10c

	IC_{50} Whole Cell	r^2	IC_{50} DAT	r^2
Whole Cell Uptake	13.47	0.9936	91.9	0.9889



3-15a
HD-350

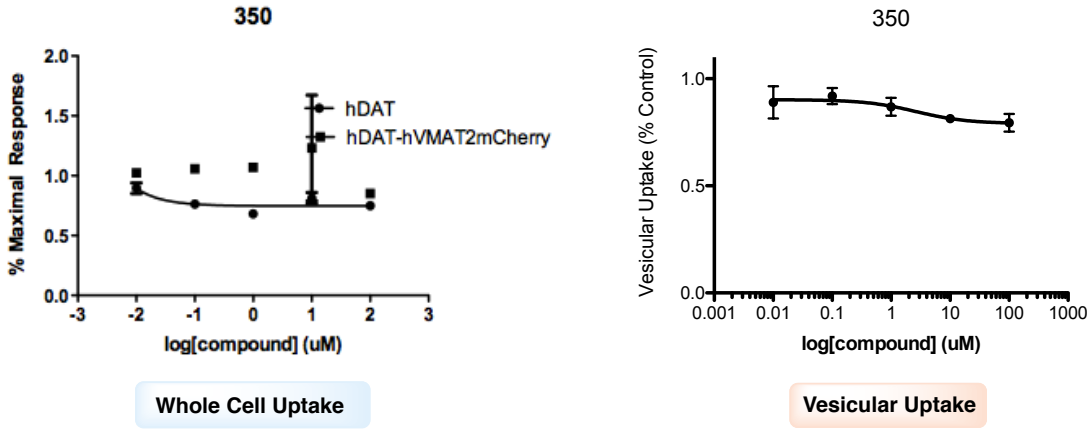
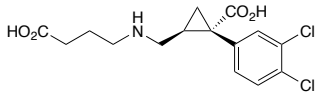


Figure 30 *In Vitro* Data for 3-15a

	IC_{50}	r^2	IC_{50} DAT	r^2
Whole Cell Uptake	Not Converged	-	-	-
Vesicular Uptake	2.66 (VMAT2)	0.3202	-	-

The Whole Cell Uptake data for compound **3-15a** was not converged (Figure 30). To understand the role of compound **3-15a**, a Vesicular Uptake screening reaction was carried out and a curve was generated corresponding to the data. Judging by the shape of the curve obtained through the Vesicular Uptake assay, it is clear that compound **3-15a** was another VMAT2 inhibitor.



ent-3-15a
HD-353

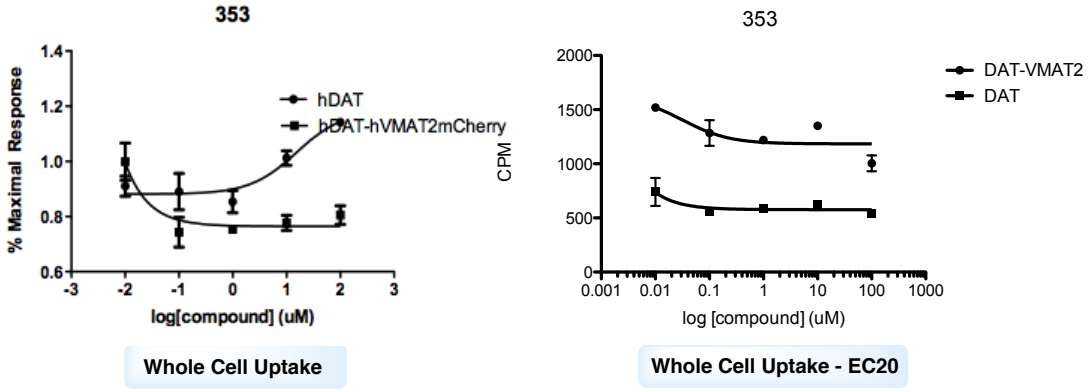
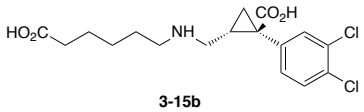


Figure 31 *In Vitro* Data for *ent*-3-15a

	IC_{50} Whole Cell	r^2	IC_{50} DAT	r^2
Whole Cell Uptake	-	-	15.42	0.8194
Whole Cell Uptake-EC20	0.03195	0.5031	Ambiguous	-

The Whole Cell Uptake results for compound ***ent*-3-15a** was initially thought to be intriguing as the hDAT curve showed an enhancing effect of compound ***ent*-3-15a** (Figure 31). However, with a more accurate screening method, Whole Cell Uptake-EC20, it was found that compound ***ent*-3-15a** was an inhibitor like all previous compounds. Compounds **3-10c**, ***ent*-3-15b**, ***ent*-3-15c** were found to be incompatible with the experimental conditions used in the biological testing, and; therefore, no *in vitro* data was provided for these compounds.

The in vitro result of **3-15b** and **3-15c** were shown in Figure 32 and Figure 33, and unfortunately neither of them displayed any VMAT2 enhancing ability.



3-15b
HD-351

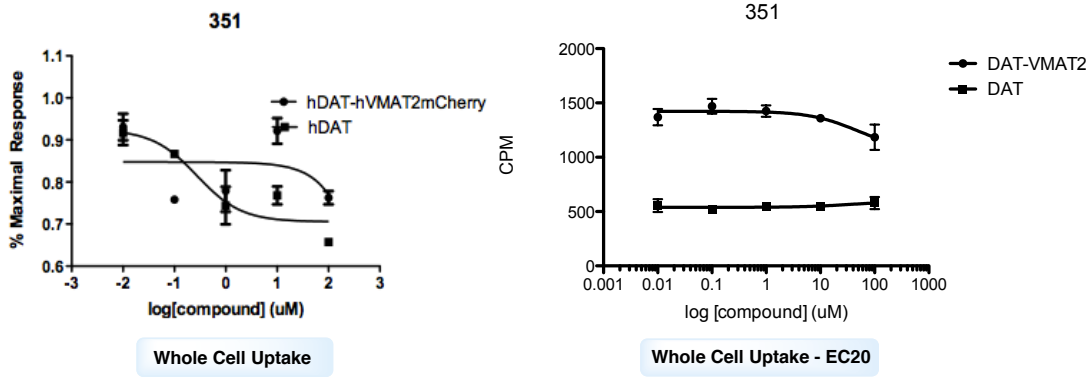
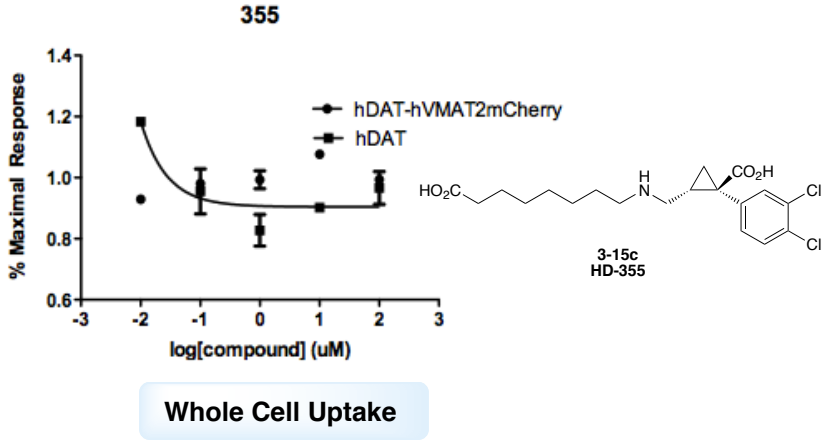


Figure 32 *In Vitro* Data for 3-15b

	IC_{50} Whole Cell	r^2	IC_{50} DAT	r^2
Whole Cell Uptake	-	-	0.2745	0.8015
Whole Cell Uptake-EC20	45.66	0.5673	33.8	0.1181



3-15c
HD-355

Figure 33 *In Vitro* Data for 3-15c

	IC50 Whole Cell	r^2	IC50 DAT	r^2
Whole Cell Uptake	Not Converged	-	Ambiguous	-

3.6 Conclusion

A series of diaryl and monoaryl cyclopropylaminocarboxylic acids were successfully synthesized utilizing Rh_2(*S*-DOSP)$_4$ and Rh_2(*R*-DOSP)$_4$ catalyzed cyclopropanation as the key step. These reaction protocols proved to be effective in constructing pharmaceutically important molecules that contain cyclopropane as one of the core structures.

The *in vitro* data obtained in Dr. Gary Miller's research group showed that the majority of the compounds tested were DAT, VMAT2 inhibitors. Although the inhibitory effect of those compounds was not desirable in the current search for a drug to treat PD, it showed the potential relevance of these compounds in treating Huntington's disease. The application of these compounds has not been established at the moment; however, the successful synthesis of these compounds has made it possible for future studies of their biological activities when an appropriate target comes in sight.

Chapter 4. Combinatorial Approach to The Design and Synthesis of Cyclopropylamines for Neuropathic Pain Treatment

4.1 Introduction

The neuronal circuitry involved in pain processing is composed of a complex equilibrium of pain-signaling and pain-relieving pathways that connect the peripheral nervous system (PNS) and the central nervous system (CNS). The ability of the PNS to sense and perceive pain is an essential protective mechanism that warns against threatened or ongoing tissue damage. Disruption of this protective mechanism by disease, drug, or injury may result in the development of chronic pain.[139] Chronic pain is a major health issue that presents a considerable social and economic burden worldwide. Recent studies and surveys have suggested that up to 30% of adults in the US report suffering from moderate to severe chronic pain.[140] The debilitating nature of the disease drastically influences the quality of life for patients with chronic pain. Depending on the origin of the pain syndrome, it can be classified as either inflammatory or neuropathic pain, with complex syndromes commonly involving aspects of both. [141] Although the exact cause of neuropathic pain is unknown, typical triggers for developing neuropathic pain were thought to be associated with surgery, bone compression in cancer, diabetes, or infection.[142] While inflammatory pain is the result of tissue injury or an invading foreign substance, neuropathic pain develops specifically due to nervous system damage or dysfunction.[143] Due to the complex central and peripheral mechanisms involved in neuropathic pain, the range of therapeutic targets is extensive. Consequently, there have been few drugs specifically approved for the treatment of neuropathic pain.[144] Re-

evaluation of existing therapies for other indications has resulted in a greater number of therapeutic options for symptomatic pain relief. However these drugs are frequently required in high doses, have limited efficacy for this indication, are effective in a small subset of patients and are associated with a range of adverse effects.[145]

Compared to systemic administration of medications, intrathecal (i.t.) administration of the drug has proven to be more effective in many cases, providing greater analgesia while significantly reduces side effects.[146,147] However, undesired side effects that include sedation, cognitive impairment , hypotension, and psychiatric changes occur with i.t. administration of opioids, chlondine, and ziconotide.[139,148] Due to the lack of highly potent non-opioid drugs that are suitable for i.t. administration, new drug development is in great need to meet the clinical need.

4.2 Major Mechanisms Involved in Neuropathic Pain

The mechanisms of neuropathic pain have been the subject of extensive clinical and fundamental investigation.[149] Because of the complexity of the disease, it is unlikely that NP is related to only one mechanism. Each of the painful symptoms may correspond to distinct mechanisms and thus respond to specific treatments. It has been recently established that there are two major classes of mechanisms involved in NP: Peripheral Mechanism and Central Mechanism.[143]

4.2.1 Peripheral Mechanisms

Different types of peripheral mechanisms have been described in animal models of peripheral nerve injury.[150] Abnormal neuronal activity has been reported in the dorsal root ganglion (DRG) and appears to be mainly related to dysfunction of the synthesis or the functioning of sodium channels.[151] Peripheral noxious stimuli activate ion channels as well as transducer proteins, which in turn cause membrane depolarization in sensory DRG cells. Such pathologic activation may induce hyperalgesia.[152]

4.2.2 Central Mechanisms

An animal study of the central mechanism involved in neuropathic pain was reported in 2010.[153] Studies have suggested that changes in the CNS might also cause neurons along the pain-signaling pathway hyperexcitable. Under normal circumstances, a painful stimulus results in the release of excitatory amino acids (glutamate, aspartate), neurotrophins, and peptides (such as SP, Neurokinin A and CGRP) from the central

terminals of nociceptive A- and C-fibers in the dorsal horn.[154] However, in the neuropathic pain patient, first-order DRG neurons are hyperexcitable, generating impulses in the absence of noxious stimuli. In addition, VPL thalamic neurons generate and amplify pain signals, thereby contributing to chronic pain.[147]

4.3 Current Treatment of Neuropathic Pain

Current treatment options include opioids, Nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, anticonvulsants, skeletal muscle relaxants and topical agents.[155] Although opioids are the most commonly used therapeutic class for neuropathic pain treatment, their efficacy is highly debated. Endogenous opioids inhibit transmission originating in nociceptors by binding to opioid receptors located on presynaptic terminals of nociceptors, postsynaptic surfaces of dorsal horn neurons, and the inhibitory interneurons in the substantia gelatinosa of the dorsal horn.[156] The net result is the release of γ-Aminobutyric acid (GABA) and other chemical messengers, which subsequently results in the opening of K^+ channels. In the normal nonexcitable state, the K^+ concentration is higher inside the cell than outside. The ability of endogenous opioids to open K^+ channels facilitates the outflow of positive charge from K^+ ions out of the cell, resulting in an internal negative charge. This creates the state of suppressed neuronal activity and hyperpolarization essential for analgesia.[157]

NSAIDs are used to treat inflammation, pain, and fever. The analgesic effect of NSAIDs results from their ability to block prostaglandin synthesis by inhibiting the precursor enzyme, cyclooxygenase (COX).[158] The NSAIDs are mainly used for the treatment of acute pain, but have shown efficacy in osteoarthritis, rheumatoid arthritis and back pain; however, these drugs have limited utility for neuropathic pain syndromes.[148]

The efficacy of tricyclic antidepressants (TCA) has mainly been investigated in patients with peripheral neuropathic pain.[159] Selective serotonin reuptake inhibitors (SSRIs) such

as sertraline, paroxetine, fluoxetine, and citalopram (Figure 34) represent another subclass of antidepressants that have been studied in the treatment of neuropathic pain.[160] SSRIs differ from traditional TCAs in their ability to selectively inhibit 5-HT reuptake without affecting NE.[161] Unlike serotonin norepinephrine reuptake inhibitors (SNRIs), which inhibit the reuptake of both NE and 5-HT, SSRIs selectively block the reuptake of 5-HT. According to the European Federation of Neurological Societies (EFNS), the recommended first line treatments for neuropathic pain are the tricyclic antidepressants and the calcium current blocking gabapentinoids.[162]

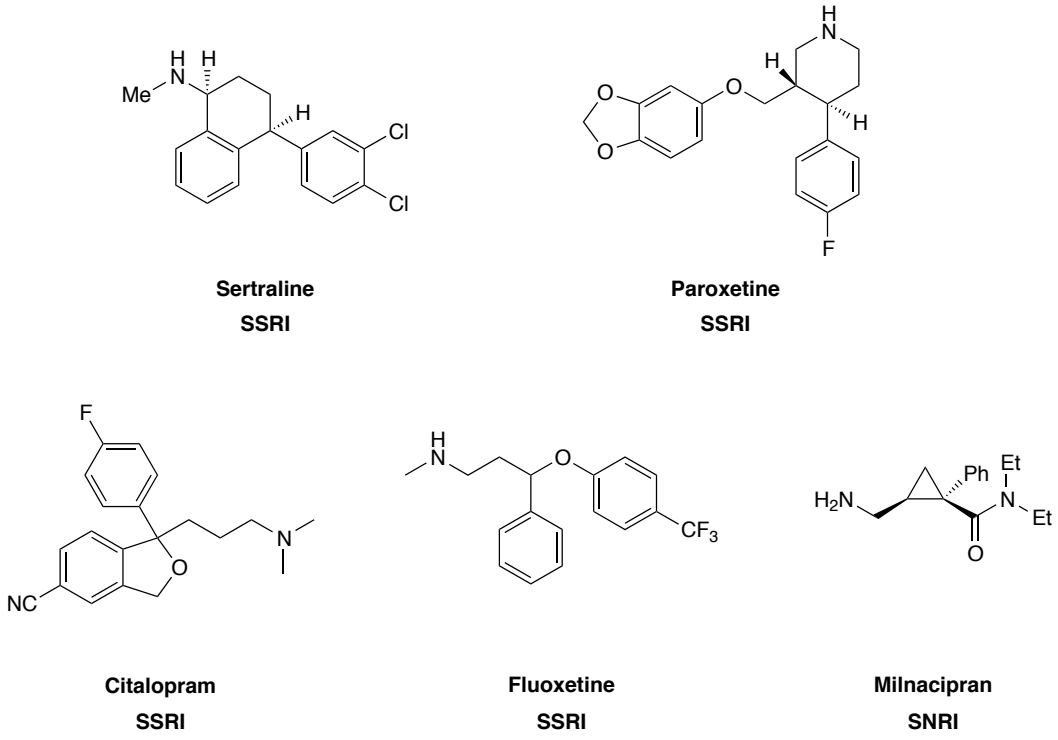
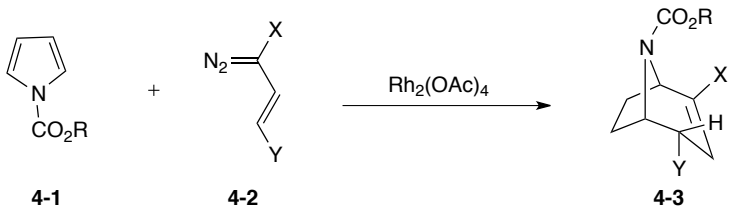


Figure 34 Common TCA Drugs

4.4 CNS drug development in the Davies group

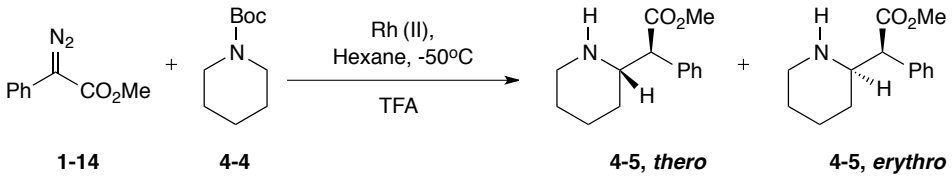
The development of novel CNS drugs using catalytic enantioselective C-H activation reactions as the key step is another key component in the Davies group. Over the past decades, the Davies group has reported concise synthesis of biologically active CNS drugs and analogs utilizing the methodologies that are developed within the group. A formal [3+4] cycloaddition of **4-1** and **4-2** for the synthesis of tropanes (**4-3**) was reported back in 1989 (Scheme 50).[163] After that, a number of asymmetric synthesis of tropanes were reported, and a series of tropane analogs which would be otherwise difficult to obtain using traditional synthetic routes were synthesized via vinyl carbenoid formal [3+4] reaction.[164]



4-1 **4-2** **4-3**

Scheme 50 Formal [3+4] Synthesis of Tropanes

Enantioselective C-H activation adjacent to nitrogen was utilized in the 2-step synthesis of *threo*-methylphenidate (Ritalin), a commercially available monoamine reuptake inhibitor for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).[165] Compared to the previously reported asymmetric synthesis of Ritalin which involved 8 and 9 steps respectively, this methodology was definitely more attractive and provided more synthetic utility (Scheme 51).[166] As shown in Table 13, when using Rh_2(*S*-biDOSP)$_4$ as catalyst and using diazo as limiting agent, reaction gave the best result.



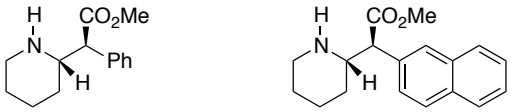
1-14 **4-4** **4-5, *thero*** **4-5, *erythro***

Scheme 51 Enantioselective Synthesis of Ritalin

Rh(II)	Equiv. of 4-4	Combined yield%	*thero:erythro*	*thero* ee%	*erythro* ee%
Rh_2(*S*-DOSP)$_4$	4	49	43:57	34 (2*S*)	81 (2*S*)
Rh_2(*S*-DOSP)$_4$	0.25	86	50:50	25 (2*S*)	79 (2*S*)
Rh_2(*S*-biDOSP)$_4$	0.25	73	71:29	86 (2*R*)	65 (2*S*)

Table 13 Screening Reactions

A series of new methylphenidate analogues were prepared with the same protocol, and were submitted for biological screening. Interestingly, it was found that the analogs prepared display a greater range of binding selectivity than Ritalin (Figure 35).[167]



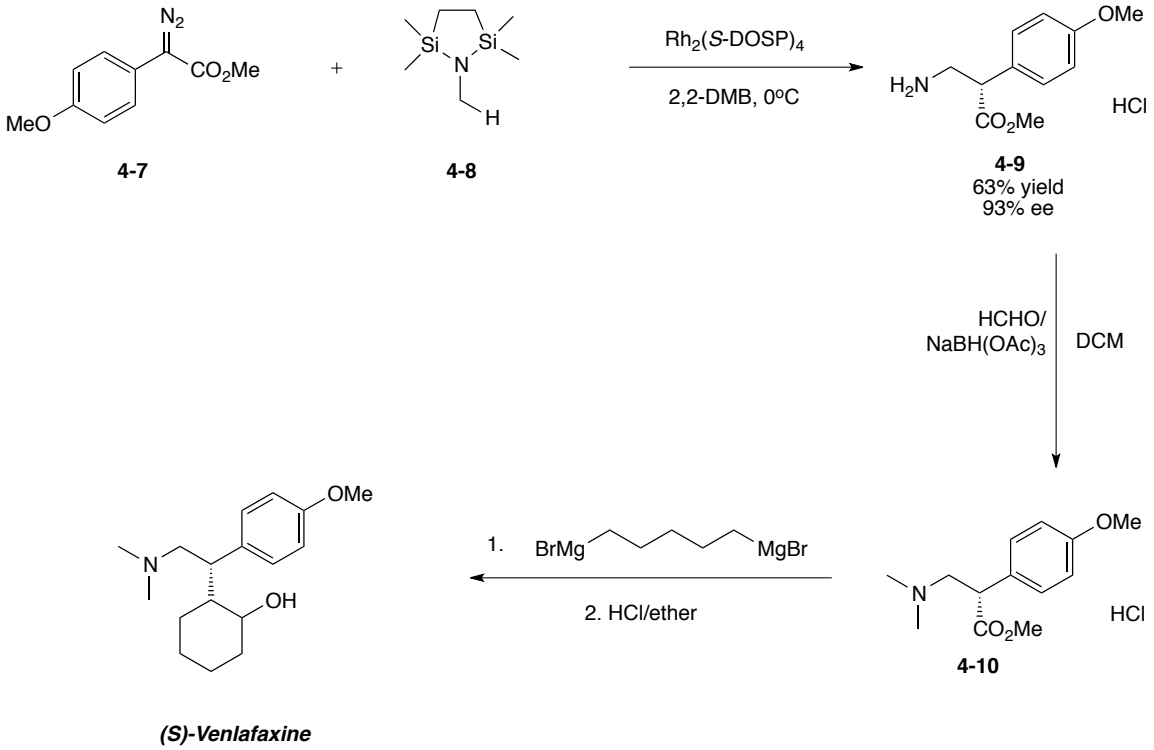
Ritalin **Analogue**

DA (IC_{50} nM) 164±40
5-HT (Ki nM) >10,000

DA (IC_{50} nM) 11.1±2.2
5-HT (Ki nM) 94.8±23.7

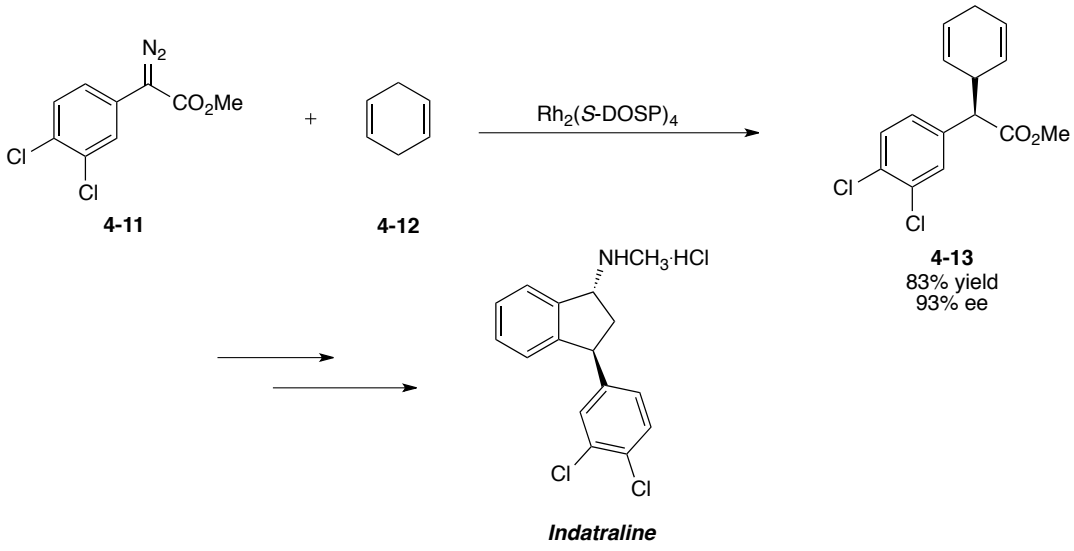
Figure 35 *In Vitro* Data for Analogue of Ritalin

The enantiomer of the antidepressant Venlafaxine was synthesized in three simple steps with high enantioselectivity (Scheme 52).[168] The C–H insertion reactions of the bis-silylmethylamine (**4-8**) with various aryldiazoacetates afforded β-amino esters in good yields and high enantioselectivity. A major advantage of using the bis-silyl protecting group is that it is stable under carbenoid reaction; however, under mildly acidic conditions, the protecting group is very labile and the β-amino ester is obtained readily.



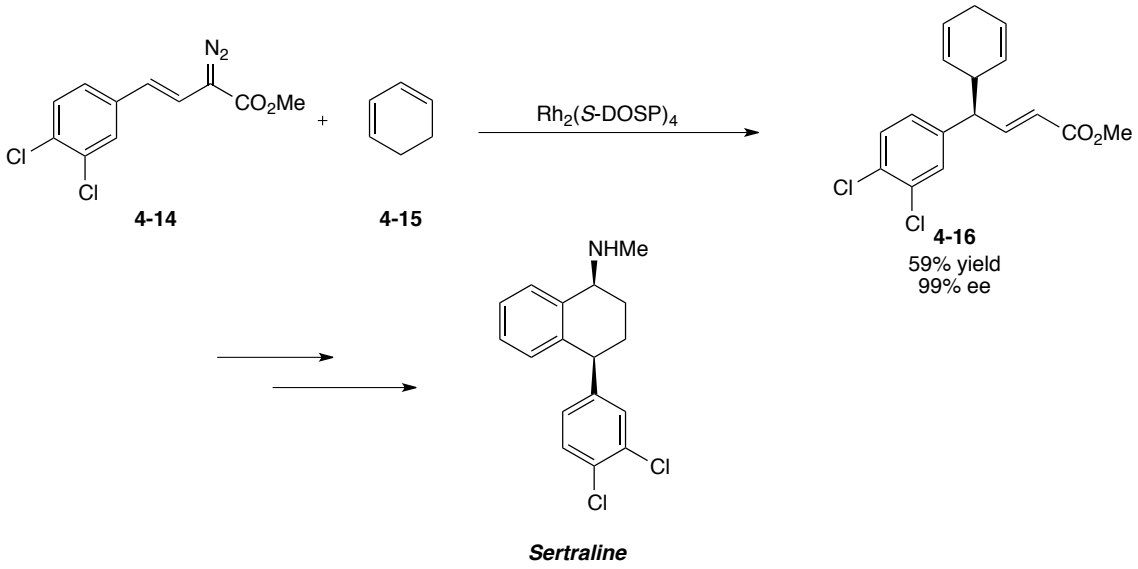
Scheme 52 Synthesis of (*S*)-Venlafaxine

A novel C-H activation process was applied to the asymmetric synthesis of Indatraline, a potent compound that has been used for the treatment of cocaine addiction.[169] The intermolecular asymmetric C–H activation of 1,4-cyclohexadiene (**4-12**) catalyzed by Rh_2(*S*-DOSP)$_4$ provided a quick access to the key intermediate (**4-13**) in the synthesis of the potent dopamine reuptake inhibitor, (+)-Indatraline (Scheme 53).[170]



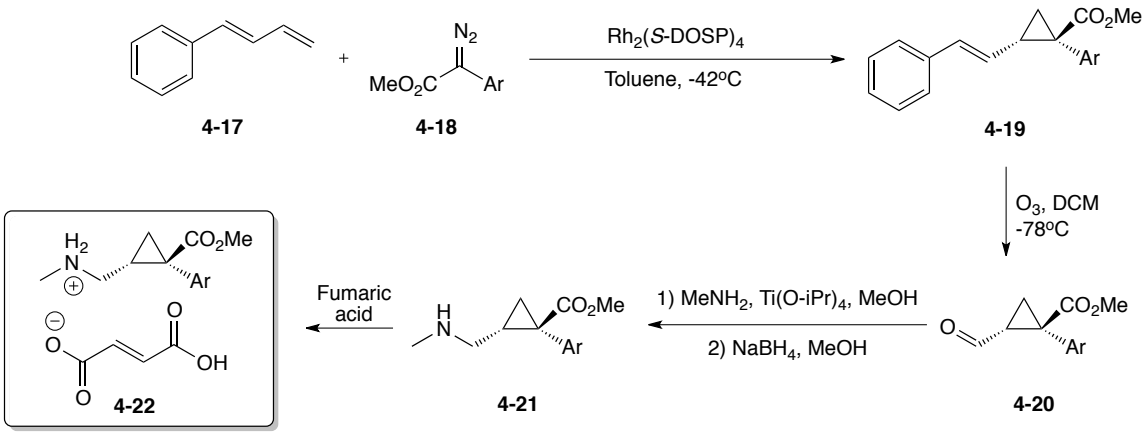
Scheme 53 Asymmetric Synthesis of Indatraline

The closely related reaction of phenyldiazobutenoates (**4-14**) with 1,3-cyclohexadiene (**4-15**) provided 4,4-diarylbutanoates (**4-16**) with high enantioselectivity, and has been used in a formal total synthesis of (+)-Sertraline (Scheme 54).[171] Unlike the direct C-H insertion reaction occurred in the key step of the synthesis of Indatraline, the key step adopted in the synthesis of Sertraline was combined C–H activation/Cope rearrangement.



Scheme 54 Synthesis of Sertraline

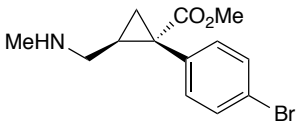
A five-step protocol was developed in the Davies group during the development of drug candidates for the treatment of neuropathic pain (Scheme 55).[172]



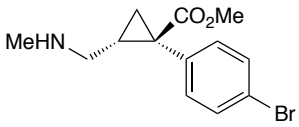
Scheme 55 Five-step Protocol For Synthesizing Neuropathic Pain Drug Candidates

Cyclopropanation of (*E*)-buta-1,3-dien-1-ylbenzene (**4-17**) with the appropriate aryl diazoacetates (**4-18**) catalyzed by Rh_2(*S*-DOSP)$_4$ proceeded smoothly under standard condition to give cyclopropanated product (**4-19**) in high yield and ee. Ozonolysis of the vinyl cyclopropane (**4-19**) gave rise to the cyclopropyl aldehyde (**4-20**), which was purified and subjected to the following reaction immediately. Reductive amination with methylamine yielded the desired aminated product (**4-21**). After the salt formation with fumaric acid, the final drug candidates (**4-22**) were obtained as off-white solid.

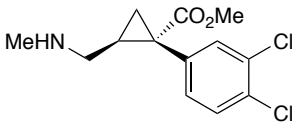
A series of drug candidates were synthesized by former group member Dr. Spandan Chennamadhavuni and the biological activities of these compounds were tested by Dr. Steven Childers' laboratory. Among the compounds synthesized, six of them exhibited intriguing biological activities (Figure 36).



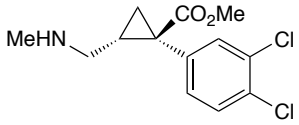
4-23



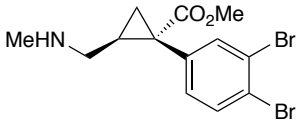
4-24



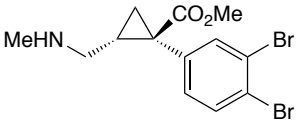
4-25



4-26



4-27



4-28

Figure 36 Previously Synthesized Drug Candidates for Treating Neuropathic Pain

Judging from the *in vitro* data in Table 14, it can be concluded that the (1*R*, 2*R*) isomer generally displays higher potency towards either SERT or NET. Compound **4-26** has the highest potency towards NET (K_i = 0.20±0.01 nM) and its binding affinity towards SERT is extremely high as well.

	4-23	**4-24**	**4-25**	**4-26**	**4-27**	**4-28**
SERT, K_i(nM)	630.7±47.5	31.34±1.97	26.6±2.8	1.59±0.2	13.1±1.8	1.22±0.04
NET, K_i(nM)	29.9±0.7	1.66±0.05	5.34±0.53	0.20±0.01	3.26±0.47	0.45±0.08

Table 14 *In Vitro* Data

Although compound **4-26** displayed extremely high potency towards SERT and NET, the optimum drug candidate for treating neuropathic pain is yet to be found. Therefore, computational modeling was performed in order to aid in the rational design of drug candidates.

4.5 Computational Modeling and Design of Novel Cyclopropylamine Drug Candidates for Treating Neuropathic Pain

The computational results were obtained by Qi Shi from Dr. Jim Snyder's laboratory. Although there is no firm evidence for the exact cause of neuropathic pain, current treatment of selective NE/5-HT reuptake inhibitors (SNRI) appear to be more efficacious than selective NET or SERT inhibitors alone.[173] Therefore, it is hypothesized that an optimal ratio of SERT:NET potency profile exists for a drug that would display excellent efficacy with the least amount of side effects when administrated via i.t. route. In order to test the hypothesis, computational modeling and screening were carried out to provide a list of highly potent NET and SERT dual inhibitors with different potency ratios.

The dopamine transporter (DAT), serotonin transporter (SERT), and noradrenalin transporter (NET) are molecular targets for psychotropic drugs acting in the brain. The neurotransmitter: sodium symporter (NSS), belongs to the secondary transporter group of membrane proteins, and includes DAT, SERT, NET, and several other neurotransmitters and hormones.[174] Although the detailed 3-dimensional molecular structure is not known for any secondary transporter protein, their primary structures indicate 12 membrane spanning domains and intracellular localization of the amino and carboxy terminals.[175] Structural information about DAT, SERT and NET together with their drug interactions is important for understanding their molecular mechanisms of action, and providing insights for new drug discovery.

The crystal structure of leucine transporter (LeuT) from *Aquifex aeolicus* was reported, and the structure revealed the architecture of this important class of transporter.[176] The

transport mechanism of LeuT utilized an electrochemical sodium gradient to provide an inward movement of substrate against a concentration gradient, which resembles the transport mechanisms of DAT, SERT and NET.[177] Homology modeling can provide valuable insights into their structure and molecular mechanisms when the crystal structure of the target protein is not known.[178] While DAT, SERT and NET have not been successfully crystalized so far, their related functional mechanisms and amino acid sequence indicate that these proteins and LeuT share a common overall folding of their membrane spanning regions. Therefore, the LeuT crystal structure may serve as a suitable template for homology modeling of DAT, SERT and NET.

To build a method of the calculation, 6 previously obtained experimental data sets from Table 14 were used. Since the size of the known binding site is about 350 $Å^3$ and the ligands (**4-23** to **4-28**) have a volume around 900 $Å^3$, an induced-fit docking method was used to gain extra docking space for ligands and subsequent calculation was performed with standard Glide docking. This two-part strategy provided target protein with a degree of flexibility without compromising the library processing speed. Among the ligands in Figure 36, the two largest compounds **4-27** and **4-28** were chosen for induced-fit docking, and for each compound, only one pose was requested. The receptors derived from the resulting pose were extracted and subsequently used as the receptor for the normal Glide docking. After examination of different results, the docking receptors generated by Compound **4-28** delivered better correlations (Figure 37).

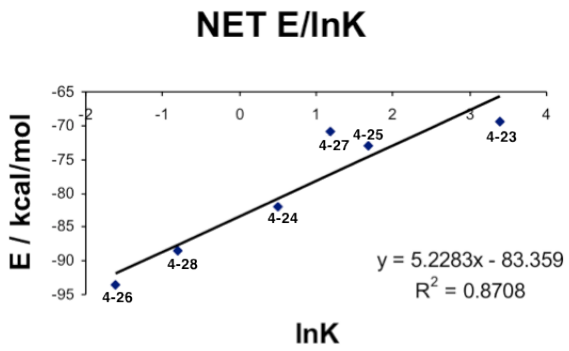
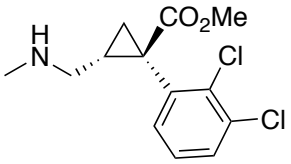
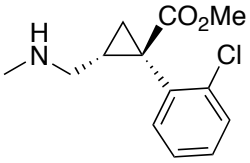
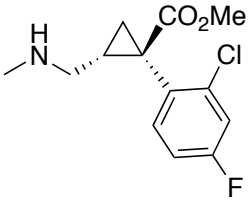
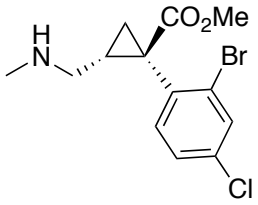
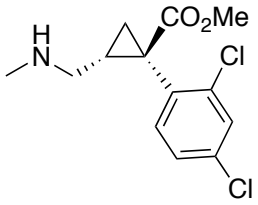
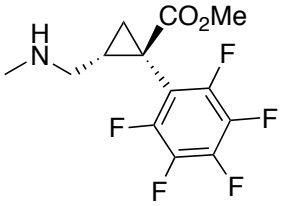
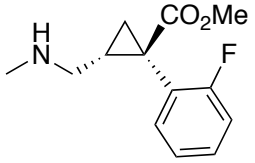
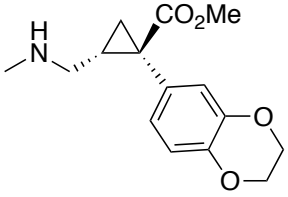
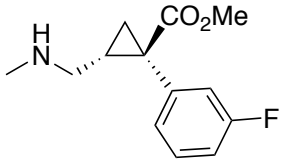
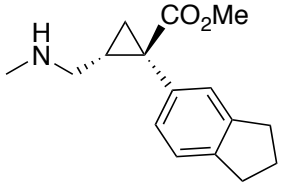
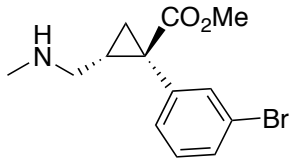
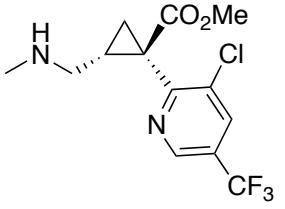
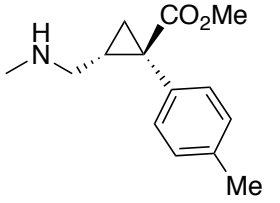
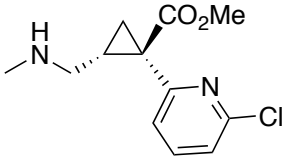
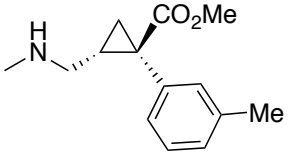
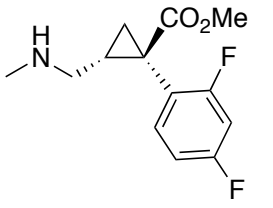
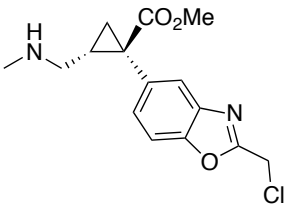


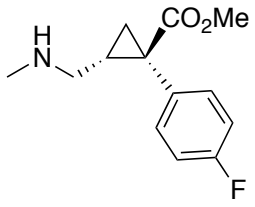
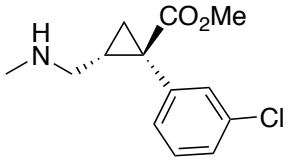
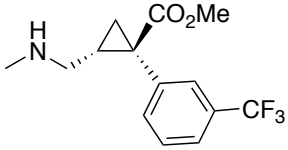
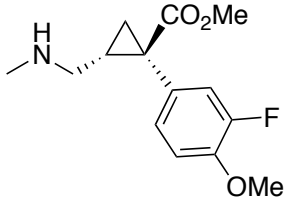
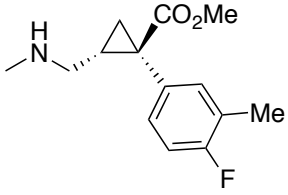
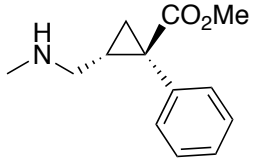
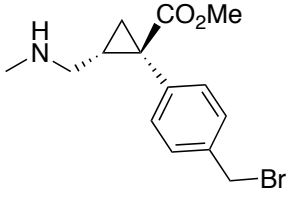
Figure 37 Diagram for Induced-fit Docking Result

It is worth mentioning that these correlations were based on preliminary results from only six experimental data points. Nevertheless, they provide a good starting point for generating prospective compounds for further synthesis. Pipeline Pilot, Qikprop, Glide, Prime software were used for the design of new aryl cyclopropylamine drugs, and the initial 30 drug candidates that have a wide range of SERT/NET ratio were generated from the calculation (Table 14, data was provided by Qi Shi From Dr. Jim Snyder's lab).

Number	Molecule	NET potency	SERT potency	SERT:NET
QS-1		21.72	4.42	0.204
QS-2		46.60	9.69	0.208
QS-3		18.99	5.62	0.296

QS-4		40.75	13.23	0.325
QS-5		18.64	8.92	0.478
QS-6		4.50	2.61	0.581
QS-7		7.76	6.75	0.870
QS-8		14.83	23.13	1.559
QS-9		2.01	3.68	1.833
QS-10		20.84	38.51	1.848

QS-11		1.24	2.48	2.004
QS-12		2.63	5.30	2.013
QS-13		2.23	5.30	2.381
QS-14		0.59	1.59	2.687
QS-15		2.71	8.11	2.986
QS-16		2.14	7.66	3.579
QS-17		46.70	182.40	3.906

QS-18		1.49	5.99	4.024
QS-19		1.21	5.04	4.173
QS-20		2.16	9.59	4.450
QS-21		0.99	5.10	5.117
QS-22		0.86	4.59	5.336
QS-23		2.21	12.91	5.850
QS-24		11.01	81.54	7.407

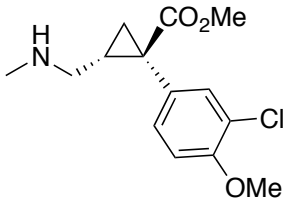
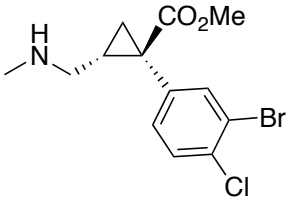
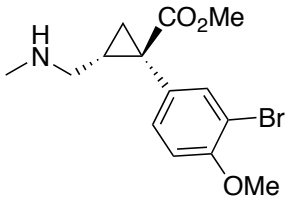
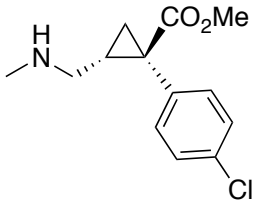
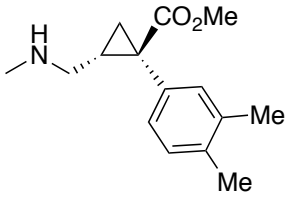
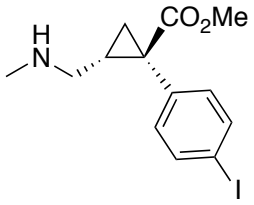
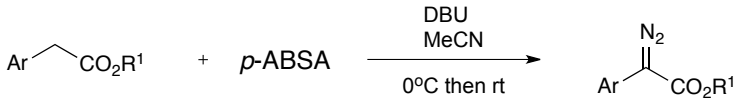
QS-25		0.62	4.88	7.846
QS-26		0.36	2.93	8.065
QS-27		0.57	5.21	9.095
QS-28		0.66	6.70	10.14
QS-29		2.84	36.41	12.84
QS-30		1.49	44.60	29.89

Table 15 Induced-fit Docking Generated Drug Candidates (data provided by Qi Shi from Dr. Snyder's lab)

4.6 Synthesis of Novel Cyclopropylamine Drug Candidates

With the list of drug candidates in hand, a synthetic effort was made towards the synthesis of 12 representative molecules. The synthesis started with the preparation of a series of substituted aryldiazoacetates with established diazo transfer reaction (Table 16).[63]



4-29 **4-30**

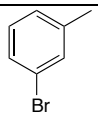
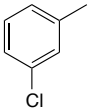
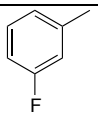
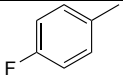
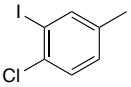
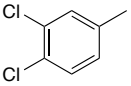
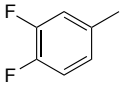
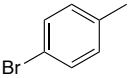
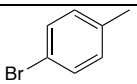
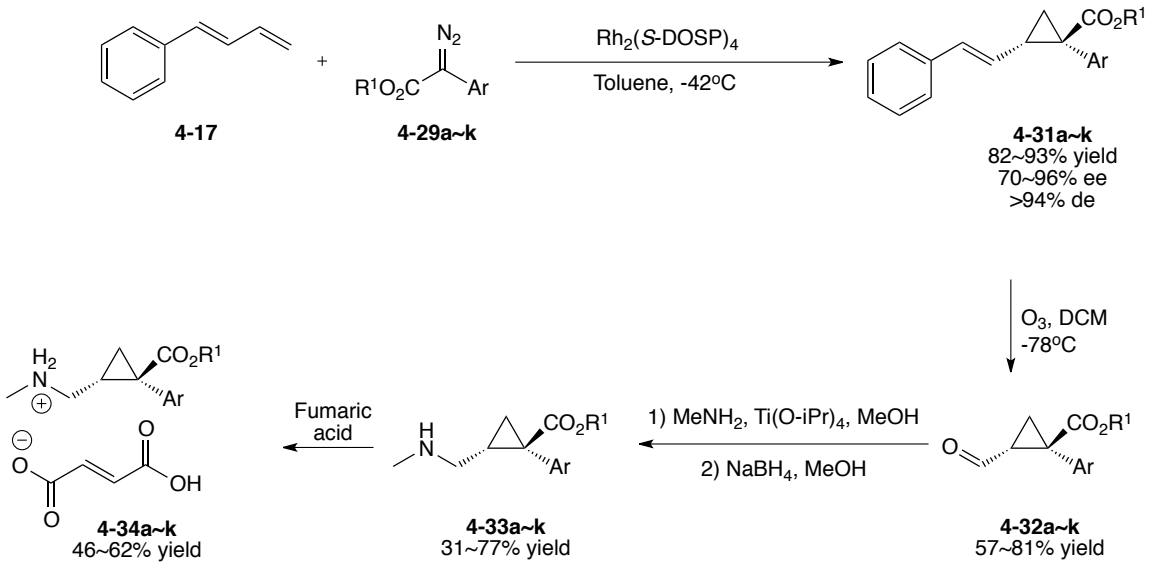
Compound	Ar	R^1	Yield, %
4-29a		CO_2Me	96
4-29b		CO_2Me	89
4-29c		CO_2Me	92
4-29d		CO_2Me	79
4-29e		CO_2Me	67
4-29f		CO_2Me	91
4-29g		CO_2Me	83
4-29h		CO_2Me	81
4-29i		CO_2Me	88
4-29j		CO_2Et	90
4-29k		$CO_2{}^iPr$	87

Table 16 Diazo Synthesis

The five-step synthetic protocol was then followed by the synthesis of cyclopropylamine drug candidates.[172] Cyclopropanation of (*E*)-buta-1,3-dien-1-ylbenzene (**4-17**) with **4-29** using Rh_2(*S*-DOSP)$_4$ as catalyst gave rise to the corresponding cyclopropanes **4-31** in high yield and ee (Scheme 56).



Scheme 56 Synthesis of Aryl Cyclopropylamines 4-34a~k

Due to the instability of the cyclopropyl aldehyde (**4-32**), the reductive amination was performed immediately after **4-32** was purified. Reductive amination of **4-32** and methylamine generated the desired aminated product **4-33** in moderate yield (31~77% yield). After the salt formation with fumaric acid, the first batch of 6 compounds were obtained, and submitted for biological activity screening (Figure 38).

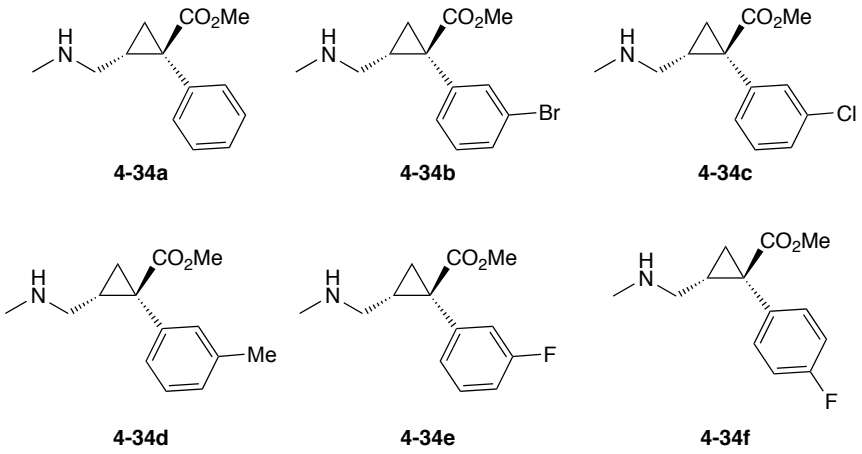


Figure 38 First Batch of Drug Candidates Synthesized (fumaric salt omitted for clarity)

To better understand the structure-activity relationship (SAR) of the aryl cyclopropylamines, another 6 aryl cyclopropylamines were synthesized following the same protocol (Figure 39).

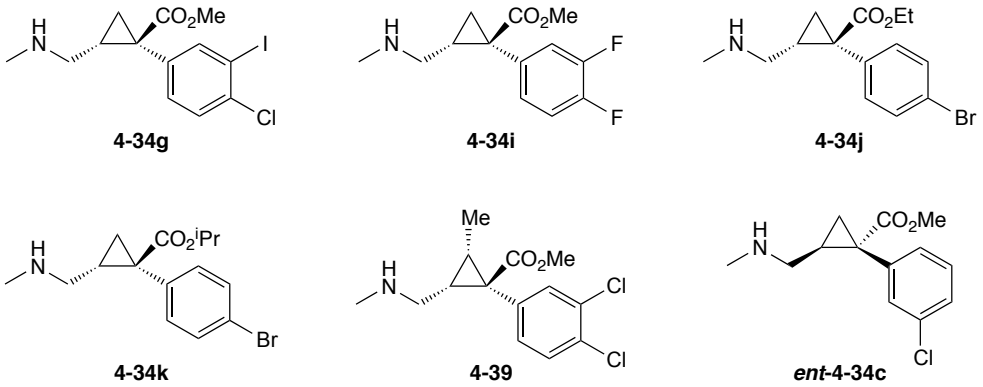
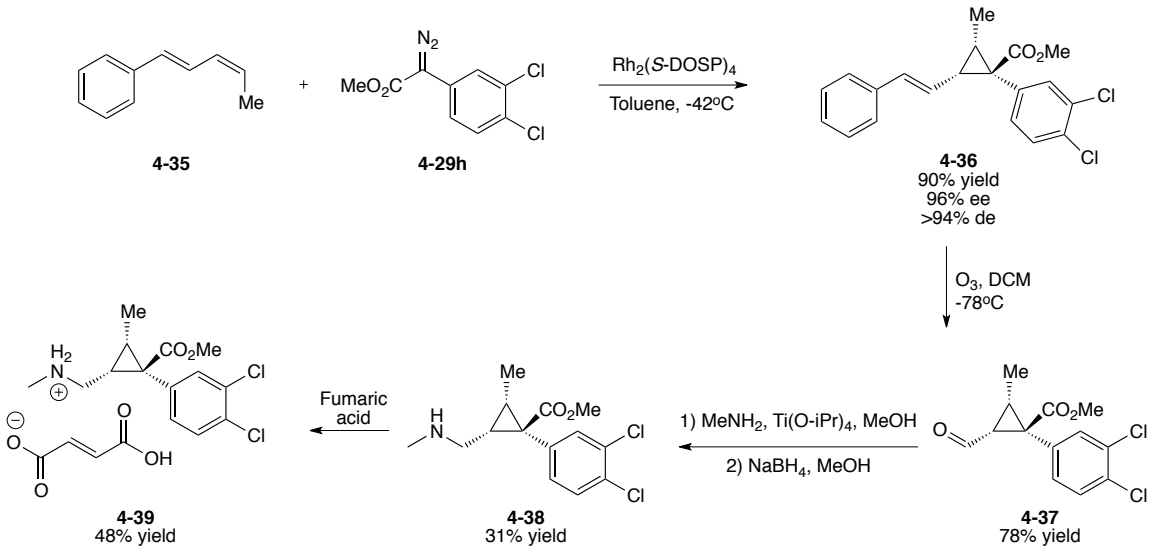


Figure 39 Second Batch of Drug Candidates Synthesized (fumaric salt omitted for clarity)

Compounds **4-34j** and **4-34k** share the same aryl group as Compound **4-34b**; however, the different ester groups would indicate if the size of ester group affects the binding affinity. As all of the initial evaluations were carried out with di-substituted cyclopropane core, it was intriguing to determine if the substitution pattern on the cyclopropane ring affects the potency towards SERT or NET. The synthesis of **4-39** is outlined in Scheme 57. Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of **4-29h** in the presence of **4-35** gave the cyclopropanation product **4-36** in 90% yield and 96% *ee*. Cleavage of the double bond by

ozonolysis, followed by reductive amination with methylamine provided **4-38** in 31% yield. Treatment with fumaric acid of 4-38 resulted in the fumaric salt **4-39** as white solid in 48% yield.



Scheme 57 Synthesis of 4-39

The unique structure of **4-39** would provide ample information about the SAR of this series of molecules, and broaden the drug candidate pool if **4-39** is found to be more reactive than di-substituted cyclopropanes. Compound ***ent*-4-34c** is the enantiomer of compound **4-34c**, the purpose of synthesizing both enantiomers is to test the hypothesis that the (*R,R*)-enantiomer is more active than (*S,S*)-enantiomer. Compounds **4-34g,i~k** together with **4-39** and ***ent*-4-34c** were submitted for biological screening in Dr. Steven Childers' laboratory.

4.7 *In Vitro* Data for Neuropathic Pain Drug Candidates

The *in vitro* data was provided by Dr. Steven Childers' laboratory. Six compounds in Figure 40 were tested for their binding affinity to SERT and NET, and the result is shown in Table 17.

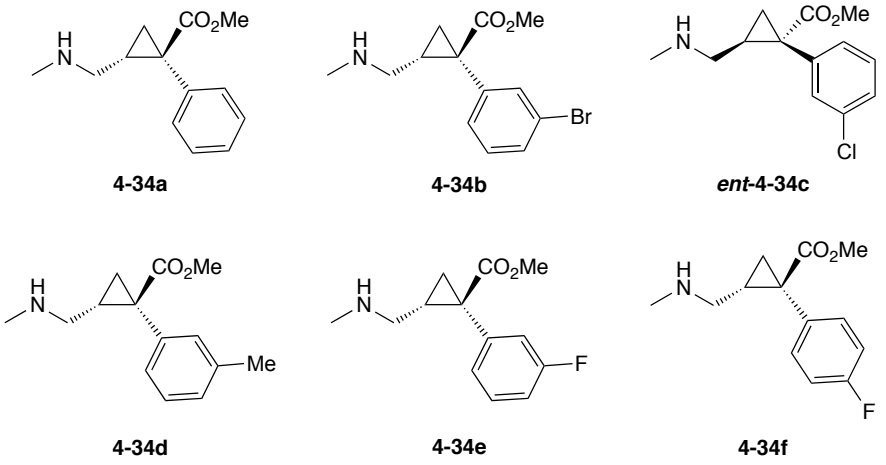


Figure 40 *In Vitro* Tested Compounds

Compound	Calcd NET	Calcd SERT	NET IC_{50} (nM)	SERT IC_{50} (nM)	SERT:NET experimental	SERT:NET calculated
4-34a	2.2	12.91	48.3±11	39.5±6.3	0.82	5.85
4-34b	1.2	2.48	15.4±2.7	4.81±0.25	0.3	2.0
***ent*-4-34c**	N/A*	N/A*	72.6±20	207±21	2.85	N/A*
4-34d	2.7	8.11	34.7±1.4	114±39	3.28	2.99
4-34e	2.0	3.68	13.7±3.8	11.0±1.4	0.8	1.8
4-34f	1.5	6.00	2.9±0.9	5.21±0.47	1.78	4.02

Table 17 *In Vitro* Data
*Computational calculation was not performed on this enantiomer

As seen from Table 17, the calculated NET and SERT potencies of **4-34f** match well with the experimental data; however, the ratio of SERT to NET is quite different. Compound **4-34b** displayed a reversed ratio between the calculated and experimental SERT to NET

ratio. Although the calculated value of the SERT to NET ratio of compound **4-34d** is close to the experimental data, the experimental potencies for SERT and NET are more than tenfold lower than the calculated values. The difference between **4-34a** and the rest of the compounds synthesized in this project is that **4-34a** does not bear any substituents on the aromatic ring. The experimental result for the NET potency of **4-34a** is nearly twenty five-fold less potent than the calculated result, and the calculated SERT to NET ratio is substantially different from the experimental data as well. In summary, more experimental data is needed to modify the calculation parameters and develop a more appropriate model for calculation.

4.8 Conclusion

To determine the structure of the compound that possesses the optimal SERT to NET ratio for alleviation of neuropathic pain with minimal side effects, a two-part, induced-fit /Glide docking method was adopted in the calculation of binding affinity of potential candidates. 30 compounds were generated under strict computational screening process, which represent a wide range of SERT of NET ratio.

A 5-step reaction protocol was followed for the synthesis of 12 aryl cyclopropylamines in this study. *In vitro* data demonstrated the rough accuracy of the calculation method, and therefore, it was determined that more experimental data is needed to optimize the calculation method. Although, at the moment, the compound that displays optimum SERT to NET ratio is not identified, preliminary results obtained herein provided a clearer direction for this combinatorial approach to the design of a new neuropathic pain drug.

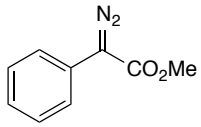
Experimental

^{1}H-Nuclear Magnetic Resonance (NMR) spectra were typically recorded on a Varian spectrometer at 300, 400, 500, or 600 MHz, and ^{13}C-NMR at 75, 100, or 125 MHz with the sample solvent being $CDCl_3$ unless mentioned otherwise. The following abbreviations are used to explain multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; m, multiplet. Coupling constants were taken directly from the spectra and are uncorrected. IR spectra were obtained using a Thermo Scientific Nicolet *i*S10 FT-IR and reported in units of cm^{-1}. High Resolution Mass spectral (HRMS) determinations (pos-APCI) were performed by the Instrument Center of the Department of Chemistry, Emory University. Optical rotations were measured at the sodium D line (589 nm) and reported as follows: $[\alpha]_D^{20}$, concentration (c in g/100 mL) and solvent. All rotations are measured at 20.0 ^{o}C. Enantiomeric excess was determined by Varian Pro Star high performance liquid chromatography (HPLC) using chiral analytical columns (Chiralcel OD, Chiralcel OD-H, Chiralcel OJ, Chiralpak AD-H, Chiralpak AS-H, Chiralpack AD-RH, (*R,R*)-Whelk, or (*S,S*)- Whelk)(UV detection at 254 or 273 nm). Chiral columns and conditions are specified for individual compounds. Analytical TLC was performed on 0.25 mm E. Merck silica gel (60F-254) plates using UV light. Phosphomolybdic acid (PMA), $KMnO_4$, Ninhydrin or dinitrophenylhydrazine (DNP) was used as stain for TLC plates if necessary.

Glassware was dried in an oven overnight prior to use. Reactions were typically conducted under an atmosphere of argon. Flash column chromatography was performed on Merck silica gel 60 (230-400 mesh). Hexanes, toluene, THF, DCM, diethyl ether and

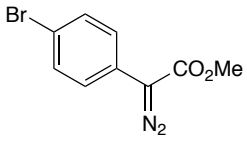
acetonitrile were dried by passage through activated alumina columns in a solvent purification system prior to use. All other reagents were purchased from Aldrich, Alfa Aesar, or Acros chemical companies and were used without additional purification unless noted. Rhodium catalysts $Rh_2(OAc)_4$, $Rh_2(S\text{-DOSP})_4$, $Rh_2(R\text{-DOSP})_4$, were obtained from lab sources and were used as is.

Methyl 2-diazo-2-phenylacetate, 1-14



All diazo compounds in this thesis were prepared according to the reported procedure.[179] Methyl phenyl acetate (1.5g, 10 mmol) and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA) (2.5 g, 11 mmol) were dissolved in acetonitrile (50 mL) and cooled to 0 °C in an ice bath. 1,8-Diazabicycloundec-7-ene (DBU) (2.7 g, 18 mmol) was added in one portion and the reaction was stirred at 0 °C for 3 h, and then was warmed up to room temperature and stirred for 3 additional hours. The reaction was poured into a saturated NH_4Cl solution (100 mL) and extracted with diethyl ether (2 × 100). The combined ether layers were dried over $MgSO_4$, filtered and concentrated to obtain the crude product. The crude product was purified by column chromatography (SiO_2, 95:5 petroleum ether/diethyl ether), and pure product was obtained as bright orange colored oil (1.68 g, 96% yield). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.46 (m, 5H), 3.84 (s, 3H). The ^{1}H-NMR data was consistent with published values.[180]

Methyl 2-(4-bromophenyl)-2-diazoacetate, 1-25

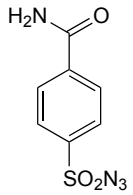


To a flame dried round bottom flask was dissolved 2-(4-bromophenyl) acetic acid (5 mmol, 1 equiv) in MeOH (10 mL) and cooled to 0 ^{o}C. Acetyl chloride (6 mmol, 1.2 equiv) was added dropwise at 0 ^{o}C. Saturated NH_4Cl solution was added to the reaction

mixture after being stirred room temperature overnight. The crude reaction mixture was then poured into a separation funnel and was extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude methyl acetate mixture was taken to next step without further purification.

Methyl acetate was dissolved in acetonitrile and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA) (6 mmol, 1.2 equiv) was added. The reaction mixture was cooled to 0 ^oC and 1,8-Diazabicycloundec-7-ene (DBU) (12 mmol, 2 equiv) was added dropwise at 0 ^oC. The reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted twice with diethyl ether (29 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography using 9:1 hexane/Et_2O as eluent and pure product was obtained as yellow solid (1.2 g, 83% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 3.87 (s, 3H). The ^{1}H-NMR data was consistent with the published values.[181]

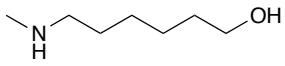
para-Acetamidobenzenesulfonyl azide (_p_-ABSA), 2-1



To a round-bottomed flask charged with a stir bar was added *para*-acetamidobenzenesulfonyl chloride (62.8 g, 0.27 mol) and acetone (200 mL). A solution

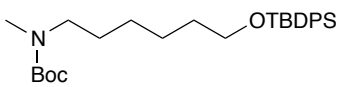
of sodium azide (29 g, 0.35 mol) in water (60 mL) was added dropwise over 1 h at ambient temperature. The solution was then stirred overnight and poured into ice water to induce precipitation. The solution was kept at 0 ^{o}C for 1 h and the precipitated was collected by vacuum filtration. The solid was washed with several portions of water and then air-dried for several hours. The solid was then dried under high vacuum over phosphorus pentoxide for 2 days to give pure *p*-ABSA as a white solid (60 g, 93% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 9.2 Hz, 2H), 7.76 (d, J = 9.2 Hz, 2H), 7.59 (broad, 1H) 2.23 (s, 3H). The ^{1}H-NMR data was consistent with published values.[63]

6-(methylamino)hexan-1-ol, 2-9



The titled compound was synthesized by a reported procedure (1.6 g, 85% yield over 2 steps).[182] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.80 (t, J = 5.0 Hz, 2 H), 3.10 (s, 2H), 2.83 (t, J = 6.0 Hz, 2 H), 2.42 (s, 3 H), 1.76–1.64 (m, 2 H). The ^{1}H-NMR data was consistent with published values.[182]

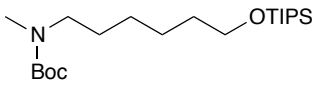
***tert*-butyl (6-((*tert*-butyldiphenylsilyl)oxy)hexyl)(methyl)carbamate, 2-12**



6-(methylamino)hexan-1-ol (577 mg, 1 equiv) was diluted in a 1:1 mixture of dioxane and water. Triethylamine (890 mg, 2 equiv) was added. The resulting mixture was stirred

at room temperature for 1 h. Then di-tertbutyl dicarbonate (1.2 g, 1.2 equiv) was added to the above reaction mixture in one shot and the reaction was stirred for 16 h. Crude reaction mixture was extracted with ethyl acetate and the organic layer was dried over $MgSO_4$. Boc-protected amino alcohol was carried on in reaction without further purification. Imidazole (599 mg, 2 equiv) was added to the Boc-protected amino alcohol in DCM. The resulting mixture was stirred for 1h. Then tert-butylchlorodiphenylsilane (1.3 g, 1.1 equiv) was added in one shot and the reaction was stirred overnight. Remove the solvent *in vacuo* and wash the reaction with water. The combined organic layer was dried over $MgSO_4$ and was purified *via* column chromatography (10:1 pentane/ diethyl ether) yielding the titled compound as colorless oil (1.2 g, 58% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.37 (m, 6H), 3.63 (t, J = 7.2 Hz, 2H), 3.14(s, 2H), 2.80(s, 3H), 1.58~1.20(m, 8H), 1.42(s, 9H), 1.02(s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.0, 135.8, 134.3, 129.7, 127.8, 79.2, 64.1, 49.0, 34.3, 32.7, 28.7, 28.1, 27.1, 26.7, 25.8, 19.4; IR (neat) 2930, 2857, 1693, 1472, 1427, 1166, 1108, 700 cm^{-1}; HRMS(ESI) calcd for [$C_{28}H_{43}NO_3Si$ + $2H^+$ minus Boc] 370.2566, Found [M + $2H^+$ minus Boc] 370.2567.

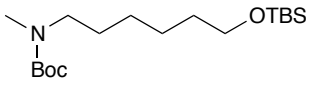
tert-butyl methyl(6-((triisopropylsilyl)oxy)hexyl)carbamate, 2-13



6-(methylamino)hexan-1-ol (236.8 mg, 1 equiv) was diluted in a 1:1 mixture of dioxane and water. Triethylamine (364.3 mg, 2 equiv) was added. The resulting mixture was stirred at room temperature for 1 h. Then di-tertbutyl dicarbonate (471.5 mg, 1.2 equiv) was added to the above reaction mixture in one shot and the reaction was stirred for 16 h.

Crude reaction mixture was extracted with ethyl acetate and the organic layer was dried over $MgSO_4$. Boc-protected amino alcohol was carried on in reaction without further purification. Imidazole (244.8 mg, 2 equiv) was added to the Boc-protected amino alcohol in DCM. The resulting mixture was stirred for 1 h. Then chlorotriisopropylsilane (381.7 mg, 1.1 equiv) was added in one shot and the reaction was stirred overnight. Remove the solvent *in vacuo* and wash the reaction with water. The combined organic layer was dried over $MgSO_4$ and was purified *via* column chromatography (10:1 pentane/ diethyl ether) yielding the titled compound as colorless oil (532 mg, 76% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.64 (dd, J = 6.4, 6.8Hz, 2H), 3.16 (s, 2H), 2.81 (s, 3H), 1,55~1.44 (m, 4H), 1.43 (s, 9H), 1.42~1.22 (m, 4H), 1.03 (d, J = 3.6 Hz, 18H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 79.5, 76.6, 63.6, 33.2, 28.7, 26.8, 25.8, 18.3, 12.2; IR (neat) 2933, 2865, 1698, 1463, 1391, 1365, 1168, 1104, 882, 680cm^{-1}; HRMS(ESI) calcd for [$C_{21}H_{45}NO_3Si$ + H^+] 388.3247, Found [M + H^+] 388.3242.

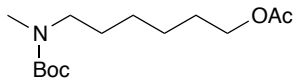
***tert*-butyl (6-((*tert*-butyldimethylsilyl)oxy)hexyl)(methyl)carbamate, 2-14**



6-(methylamino)hexan-1-ol (393.6 mg, 1 equiv) was diluted in a 1:1 mixture of dioxane and water (30 mL). Triethylamine (607.2 mg, 2 equiv) was added. The resulting mixture was stirred at room temperature for 1 h. Then di-tert-butyl dicarbonate (785.8 mg, 1.2 equiv) was added to the above reaction mixture in one shot and the reaction was stirred for 16 h. Crude reaction mixture was extracted with ethyl acetate and the organic layer

was dried over $MgSO_4$. Boc-protected amino alcohol was carried on in reaction without further purification. Imidazole (408.6 mg, 2 equiv) was added to the Boc-protected amino alcohol in DCM (20 mL). The resulting mixture was stirred for 1 h. Then tert-butylchlorodimethylsilane (497.3 mg, 1.1 equiv) was added in one shot and the reaction was stirred overnight. Remove the solvent in vacuo and wash the reaction with water. The combined organic layer was dried over $MgSO_4$ and was purified *via* column chromatography (10:1 pentane/ diethyl ether) yielding the titled compound as colorless oil (867 mg, 82% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.57 (t, J = 6.4 Hz, 2H), 3.15 (s, 2H), 2.80 (s, 3H), 1.51~1.20 (m, 8H), 1.42 (s, 9H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.4, 79.3, 63.4, 49.0, 34.2, 33.0, 28.7, 28.1, 26.7, 26.2, 26.1, 25.8, 18.6, -5.1; IR (neat) 2929, 2857, 1697, 1472, 1390, 1364, 1250, 1167, 1097, 833, 772 cm^{-1}; HRMS(ESI) calcd for [$C_{18}H_{39}NO_3Si + H^+$] 346.2777, Found [$M + H^+$] 346.2768.

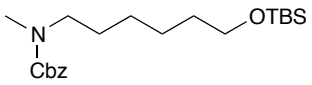
6-((*tert*-butoxycarbonyl)(methyl)amino)hexyl acetate, 2-15



6-(methylamino)hexan-1-ol (459.2 mg, 1 equiv) was diluted in a 1:1 mixture of dioxane and water (30 mL). Triethylamine (708.4 mg, 2 equiv) was added. The resulting mixture was stirred at room temperature for 1 h. Then di-tert-butyl dicarbonate (916.8 mg, 1.2 equiv) was added to the above reaction mixture in one shot and the reaction was stirred for 16 h. Crude reaction mixture was extracted with ethyl acetate and the organic layer was dried over $MgSO_4$. Boc-protected amino alcohol was carried on in reaction without

further purification. The Boc-protected amino alcohol was diluted in pyridine (5 mL). The resulting mixture was stirred for 1 h. Then acetic anhydride (393.1 mg, 1.1 equiv) was added in one shot and the reaction was stirred overnight. Remove the solvent in vacuo and wash the reaction with water. The combined organic layer was dried over $MgSO_4$ and was purified *via* column chromatography (2:1 pentane/ diethyl ether) yielding the titled compound as colorless oil (649 mg, 66% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.03 (t, J = 6.8 Hz, 2H), 3.17 (s, 2H), 2.81 (s, 3H), 2.03 (s, 3H), 1.62~1.27 (m, 8H), 1.43 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.4, 156.0, 79.3, 64.7, 48.8, 34.2, 28.7, 28.6, 27.8, 26.5, 25.9, 21.2; IR (neat) 2932, 2860, 1738, 1691, 1391, 1364, 1234, 1148, 1047, 878, 771 cm^{-1}; HRMS(ESI) calcd for [$C_{14}H_{27}NO_4$ + H^+] 274.2018, Found [M+H^+] 274.2013.

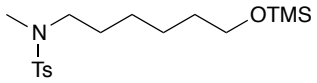
benzyl (6-((*tert*-butyldimethylsilyl)oxy)hexyl)(methyl)carbamate, 2-17



6-(methylamino)hexan-1-ol (223.1 mg, 1 equiv) was added to a round bottom flask with neutral Al_2O_3 (190.7 mg, 1.1 equiv), benzyl chloroformate (289.8 mg, 1 euqiv) was added in one shot to the above suspension. Reaction was let sit at room temperature for 10 min. Solid was filtered away and the crude reaction mixture was used without purification for next step. Dilute the crude mixture in dry DCM (10 mL), imidazole (231.5 mg, 2 equiv) was added. Then TBSCl (281.8 mg, 1.1 equiv) was added in one shot. Reaction was let run overnight at room temperature. Column chromatography was

performed on the crude reaction mixture (1:10 diethyl ether/pentane), yielding the product as pale yellow oil (526 mg, 78% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 5.11 (s, 2H), 3.57-3.54 (m, 2H), 3.28-3.24 (m, 2H), 2.89 (s, 3H), 1.50-1.24 (m, 8H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) 156.4, 137.2, 128.6, 128.0, 127.9, 67.1, 63.30, 49.3, 34.8, 32.9, 28.1, 26.7, 26.2, 25.8, 18.5, -5.1; IR (neat) 2929, 2856, 1702, 1462, 1403, 1521, 1121, 1094, 834, 773, 696 cm^{-1}; HRMS(ESI) calcd for $C_{21}H_{37}NO_3Si + H^+$] 380.2621, Found [M + H^+] 380.2616.

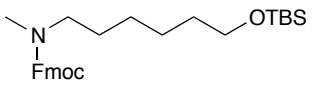
_N_,4-dimethyl-_N_-(6-((trimethylsilyl)oxy)hexyl)benzenesulfonamide, 2-18



6-(methylamino)hexan-1-ol (312.2 mg, 1 equiv) was added to a round bottom flask with pyridine(771.8 mg, 4.1 equiv). Hexamethyldisilazane (460.9 mg, 1.2 equiv) was added to the above reaction mixture and the flask was cooled to 0 ℃. Then TMSCl (284.3 mg, 1.1 equiv) was added dropwise to the reaction mixture. After the addition, reaction was warmed up to room temperature and stirred overnight. Filter away the yellow precipitate and remove solvent *in vacuo*. Crude product was used without further purification for next step. Crude product was diluted in DCM (10 mL). Triethylamine (361.3 mg, 1.5 equiv) was added to the above solution. Reaction mixture was cooled to 0 ℃. Toluene sulfonyl chloride (499.1 mg, 1.1 equiv) was dissolved in 7mL DCM and was added to the above mixture over 10 min at 0 ℃. After the addition, reaction was warmed up to room

temperature and stirred overnight. Wash the reaction with water and saturated sodium bicarbonate. Tosyl protected amino alcohol was purified *via* column chromatography (1:1:20 triethylamine/diethyl ether/pentane), yielding the product as pale yellow oil (511 mg, 60% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 3.53 (t, *J* = 6.8 Hz 2H), 2.94 (dd, *J* = 7.2, 7.6 Hz, 2H), 2.67 (s, 3H), 2.40 (s, 3H), 1.48(m, 4H), 1.30(m, 4H), 0.08(s, 9H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 143.3, 129.8, 127.6, 62.7, 50.3, 32.8, 27.8, 26.5, 25.7, 21.7, -0.3; IR (neat) 2934, 2861, 1340, 1249, 1159, 1089, 838, 815, 714, 698 cm^{-1}; HRMS(ESI) calcd for [$C_{17}H_{31}NO_3Si + H^+$] 358.1872, Found [M + H^+] 358.1864.

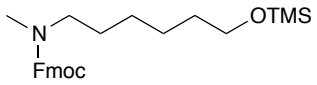
(9*H*-fluoren-9-yl) methyl (6-((*tert*-butyldimethylsilyl)oxy)hexyl)(methyl) carbamate, 2-19



6-(methylamino)hexan-1-ol (656 mg, 5 mmol) was added to a round bottom flask with 50mL DCM. Imidazole (681 mg, 10 mmol) was added to the flask and the resulting mixture was stirred at room temperature for 30min. TBSCl (829 mg, 5.5 mmol) was added in small portions and the reaction was stirred overnight. The crude mixture was filtered and used for the next step without purification. Crude product was diluted in DCM. Triethylamine (1.4 mL, 10 mmol) was added to the above solution. Reaction mixture was cooled to 0 ℃. Toluene sulfonyl chloride (927.2 mg, 5.25 mmol) was

dissolved in 7 mL DCM and was added to the above mixture over 10 min at 0 ℃. After the addition, reaction was warmed up to room temperature and stirred overnight. Wash the reaction with water and saturated sodium bicarbonate. Titled compound was purified *via* column chromatography (1:1 Ethyl acetate/Hexanes) and was obtained as light yellow oil (1.5 g, 84% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.28 (d, *J* = 8.4Hz, 2H), 3.53 (t, *J* = 6.8 Hz, 2H), 2.94 (dd, *J* = 7.2, 7.6 Hz, 2H), 2.67 (s, 3H), 2.40 (s, 3H), 1.48 (m, 4H), 1.30 (m, 4H), 0.08 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.3, 129.7, 129.8, 127.6, 62.7, 50.3, 32.8, 27.8, 26.6, 25.7, 21.7, -0.3; IR (neat) 2934, 2861, 1340, 1249, 1158, 1089, 837, 814, 714, 698 cm^{-1}; HRMS(ESI) calc for [$C_{28}H_{41}NO_3Si + H^+$] 468.2834, Found [$M + H^+$] 468.2839.

(9*H*-fluoren-9-yl)methyl methyl(6-((trimethylsilyl)oxy)hexyl)carbamate, 2-20



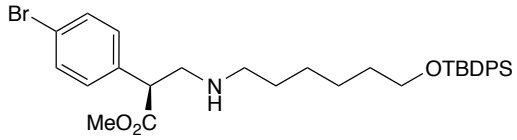
To a oven-dried round bottom flask with 50 mL dry MeCN was added 6-(methylamino)hexan-1-ol (262.8 mg, 2 mmol). Freshly distilled DIPEA (0.37 ml, 2.2 mmol) was added in one shot and resulting mixture was stirred for 30 min at room temperature. A solution of Fmoc-Cl (568 mg, 2.2 mmol) in 6 mL MeCN was added to the above mixture over 10 min. Reaction was stirred at room temperature overnight. Solvent was removed *in vacuo* and (9*H*-fluoren-9-yl)methyl (6-hydroxyhexyl)(methyl)carbamate was purified *via* column chromatography (3% MeOH in DCM). ^{1}H-NMR (400 MHz,

$CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.29 (m, 2H), 4.45 (d, *J* = 6.4 Hz, 1H), 4.37 (d, *J* = 6.8 Hz, 1H), 4.22 (m, 1H), 3.65 (s, 2H), 3.28(dd, *J* = 6.8, 7.6 Hz 1H), 3.06 (t, *J* = 7.6, 7.2 Hz, 1H), 2.87 (d, *J* = 13.6 Hz, 3H), 1.54-1.28 (m, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.4, 141.5, 127.8, 127.2, 125.2, 125.0, 120.1, 67.4, 67.0, 63.0, 62.7, 49.0, 47.6, 34.8, 34.1, 32.9, 28.1, 27.5, 26.7, 26.3, 25.7, 25.4; IR (neat) 3423, 2930, 2858, 1682, 1478, 1449, 1405, 1305, 1178, 1139, 1054, 758, 738 cm^{-1}; HRMS(ESI) calcd for [$C_{22}H_{27}NO_3$ + H^+] 354.2069, Found [M + H^+] 354.2068.

To a round bottom flask with pyridine (0.4 mL, 4.1 mmol) was added (9*H*-fluoren-9-yl) methyl (6-hydroxyhexyl)(methyl)carbamate (635.4 mg, 1.9 mmol). Hexamethyldisilazane (367.9 mg, 2.3 mmol) was added to the above reaction mixture and the flask was cooled to 0 ℃. Then TMSCl (0.26 mL, 2.1 mmol) was added dropwise to the reaction mixture. After the addition, reaction was warmed up to room temperature and stirred overnight. Filter away the yellow precipitate and remove solvent *in vacuo*. Product was purified via column chromatography (1% MeOH in DCM), yielding pale yellow oil (610 mg, 72% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.58 (dd, *J* = 7.6, 8.4 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.29 (m, 2H), 4.45 (d, *J* = 6.4 Hz, 1H), 4.37 (t, *J* = 7.6 Hz, 2H), 4.22 (m, 1H), 3.55 (dd, *J* = 6.4, 6.8 Hz 2H), 3.26 (dd, *J* = 6.4, 6.8 Hz 1H), 3.06 (t, *J* = 7.6 Hz, 1H), 2.87 (d, *J* = 14 Hz, 3H), 1.51-1.48 (m, 3H), 1.33-1.25 (m, 4H), 1.14-1.12 (m, 1H), 0.09 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.4, 144.4, 141.5, 127.8, 127.2, 125.4, 125.0, 120.1, 67.0, 67.4, 62.7, 49.3, 47.6, 39.1, 34.8, 34.1, 32.9, 28.1, 27.7, 26.7, 25.9, -0.3; IR (neat) 2933, 2859, 1700, 1478, 1449,

1403, 1360, 1304, 1248, 1181, 1148, 1089, 868, 838, 737 cm^{-1}; HRMS(ESI) calcd for $C_{25}H_{35}NO_3Si + H^+$] 426.2464, Found [M + H^+] 426.2463.

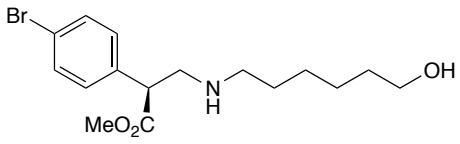
(*S*)-methyl 2-(4-bromophenyl)-3-((6-((*tert*-butyldiphenylsilyl)oxy)hexyl)amino)propanoate , 2-25



To a solution of substrate **2-12** (156 mg, 0.3 mmol, 1 equiv) and Rh_2(*S*-DOSP)$_4$ (6 mg, 0.003 mmol, 1 mol%) in freshly distilled 2,2-dimethylbutane (5 mL) was added a solution of methyl 2-(4-bromophenyl)-2-diazoacetate **1-25** (179 mg, 0.7 mmol, 2.1 equiv) in 10 mL 2,2-dimethylbutane over 5 h. The reaction was stirred overnight after the addition was over. Then an access of trifluoroacetic acid (1.23 mL) was added to the crude reaction mixture and was let stir for 16 h. Product was purified via flash column chromatography (1:1:10 triethylamine/ diethyl ether / pentane) to give pale yellow oil as the titled compound (101.3 mg, 52% yield). [α]$^{20}_D$: -13.56° (c=0.1 w/v, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.38 (m, 8H), 7.15 (d, *J* = 8.4 Hz, 2H), 3.76 (dd, *J* = 6.8, 8.0 Hz, 1H), 3.65 (s, 3H), 3.62 (t, *J* = 6.8 Hz, 2H), 3.22 (dd, *J* = 12.0, 12.4 Hz, 1H), 2.84 (dd, *J* = 12.0, 12.4 Hz, 1H), 2.55 (t, *J* = 6.4 Hz, 2H), 1.59 (s, 1H), 1.52~1.20 (m, 8H), 1.02 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.5, 136.5, 135.8, 134.3, 132.1, 130.0, 129.7, 127.8, 121.8, 64.1, 51.5, 52.7, 49.8, 32.7, 30.1, 29.9, 27.1, 25.9, 21.2, 19.4; IR (neat) 2929, 2855, 1735, 1110, 702 cm^{-1}; HRMS(ESI) calcd for

[$C_{32}H_{42}BrNO_3Si$ + H^+] 596.2196, Found [M + H^+] 596.2194; To determine the enantiomeric excess of the product, **2-25** was converted to its trifluoroacetic amide by treating it with pyridine and trifluoroacetic anhydride. TFAA (2 equiv) was added to a round bottom flask charged with **2-25** (1 equiv) in 2 mL pyridine. The resulting mixture was stirred at room temperature for 6 h. The acylation product of **2-25** was purified by preparative TLC (5:1 pentane / diethyl ether) giving the amide in 73% ee. HPLC analysis: Chiralcel-OD-H column, 1% 2-propanol in hexanes, 0.5mL/min, t_R = 11.57min (major), 12.69min (minor), UV 254 nm).

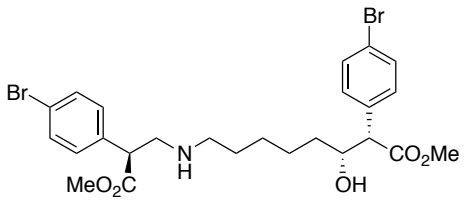
(*S*)-methyl 2-(4-bromophenyl)-3-((6-hydroxyhexyl)amino)propanoate, 2-27



To a solution of substrate **2-13** (155 mg, 0.45 mmol, 1 equiv) and Rh_2(*S*-DOSP)$_4$ (18 mg, 0.009 mmol, 2 mol%) in freshly distilled 2,2-dimethylbutane (5 mL) was added a solution of methyl 2-(4-bromophenyl)-2-diazoacetate **1-25** (345 mg, 1.35 mmol, 3equiv) in 10 mL 2,2-dimethylbutane over 5 h. The reaction was stirred overnight after the addition was over. Then an access of trifluoroacetic acid (1.23 mL) was added to the crude reaction mixture and was let stir for 16 h. Product was purified *via* flash column chromatography (1:1:1 triethylamine/ diethyl ether / pentane) to give pale yellow oil as the titled compound (69 mg, 43% yield, 47% ee, >94% de). [α]$^D_{20}$: -29.60° (c = 0.5 w/v, $CHCl_3$); HPLC analysis: SS-Whelk column, 5 % 2-PrOH in hexanes, 1.0 mL/min,

1mg/mL, t_R = 44.81 (minor) and 41.97 (major) min, UV 254 nm; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 1.6, 6.8 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 3.75 (dd, *J* = 6.8, 6.4 Hz, 1H), 3.64 (s, 3H), 3.58 (dd, *J* = 6.8, 6.4 Hz, 2H), 3.21 (t, *J* = 8.4 Hz, 1H), 2.83 (dd, *J* = 6.8, 6.4 Hz, 1H), 2.57 (t, *J* = 7.2 Hz, 2H), 1.61~1.51 (broad, 1H), 1.54~1.29 (m, 8H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.4, 136.4, 132.1, 129.9, 121.8, 62.9, 52.6, 52.4, 51.5, 49.7, 32.8, 30.0, 27.1, 25.7; IR (neat) 3315 (broad), 2929, 2855, 1731, 1488, 1164, 1011, 822, 758 cm^{-1}; HRMS(ESI) calcd for [$C_{16}H_{24}BrNO_3$ + H^+] 358.1018, Found [M + H^+] 358.1013.

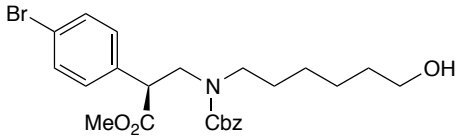
(2*S*,3*R*)-methyl 2-(4-bromophenyl)-8-(((*S*)-2-(4-bromophenyl)-3-methoxy-3-oxopropyl)amino)-3-hydroxyoctanoate, 2-29



To a solution of substrate **2-14** (104 mg, 0.3 mmol, 1 equiv) and Rh_2(*S*-DOSP)$_4$ (6 mg, 0.003 mmol, 1 mol%) in freshly distilled 2,2-dimethylbutane (5 mL) was added a solution of methyl 2-(4-bromophenyl)-2-diazoacetate **1-25** (152 mg, 0.6 mmol, 2 equiv) in 10 mL 2,2-dimethylbutane over 5 h. The reaction was stirred overnight after the addition was over. Then an access of trifluoroacetic acid (1.23 mL) was added to the crude reaction mixture and was let stir for 16 h. Product was purified via flash column chromatography (1:1:10 triethylamine/ diethyl ether / pentane) to give pale yellow oil as

the titled compound (24 mg, 14% yield, 58% ee, >94% de). $[\alpha]^{20}_{D}$: 36.2° (c = 0.7 w/v, $CHCl_3$); HPLC analysis: Chiralcel-AD-H column, 1% 2-propanol in hexanes, 0.5 mL/min, t_R = 11.78min (major), 10.29min (minor), UV 254 nm; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44 (m, 4H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 4.14 (m, 1H), 3.75 (d, *J* = 6.8, 8.0 Hz, 1H), 3.66 (s, 3H), 3.64 (s, 3H), 3.51 (d, *J* = 5.6 Hz, 1H), 3.20 (dd, *J* = 6.8, 8.0 Hz, 1H), 2.82 (dd, *J* = 6.8, 8.0 Hz, 1H), 2.15(t, *J* = 7.2 Hz, 2H), 1.50-1.18 (m, 8H+2H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 173.6, 173.4, 136.5, 134.2, 132.1, 131.9, 130.0, 122.1, 121.8, 72.0, 56.6, 52.7, 52.5, 52.4, 51.6, 51.6, 49.7, 34.5, 30.0, 27.2, 25.7; IR (neat) 3600-3200(broad peak), 2934, 2856, 1727, 1685, 1488, 1210, 1138, 1011, 844, 803, 765, 725 cm^{-1}; HRMS(ESI) calcd for $[C_{25}H_{31}Br_2NO_5 + H^+]$ 584.0647, Found $[M + H^+]$ 584.0647.

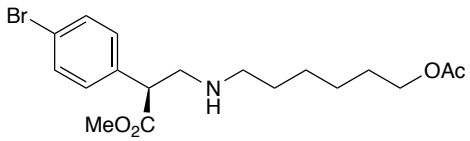
(*S*)-methyl 3-(((benzyloxy)carbonyl)(6-hydroxyhexyl)amino)-2-(4-bromophenyl) propanoate, 2-30



To a solution of substrate **2-17** (170 mg, 0.45 mmol, 1 equiv) and Rh_2(*S*-DOSP)$_4$ (9 mg, 0.005 mmol, 1 mol%) in freshly distilled 2,2-dimethylbutane (5 mL) was added a solution of methyl 2-(4-bromophenyl)-2-diazoacetate **1-25** (229 mg, 0.90 mmol, 2 equiv) in 10 mL 2,2-dimethylbutane over 5 h. The reaction was stirred overnight after the addition was over. Product was purified *via* flash column chromatography (1:1:30

triethylamine/ diethyl ether / pentane) to give pale yellow oil as the titled compound (156 mg, 60% yield). $[\alpha]^{20}_{D}$: -40.94° (c = 1.02 w/v, $CHCl_3$); HPLC analysis: ee=84%, Chiralcel-OD-H, 0.75% *i*-PrOH in hexane, 0.7mL/min, t_R = 11.78min (major), 10.29min (minor), UV 254 nm; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41~7.29 (m, 7H), 7.14 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 5.10 (m, 2H), 3.74 (dd, *J* = 8.4, 8.0 Hz, 1H), 3.65 (s, 3H), 3.21 (t, *J* = 8.4 Hz, 1H), 2.84 (dd, *J* = 8.4, 8.0 Hz, 1H), 4.11 (m, 0.45H), 3.85 (m, 0.45H), 3.70 (m, 1H), 3.63 (s, 3H), 3.53 (m, 2H+1H), 3.08 (m, 1.5H), 2.97 (m, 0.5H), 1.5~1.1(m, 8H), 0.87(s, 9H), 0.02(s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.2,145.5, 156.0, 132.1, 130.1, 129,9, 129.0, 128.7, 128.4, 128.0, 121.9, 67.5, 67.2, 63.3, 52.4, 51.6, 50.7, 50.6, 49.6, 48.9, 32.9, 30.1, 28.8, 28.1, 26.7, 26.1, 25.8, 18.6; IR (neat) 2929, 2856, 1735, 1698, 1251, 1165, 1131, 834, 773, 731, 697 cm^{-1}; HRMS(ESI) calcd for $[C_{24}H_{30}BrNO_5 + H^+]$ 492.1386, Found $[M + H^+]$ 492.1391;

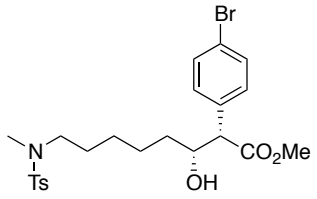
(*S*)-methyl 3-((6-acetoxyhexyl)amino)-2-(4-bromophenyl)propanoate, 2-31



To a solution of substrate **2-15** (136 mg, 0.5 mmol, 1 equiv) and Rh_2(*S*-DOSP)$_4$ (6 mg, 0.003 mmol, 1mol%) in freshly distilled 2,2-dimethylbutane (5 mL) was added a solution of methyl 2-(4-bromophenyl)-2-diazoacetate **1-25** (255 mg, 1 mmol, 2 equiv) in 10 mL 2,2-dimethylbutane over 5 h. The reaction was stirred overnight after the addition was over. Then an access of trifluoroacetic acid (1.5 mL) was added to the crude reaction

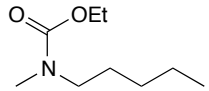
mixture and was let stir for 16 h. Product was purified via flash column chromatography (1:1:10 triethylamine/ diethyl ether / pentane) to give pale yellow oil as the titled compound (136 mg, 69% yield). $[\alpha]^{20}_{D}$: -30.70° (c = 1.4 w/v, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.15 (m, 2H), 4.01 (dd, *J* = 6.8, 6.4 Hz, 2H), 3.74 (dd, *J* = 8.4, 8.0 Hz, 1H), 3.65 (s, 3H), 3.21 (t, *J* = 8.4 Hz, 1H), 2.84 (dd, *J* = 8.4, 8.0 Hz, 1H), 2.56 (t, *J* = 7.2 Hz, 2H), 2.02 (s, 3H), 1.57 (m, 2H), 1.47 (m, 2H), 1.28 (m, 4H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 173.4, 171.4, 136.5, 132.1, 129.9, 121.8, 64.7, 52.7, 52.4, 51.7, 49.8, 30.1, 28.7, 27.1, 26.0, 21.2; IR (neat) 2933, 1735, 1488, 1364, 1239, 1163, 1011cm^{-1}; HRMS(ESI) calcd for [$C_{13}H_{26}BrNO_4$ + H^+] 400.1123, Found [M + H^+] 400.1115; To determine the enantiomeric excess of the product, **2-31** was converted to its trifluoroacetic amide by treating it with pyridine and trifluoroacetic anhydride. TFAA (2 equiv) was added to a round bottom flask charged with **2-31** (1 equiv) in 2 mL pyridine. The resulting mixture was stirred at room temperature for 6 h. The acylation product of **2-31** was purified by preparative TLC (10:1 pentane/diethyl ether) giving the amide in 83% ee (HPLC, Chiralcel-OD-H column, 5% 2-propanol in hexanes, 0.5mL/min, t_R = 28.26 min (major), 23.09 min (minor), UV 254 nm).

(2*S*,3*R*)-methyl 2-(4-bromophenyl)-8-(*N*,4-dimethylphenylsulfonamido)-3-hydroxy-octanoate, 2-32



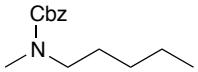
To a solution of substrate **2-18** (89 mg, 0.25 mmol, 1 equiv) and Rh_2(*S*-DOSP)$_4$ (5 mg, 0.0026 mmol, 1mol%) in freshly distilled 2,2-dimethylbutane (5 mL) was added a solution of methyl 2-(4-bromophenyl)-2-diazoacetate **1-25** (128 mg, 0.5 mmol, 2 equiv) in 10 mL 2,2-dimethylbutane over 5 h. The reaction was stirred overnight after the addition was over. Then an access of trifluoroacetic acid (1.5 mL) was added to the crude reaction mixture and was let stir for 16 h. Product was purified *via* flash column chromatography (1:1:10 triethylamine/ diethyl ether / pentane) to give pale yellow oil as the titled compound (53.8 mg, 42% yield). $[\alpha]^{20}_{D}$: -18.67° (c = 0.12 w/v, $CHCl_3$); HPLC analysis: ee=88%, Chiralcel-OD-H, 1% *i*-PrOH in hexane, 1mL/min, t_R = 7.34 min (minor), 9.18 min (major), UV 254 nm; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.15 (m, 2H), 4.01 (dd, *J* = 6.8, 6.4 Hz, 2H), 3.74 (dd, *J* = 8.4, 8.0 Hz, 1H), 3.65 (s, 3H), 3.21 (d, *J* = 8.4 Hz, 1H), 2.84 (dd, *J* = 8.4, 8.0 Hz, 1H), 2.56 (t, *J* = 7.2 Hz, 2H), 2.02 (s, 3H), 1.57 (m, 2H), 1.47 (m, 2H), 1.28 (m, 4H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 173.4, 171.4, 136.5, 132.1, 129.9, 121.8, 64.7, 52.7, 52.4, 51.7, 49.8, 30.1, 28.7, 27.1, 26.0, 21.2; IR (neat) 2933, 1735, 1488, 1364, 1239, 1163, 1011cm^{-1}; HRMS(ESI) calcd for [$C_{23}H_{30}BrNO_5S$ + H^+] 512.1106, Found [M + H^+] 512.1108.

Ethyl methyl(pentyl)carbamate, 2-37a



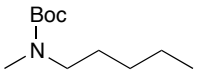
N-methylpentylamine (503 mg, 5 mmol, 1 equiv) was added to a round bottome flask with 50 mL DCM. Triethylamine (1 g, 10 mmol, 2 equiv) was added and the reaction mixture was cooled down to 0 ^{o}C and stirred for 30 min. Ethylchloroformate (1.1 g, 10 mmol, 2 equiv) was added dropwise and reaction was kept at 0 ^{o}C for 10 min. Reaction was let warmed up to room temperature and stirred at room temperature overnight. Reaction was quenched with 5 mL 1M HCl, and the crude mixture was extracted with DCM. The combined organic layer was washed with water. The combined aqueous layer was then extracted with DCM. The combined organic layer was washed with brine and then dried over $MgSO_4$. Solvent was removed *in vacuo* and the crude reaction mixture was subjected to column chromatography (1:5 diethyl ether/ hexanes), yielding the title product as colorless oil (700 mg, 81% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.08 (t, J = 6.8 Hz, 2H), 3.20 (broad, 2H), 2.85 (broad, 3H), 1.48 (m. 2H), 1.31-1.27 (m. 4H), 1.22 (t, J = 6.8 Hz, 3H), 0.87(t, J = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 61.2; 49.0; 34.6; 29.0; 27.6; 22.6; 14.9; 14.2; IR (neat) 2957; 2931; 2861; 1702; 1468; 1404; 1383; 1206; 1172; 1100; 771 cm^{-1}; HRMS(ESI) calcd for [$C_9H_{19}NO_2$ + H^+] 174.1494, Found [M + H^+] 174.1487.

Benzyl methyl(pentyl)carbamate, 2-37b



Phosphotungstic acid hydrate (29 mg, 0.1 mmol, 0.05 equiv) and benzyl chloride (280 mg, 2.2 mmol, 1.1 equiv) were added to the flask. A solution of N-methylpentylamine (201 mg, 2 mmol, 1 equiv) in 8 mL DCM was added to the above mixture. Reaction mixture was stirred at room temperature overnight. Crude reaction mixture was filtered through a pad of celite. Solvent was removed *in vacuo* and the crude reaction mixture was subjected to column chromatography (1:10 diethyl ether/hexanes), yielding the title product as colorless oil (314 mg, 67% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (m, 5H), 5.11 (s, 2H), 3.25 (broad, 2H), 2.88 (s, 3H), 1.50 (m, 2H), 1.28-1.22 (m, 4H), 0.87-0.85 (broad, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.3; 128.6; 128.0; 127.9; 67.1; 49.1; 34.4; 29.0; 27.5; 22.6; 14.2; IR (neat) 2930; 2860; 1699; 1455; 1403; 1308; 1208; 1162; 1098; 1053; 733; 697cm^{-1}; HRMS(ESI) calcd for [$C_{14}H_{21}NO_2$ + H^+] 236.1651, Found [M + H^+] 236.1645.

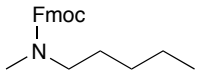
***tert*-butyl methyl(pentyl)carbamate, 2-37c**



N-methylpentylamine (1 g, 10 mmol, 1 equiv) was added to a round bottom flask with 50mL DCM. Triethylamine (2 g, 20 mmol, 2 equiv) was added and the reaction mixture

was stirred for 30 min. Di-tert-butyl dicarbonate (2.4 g, 11 mmol, 1.1 equiv) was then added in one shot and reaction was stirred at room temperature overnight. Crude reaction mixture was washed with D.I. water. Then the aqeous layer was extracted with DCM. The combined organic layer was washed with brine and then dried over $MgSO_4$. Solvent was removed *in vacuo* and the crude reaction mixture was subjected to column chromatography (1:10 diethyl ether/ hexanes), yielding the title product as colorless oil (1.7 g, 82% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.15 (broad, 2H), 2.80 (s, 3H), 1.47 (m, 2H), 1.43 (s, 9H), 1.21-1.23 (m, 4H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.1; 79.2; 49.0; 34.1; 29.0; 28.7; 27.6; 22.6; 14.3; IR (neat) 2959; 2929; 2862; 1693; 1391; 1364; 1152; 876; 770 cm^{-1}; HRMS(ESI) calcd for [$C_{11}H_{23}NO_2 + H^+$] 202.1807, Found [$M + H^+$] 202.1803.

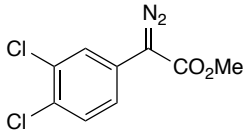
(9*H*-fluoren-9-yl)methyl methyl(pentyl)carbamate, 2-37d



N-methylpentylamine (200 mg, 2 mmol, 1 equiv) was added to a round bottom flask with 50 mL DCM. Freshly distilled DIPEA (0.37 ml, 2.2 mmol, 1.1 equiv) was added in one shot and resulting mixture was stirred for 30 min at room temperature. A solution of Fmoc-Cl (568 mg, 2.2 mmol, 1.1 equiv) in 6 mL MeCN was added to the above mixture over 10 min. Reaction was stirred at room temperature overnight. Solvent was removed *in vacuo* and was purified via column chromatography (1:5 diethyl ether/ hexanes), yielding the title product as colorless oil (471 mg, 72% yield). ^{1}H-NMR (400 MHz,

$CDCl_3$) δ 7.78 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 6.8 Hz, 2H), 7.38 (dd, *J* = 7.2, 6.8 Hz, 2H), 7.30 (dd, *J* = 7.2, 7.6 Hz, 2H), 4.45 (dd, *J* = 6.8, 9.6 Hz, 2H), 4.22 (m, 1H), 3.27 (t, *J* = 7.2 Hz, 1H), 3.08 (t, *J* = 7.2 Hz, 1H), 2.87 (d, *J* = 12.8 Hz, 3H), 1.52 (m, 1H), 1.34-1.22 (m, 4H), 1.12 (m, 1H), 0.88 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.5; 144.4; 141.6; 127.8; 127.2; 125.2; 125.0; 120.1; 67.2; 49.2; 47.6; 34.4; 29.0; 27.5; 22.7; 14.2; IR (neat) 2929; 2860; 1698; 1478; 1449; 1403; 1205; 1163; 1099; 757; 739 cm^{-1}; HRMS(ESI) calcd for [$C_{21}H_{25}NO_2 + H^+$] 324.1964, Found [$M + H^+$] 324.1959.

Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate, 3-2



3,4-dichlorophenylacetic acid (5.1 g, 25 mmol) was dissolved in MeOH (50 mL) in a flame dried round bottom flask, the reaction mixture was cooled to 0 ^{o}C. Acetyl chloride (3.9 g, 50 mmol) was added dropwise at 0 ^{o}C, and the reaction mixture was stirred at room temperature overnight. Saturated NH_4Cl solution was added to the crude reaction mixture, and the mixture was extracted with diethyl ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude mixture was taken to next step without further purification. The resultant methyl ester was dissolved in acetonitrile and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA) (6.4 g, 27.5 mmol) was added. The reaction mixture was cooled to 0 ^{o}C and 1,8-Diazabicycloundec-7-ene (DBU) (7.40 mL, 48.7 mmol) was added dropwise at 0 ^{o}C. The reaction mixture

was stirred at room temperature overnight. Reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with diethyl ether. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (9:1 hexane/Et_2O) and pure product was obtained as yellow solid (4.8 g, 81% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 1.9 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.29 (dd, J = 8.6, 2.3 Hz, 1H), 3.88 (s, 3H). The ^{1}H-NMR data was consistent with published values.[173]

General Procedure A (Cyclopropanation)

To a solution of substituted aryl styrene (3 equiv) in dry toluene was added Rh_2(*S*-DOSP)$_4$ (1 mol%). The resulting mixture was degassed with argon and cooled to -45 ^{o}C. A solution of diazo compound (1 equiv) in dry toluene was added to the above mixture over 5 h at -45 ^{o}C, and the reaction was let warmed up to room temperature slowly and was stirred overnight. Solvent was then removed under reduced pressure and the crude reaction mixture was purified by column chromatography (SiO_2, 1:19 diethyl ether/hexanes).

General Procedure B (Reduction-Oxidation)

In a 50 mL round bottom flask equipped with a magnetic stir bar, aryl cyclopropanecarboxylate (1 equiv) was dissolved in diethyl ether (15 mL) and flushed

with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (2.1 equiv) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 1 hour. The reaction was quenched with $NaSO_4 \bullet 10H_2O$ (added until bubbling ceased), dried with $MgSO_4$, and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure. The residue was re-dissolved in methylene chloride (10 mL) and Dess-Martin reagent (2.1 equiv) was added. The reaction was covered in Aluminum foil and stirred at room temperature for 1 hour (TLC monitored) until starting material disappeared. It was then diluted with ether and washed with aqueous 1M NaOH (x2). The organic phase was dried with $MgSO_4$, filtered through a short path of silica, and concentrated under reduced pressure. The residue was purified via column chromatography (SiO_2, 8:1 hexanes/ethyl acetate) to give the corresponding diarylcyclopropyl carbaldehyde.

General Procedure C (Reductive Amination)

In a 50 mL round bottom flask equipped with a magnetic stir bar, diaryl cyclopropane carbaldehyde (1 equiv) was dissolved in methanol (15 mL) and flushed with argon. This solution was treated with the appropriate methyl aminocarboxylic ester (2 equiv) and $Ti(O\text{-}i\text{Pr})_4$ (2 equiv) and stirred at room temperature for 48 hours. After the allotted time had passed, $NaBH_4$ (2 equiv) was added and the reaction was stirred overnight at room temperature. The reaction was quenched with H_2O (1 mL) and concentrated under reduced pressure. The residue was re-dissolved in ethyl acetate with 10% triethylamine

and filtered through a short pad of silica. The filtrate was then concentrated under reduced pressure and the resulting residue was purified by column chromatography (SiO_2, 9:1 ethyl acetate: triethylamine) to give the desired diarylcyclopropylamines.

General Procedure D (Cyclopropanation)

To a 100 mL round bottom flask equipped with a magnetic stir bar were added *(E)*-buta-1, 3-dienylbenzene (2 equiv), Rh_2(*S*-DOSP)$_4$ (1 mol%) and dry, degassed toluene (50 mL). The reaction mixture was cooled to -45 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-phenylacetate (1 equiv) was dissolved in dry, degassed toluene (10 mL) and added by syringe pump over 5 h. The reaction was stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, 10:1 hexanes/ethyl acetate)

General Procedure E (Ozonolysis):

In a 50 mL round bottom flask equipped with a magnetic stir bar, styryl cyclopropane carboxylate (1 equiv) was dissolved in dichloromethane (50 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 15 min. Triphenylphosphine (1.1 equiv) was added to quench the reaction and the crude mixture was stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure and the residue was

purified *via* column chromatography (SiO_2, 5:1 hexanes/ ethyl acetate) to give the corresponding aryl cyclopropylcarbaldehyde.

General Procedure F (Reductive Amination):

To an oven-dried round bottom flask flushed with argon was added dry MeOH (15mL), methyl 1-(3,4-dichlorophenyl)-2-formylcyclopropanecarboxylate (1 equiv), and molecular sieves (activated). The appropriate methyl aminocarboxylate (2 equiv) was then added to the above reaction mixture. Reaction was stirred under argon for 2 days until the aldehyde disappears. After the allotted time had passed, $NaBH_4$ (1.5 equiv) was added and the reaction was stirred for an additional 2 hours at room temperature. The reaction was quenched with sodium sulfate, filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, brine and dried over $MgSO_4$. The crude reaction mixture was concentrated under reduced pressure and product was purified by column chromatography (SiO2, 9:1 ethyl acetate/triethylamine).

General Procedure G (Hydrolysis):

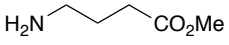
To a round bottom flask with THF/H2O (1:1) was added the cyclopropylcarboxylate (1 equiv). LiOH (1.2 equiv) was added to the above reaction mixture in one shot, and the resulting mixture was stirred at room temperature for 16 hours. After the allotted time has

passed, solvent was removed under reduced pressure. The crude product was crystalized in MeOH/acetone.

General Procedure H (Fumaric Salt Formation)

Substrate (1 equiv) was dissolved in isopropanol (20 mL) and then treated with fumaric acid (1 equiv). The resulting mixture was stirred for 30 minutes at room temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to room temperature and solvent was removed under reduced pressure. The resulting crude mixture was dissolved with minimum amount of acetone and n-hexane was then added slowly to the saturated acetone solution. The resulting solution was let stand at room temperature to crystalize and pure product was washed with cold n-hexane and dried *in vacuo*.

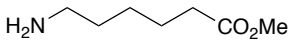
Methyl 4-aminobutanoate, 3-8a



4-aminobutanoic acid (515 mg, 1 equiv) was added to a round bottom flask with MeOH (15 mL). To the reaction mixture was added TMSCl (594 mg, 1.1 equiv), and the resulting mixture was stirred at room temperature overnight. Solvent was removed under reduced pressure and the crude mixture was purified by column chromatography

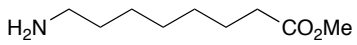
(Et_3N/ethyl acetate=1:10) to yield the titled compound as white solid (513 mg, 88% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.97 (broad, 2H), 3.65(s, 3H), 3.10 (t, J = 7.6 Hz, 2H), 2.50(t, J = 6.8 Hz, 2H), 2.07(m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.7, 52.2, 39.7, 31.2, 23.0; IR (neat) 3400, 2955, 1723, 1439, 1209, 1183 cm^{-1}; HRMS(ESI) calcd for [$C_5H_{11}NO_2 + H^+$] 118.0868, Found [$M + H^+$] 118.0860.

Methyl 6-aminohexanoate, 3-8b



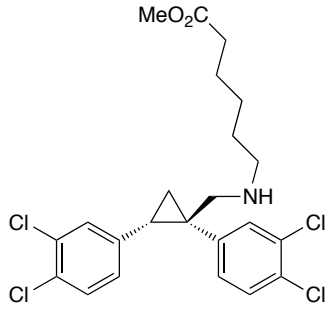
4-aminobutanoic acid (446 mg, 1 equiv) was added to a round bottom flask with MeOH (15 mL). To the reaction mixture was added TMSCl (369 mg, 1.1 equiv), and the resulting mixture was stirred at room temperature overnight. Solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (Et_3N/ethyl acetate=1:10) to yield the titled compound as white solid (337 mg, 69% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 2H), 3.65 (s, 3H), 2.99 (t, J = 7.6 Hz, 2H), 1.78 (m, 2H), 1.65 (m, 2H), 1.44 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.1, 51.9, 39.9, 33.8, 27.5, 26.1, 24.4; IR (neat) 3412, 2944, 1732, 1438, 1254, 1196, 1177, 1116 cm^{-1}; HRMS(ESI) calcd for [$C_7H_{15}NO_2 + H^+$] 146.1181, Found [$M + H^+$] 146.1173.

Methyl 8-aminooctanoate, 3-8c



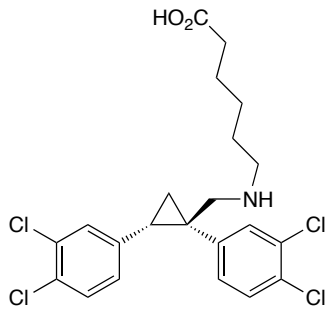
4-aminobutanoic acid (954 mg, 1 equiv) was added to a round bottom flask with MeOH (15 mL). To the reaction mixture was added TMSCl (712 mg, 1.1 equiv), and the resulting mixture was stirred at room temperature overnight. Solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (Et_3N/ethyl acetate=1:10) to yield the titled compound as white solid (827 mg, 78% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.28 (broad, 2H), 3.64 (s, 3H), 2.96 (dd, J = 7.2, 8.0 Hz, 2H), 2.27 (t, J = 7.6, 7.2 Hz, 2H), 1.74 (m, 2H), 1.59 (m, 2H), 1.41~1.30 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.4, 51.7, 46.0, 40.1, 34.1, 28.8, 27.7, 26.5, 24.9; IR (neat) 2939, 2864, 1733, 1623, 1516, 1194 cm^{-1}; HRMS(ESI) calcd for [$C_9H_{19}NO_2$ + H^+] 174.1494, Found [M + H^+] 174.1486.

Methyl 6-((((1*R*,2*S*)-1,2-bis(3,4-dichlorophenyl)cyclopropyl)methyl)amino)hexanoate, 3-9b



The titled compound was synthesized by general procedure A~C (87 mg, 48% yield over 3 steps). $[\alpha]^{20}_{D}$: 17.84° (c = 1.13 w/v, CH_3OH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 2.0 Hz, 1H), 7.19 (d, *J* = 4.4 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.79 (d, *J* = 2.0 Hz, 1H), 6.43 (d, *J* = 2.0 Hz, 1H), 6.41 (d, *J* = 2.0 H, 1H), 3.02(d, *J* = 12.4 Hz, 1H), 2.60 (d, *J* = 12.4 Hz, 1H), 2.54 (m, 2H), 2.26 (t, *J* = 7.6 Hz, 2H), 2.19 (dd, *J* = 6.0, 6.4 Hz, 1H), 1.57 (m, 2H), 1.39 (m, 4H), 1.24 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.3, 139.3, 139.0, 132.7, 132.5, 132.1, 131.1, 130.4, 130.2, 130.1, 129.9, 126.7, 60.2, 51.7, 49.8, 35.8, 34.2, 29.8, 27.6, 26.9, 24.9, 17.9; IR (neat) 2935, 2359, 2342, 1734, 1474, 1376, 1135, 1029, 823, 678 cm^{-1}; HRMS(ESI) calcd for $[C_{23}H_{25}Cl_4NO_2 + H^+]$ 488.0718, Found $[M + H^+]$ 488.0709.

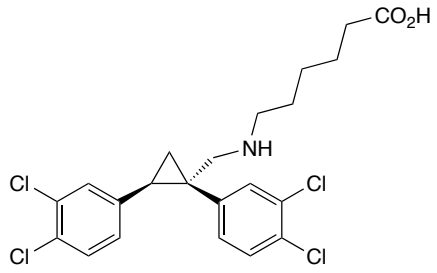
6-((((1*R*,2*S*)-1,2-bis(3,4-dichlorophenyl)cyclopropyl)methyl)amino)hexanoic acid, 3-10b



The titled compound was obtained by procedure G as white solid (43 mg, 64% yield). $[\alpha]^{20}_{D}$: 130.23° (c = 1.41 w/v, CH_3OH); ^{1}H-NMR (400 MHz, CD_3OD) δ 7.27 (d, *J* = 2.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.95 (m, 2H), 6.60 (dd, *J* = 2,

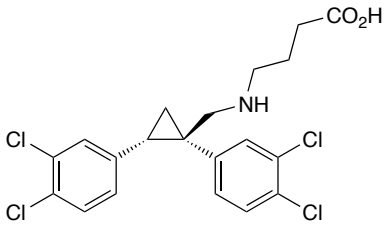
8.4 Hz, 1H), 3.45 (d, J = 13.2 Hz, 1H), 2.71 (d, J = 13.2 Hz, 1H), 2.68 (m, 2H), 2.39 (dd, J = 6.4, 8.8Hz, 1H), 2.01 (t, J = 6.8 Hz, 2H), 1.70 (t, J = 2.0 Hz, 1H), 1.47 (m, 5H), 1.22 (m, 5H), 1.21(m, 2H); ^{13}C-NMR (100 MHz, CD_3OD) δ 182.6, 139.8, 139.1, 134.4, 133.5, 132.9, 132.6, 132.0, 131.8, 131.4, 131.0, 130.9, 128.7, 59.2, 49.9 38.8, 34.2, 29.4, 27.9, 27.1, 17.7; IR (neat) 2935, 2857, 1558, 1474, 1402, 1379, 1135, 1029, 907, 823, 732, 679 cm^{-1}; HRMS(ESI) calcd for [$C_{22}H_{23}Cl_4NO_2 + H^+$] 474.0561, Found [$M + H^+$] 474.0564.

6-((((1*S*,2*R*)-1,2-bis(3,4-dichlorophenyl)cyclopropyl)methyl)amino)hexanoic acid, *ent*-3-10b



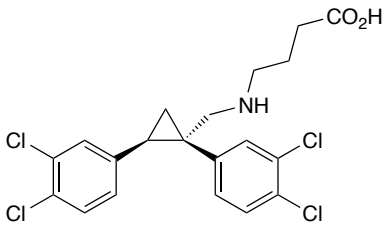
The titled compound was obtained by procedure A-B-C-G as white solid (31 mg, 27% overall yield). [α]$^{20}_D$: -0.95° (c = 2.10 w/v, CH_3OH); Other experimental data was the same as **3-10b**.

4-((((1*R*,2*S*)-1,2-bis(3,4-dichlorophenyl)cyclopropyl)methyl)amino)butanoic acid, 3-10a



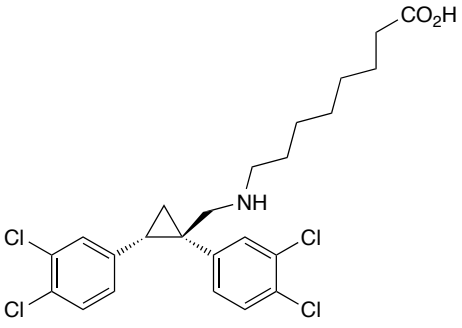
The titled compound was obtained by procedure A-B-C-G as white solid (55 mg, 31% overall yield). $[\alpha]^{20}_{D}$: 47.35° (c = 0.82 w/v, CH_3OH); ^{1}H-NMR (400 MHz, CD_3OD) δ 7.33 (d, *J* = 1.6 Hz, 1H,) 7.26 (d, *J* = 8.8 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.01(d, *J* = 2.0 Hz, 1H), 7.00 (d, *J* = 2.0 Hz, 1H), 6.66 (dd, *J* = 2, 8.4 Hz, 1H), 3.62 (d, *J* = 13.2 Hz, 1H), 2.85 (m, 3H), 2.48 (dd, *J* = 6.4, 6.8 Hz, 1H), 2.25 (m, 2H), 1.78 (m, 1H), 1.70 (m, 2H), 1.54 (dd, *J* = 6.4, 6.8 Hz, 1H); ^{13}C-NMR (100 MHz, CD_3OD) δ 181.2, 139.1, 138.1, 134.4, 133.8, 133.1, 133.0, 132.1, 132.0, 131.5, 131.3, 131.0, 129.0, 58.3, 50.2, 37.0, 33.2, 33.0, 23.1, 17.4; IR (neat) 2934, 2849, 1561, 1479, 1379, 1030, 907, 831, 678 cm^{-1}; HRMS(ESI) calcd for [$C_{20}H_{19}Cl_4NO_2 + H^+$] 446.0248, Found [$M + H^+$] 446.0244.

4-((((1*S*,2*R*)-1,2-bis(3,4-dichlorophenyl)cyclopropyl)methyl)amino)butanoic acid, *ent*-3-10a



The titled compound was obtained by procedure A-B-C-G as white solid (18 mg, 24% overall yield). $[\alpha]^{20}_{D}$ = -31.80° (c = 0.59 w/v, CH_3OH); Other experimental data of this compound was the same as **3-10a**.

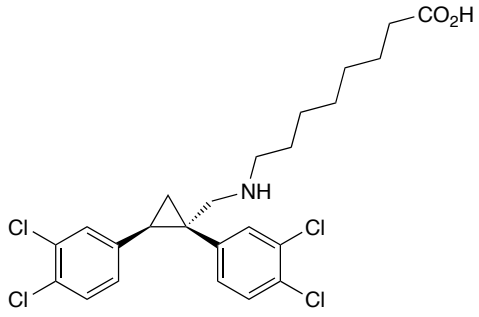
8-((((1*R*,2*S*)-1,2-bis(3,4-dichlorophenyl)cyclopropyl)methyl)amino)octanoic acid, 3-10c



The titled compound was obtained by procedure A-B-C-G as off-white solid (47 mg, 36% overall yield). $[\alpha]^{20}_{D}$ = 41.77° (c = 0.71 w/v, CH_3OH); ^{1}H-NMR (400 MHz,

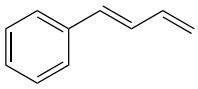
CD_3OD) δ 7.20 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 1.6 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.43 (dd, *J* = 1.6, 8.0 Hz, 1H), 5.98 (broad, 1H), 3.34 (t, *J* =6.4 Hz, 1H), 3.15 (d, *J* = 12.8 Hz, 1H), 2.77 (d, *J* = 12.4 Hz, 1H), 2.61 (broad, 1H), 2.15 (broad, 2H), 1.53~1.40 (broad, 6H), 1.20 (broad, 6H); ^{13}C-NMR (100 MHz, CD_3OD) δ 138.1, 137.8, 132.9, 132.8, 132.1, 131.7, 130.7, 130.4, 130.3, 130.2, 129.9, 126.7, 58.6, 53.9, 48.8, 35.7, 33.9, 29.5, 29.1, 28.3, 27.9, 26.8, 18.0; IR (neat) 2927, 2854, 1703, 1556, 1473, 1134, 1029, 907, 823, 729 cm^{-1}; HRMS(ESI) calc for [$C_{24}H_{27}Cl_4NO_2$ + H^+] 502.0874, Found [M + H^+] 502.0868.

8-((((1*S*,2*R*)-1,2-bis(3,4-dichlorophenyl)cyclopropyl)methyl)amino)octanoic acid, *ent*-3-10c



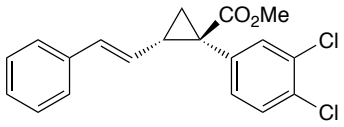
The titled compound was obtained by procedure A-B-C-G as off-white solid (24 mg, 17% overall yield). [α]$^{20}_D$: -35.11° (c = 0.61 w/v, CH_3OH); Other experimental data of this compound was the same as **3-10c**.

(*E*)-buta-1,3-dienylbenzene, 3-11



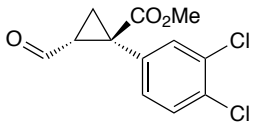
Methyltriphenylphosphine bromide (35.6 g, 10 mmol) was added to a flame dried flask and THF (100 mL) was added. The reaction flask was cooled to 0 ^{o}C and potassium *ter*-butoxide (16.8 g, 15 mmol) was added. Reaction was then stirred for 5 h at 0 ^{o}C. (*E*)-3-Phenylacrylaldehyde (13.2 g, 10 mmol) in THF (20 mL) was added dropwise over 1 h, and then the reaction was stirred for 16 additional hours. The reaction was poured into H_2O and extracted into pentane. The combined organic layer was washed with brine, dried over $MgSO_4$. Hexane (100 mL) was added to the reaction flask. Triphenyl phosphine oxide precipitated out. The reaction mixture was filtered through celite/silica gel and the solvent was removed under reduced pressure. The crude material was purified using Kughlerrohr distillation (85 °C) to obtain the titled product as colorless oil (10 g, 80 % yield). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.32 (m, 5H) 6.78 (dd, J = 10.4 Hz, 1H) 6.54 (m, 2H) 5.34 (d, J = 16.8 Hz, 1H) 5.17 (d, J = 10.4 Hz, 1H). The ^{1}H-NMR data was consistent with reported values.[172]

(1*R*,2*S*)-methyl 1-(3,4-dichlorophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate, 3-12



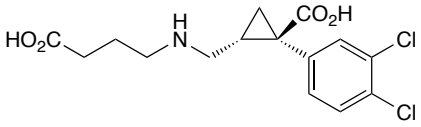
The titled compound was synthesized via procedure D (1.2g, 90% yield, >94% de). [α]$^{D}_{20}$: 81.37° (c = 1.0 w/v, MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.49~7.37 (m, 2H), 7.24~7.11 (m, 6H), 6.60 (d, *J* = 15.6 Hz, 1H), 5.21 (dd, *J* = 9.6, 10.0 Hz, 1H), 3.65 (s, 3H), 2.70 (m, 1H), 2.07 (dd, *J* = 4.8, 8.8 Hz, 1H), 1.44 (dd, *J* = 4.8, 6.4 Hz, 1H); HPLC analysis: ee = 92% (Chiralcel-OD-H, 1% *i*-PrOH in hexane, 1mL/min, t_R = 11.78min (major), 10.29min (minor), UV 254 nm). The experimental data of the titled compound was consistent with prior reported result.[172]

(1*R*,2*R*)-methyl 1-(3,4-dichlorophenyl)-2-formylcyclopropanecarboxylate, 3-13



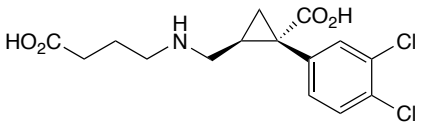
The titled compound was synthesized via procedure E (568 mg, 80% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.74 (d, *J* = 5.8 Hz, 1H), 7.46~7.38 (m, 2H), 7.14 (dd, *J* = 1.8, 8.2 Hz, 1H), 3.67 (s, 3H), 2.80 (dt, *J* = 6.1, 8.4 Hz, 1H), 2.13 (dd, *J* = 5.0, 8.7 Hz, 1H), 2.06(m, 1H). The experimental data of the titled compound was consistent with prior reported result.[172]

(1*R*,2*R*)-2-(((3-carboxypropyl)amino)methyl)-1-(3,4-dichlorophenyl)cyclopropane carboxylic acid, 3-15a



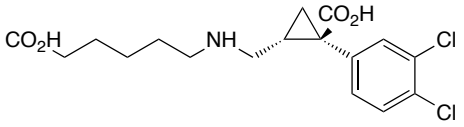
The titled compound was obtained by procedure F~G (27 mg, 39% overall yield). [α]$^{D}_{20}$: 24.52° (c = 0.66w/v, MeOH); ^{1}H-NMR (400 MHz, CD_3OD): δ 6.99 (m, 2H), 6.78 (dd, *J* = 2.4, 8 Hz, 1H), 3.16 (m, 2H), 1.98 (dd, *J* = 9.2, 13.6 Hz, 1H), 1.88 (m, 2H), 1.69~1.46 (m, 3H), 1.11 (dd, *J* = 4.4, 8.8 Hz, 1H), 0.75 (t, *J* = 6.8 Hz, 1H), 0.71(m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ165.3, 135.2, 130.3, 128.0, 126.0, 123.9, 121.8, 52.4; IR (neat): 2094, 1708, 1593, 1481, 1437, 1356, 1246, 1159, 1050 cm^{-1}; HRMS (APCI) calcd for [$C_{15}H_{17}Cl_2NO_4$ + H^+] 346.0613, Found [M + H^+] 346.0611.

(1*S*,2*S*)-2-(((3-carboxypropyl)amino)methyl)-1-(3,4-dichlorophenyl) cyclopropane carboxylic acid, *ent*-3-15a



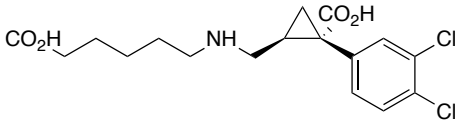
The titled compound was obtained by procedure D~G as off-white solid (14 mg, 36% overall yield). [α]$^{20}_{D}$: -29.8° (c = 0.41 w/v, CH_3OH); Other experimental data of this compound was the same as **3-15a**.

(1*R*,2*S*)-1-(3,4-dichlorophenyl)-2-(((5-(formyloxy)pentyl)amino)methyl)cyclopropyl formate, 3-15b



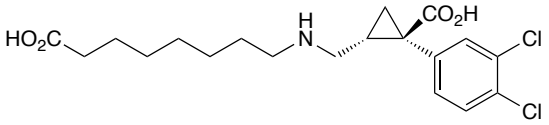
The titled compound was obtained by procedure D~G as white solid (22 mg, 36% overall yield). $[\alpha]^{D}_{20}$: 15.39° (c = 0.94w/v, MeOH); ^{1}H-NMR (400 MHz, CD_3OD): δ 7.43 (d, *J* = 2.0 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.16 (dd, *J* = 6.4, 8.8 Hz, 1H), 3.36 (dd, *J* = 6.8, 14.0 Hz, 1H), 2.81(t, *J* = 7.6 Hz, 2H), 2.20 (t, *J* = 5.6 Hz, 2H), 2.10 (m, 1H), 1.88 (dd, *J* = 6.8, 12.4 Hz, 1H), 1.72 (dd, *J* = 4.8, 8 Hz, 1H), 1.52 (m, 4H), 1.42 (t, *J* = 6.4 Hz, 1H), 1.29 (m, 2H); ^{13}C-NMR (100 MHz, CD_3OD) δ177.4, 175.5, 137.2, 134.5, 133.4, 133.1, 132.3, 131.7, 67.1, 50.0, 34.5, 34.1, 27.1, 25.5, 23.7, 21.0, 15.6; IR (neat): 3376 (broad), 2953, 1709, 1474, 1238, 1181, 713 cm^{-1}; HRMS (APCI) calcd for $[C_{17}H_{21}Cl_2NO_4 + H^+]$ 374.0926, Found $[M + H^+]$ 374.0923.

(1*S*,2*R*)-1-(3,4-dichlorophenyl)-2-(((5-(formyloxy)pentyl)amino)methyl)cyclopropyl formate, *ent*-3-15b



The titled compound was obtained by procedure D~G as off-white solid (14 mg, 26% overall yield). $[\alpha]^{20}_{D}$: -31.4° (c = 0.32 w/v, CH_3OH); Other experimental data of this compound was the same as **3-15b**.

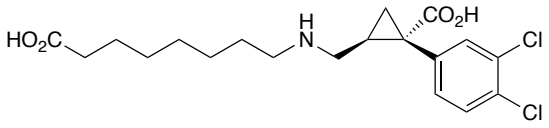
(1*R*,2*R*)-2-(((7-carboxyheptyl)amino)methyl)-1-(3,4-dichlorophenyl)cyclopropane-carboxylic acid, 3-15c



The titled compound was obtained by procedure D~G as white solid (15 mg, 19% overall yield). $[\alpha]^{D}_{20}$: 21.37° (c = 0.67 w/v, MeOH); ^{1}H-NMR (400 MHz, CD_3OD): δ 7.27 (d, *J* = 2.0 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.01 (dd, *J* = 2.4, 8.4 Hz, 1H), 3.16 (s, 3H), 2.30~2.20 (m, 3H), 1.93 (t, *J* = 7.2 Hz, 2H), 1.76 (m, 1H), 1.61 (dd, *J* = 7.6, 8.4 Hz, 1H), 1.43~1.33 (m, 3H), 1.22 (m, 2H), 1.11 (m, 6H), 0.86 (dd, *J* = 4.0, 6.0 Hz, 1H); ^{13}C-NMR (100 MHz, CD_3OD) δ183.3, 180.7, 142.3, 134.4, 132.5, 132.2, 131.0, 130.9, 51.9, 50.7, 39.5, 36.7, 31.0, 30.8, 30.7, 28.6, 27.9, 26.7, 19.6; IR (neat): 3354, 2928, 2854, 1573,

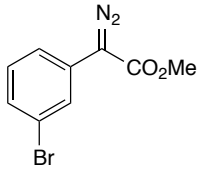
1447, 1412, 1327, 1093, 1029, 827, 724 cm^{-1}; HRMS (APCI) calcd for [$C_{19}H_{25}Cl_2NO_4$ + H^+] 402.1239, Found [M + H^+] 402.1238.

(1*S*,2*S*)-2-(((7-carboxyheptyl)amino)methyl)-1-(3,4-dichlorophenyl)cyclopropane-carboxylic acid, ent-3-15c



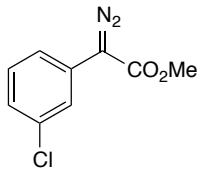
The titled compound was obtained by procedure D~G as off-white solid (14 mg, 26% overall yield). $[\alpha]^{20}_D$: -19.7° (c = 0.12 w/v, CH_3OH); Other experimental data of this compound was the same as **3-15c**.

Methyl 2-(3-bromophenyl)-2-diazoacetate, 4-29b



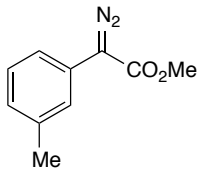
The titled compound was obtained as yellow solid by a previously reported diazo transfer reaction (1.23 g, 89% yield).[63] ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.51 (m, 1H), 7.28 (m, 2H), 7.13 (m, 1H), 3.83 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ165.3, 135.2, 130.3, 128.0, 126.0, 123.9, 121.8, 52.4; IR (neat): 2094, 1708, 1593, 1481, 1437, 1356, 1246, 1159, 1050 cm^{-1}; HRMS (APCI) calcd for [$C_9H_7BrN_2O_2$ + H^+] 254.9769, Found [M + H^+] 254.9771.

Methyl 2-(3-chlorophenyl)-2-diazoacetate, 4-29c



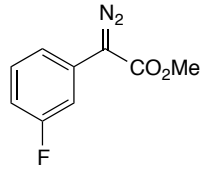
The titled compound was obtained as yellow oil by a previously reported diazo transfer reaction (520 mg, 92% yield).[63] ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.51 (m, 1H), 7.28 (m, 2H), 7.13 (m, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ165.3, 135.2, 130.3, 128.0, 126.0, 123.9, 121.8, 52.4; IR (neat): 2094, 1708, 1593, 1481, 1437, 1356, 1246, 1159, 1050 cm^{-1}; HRMS (APCI) calcd for [$C_9H_7ClN_2O_2$ +H^+] 211.0274, Found [M + H^+] 211.0274.

Methyl 2-diazo-2-(*m*-tolyl)acetate, 4-29d



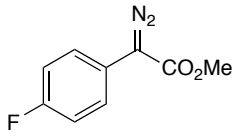
The titled compound was obtained as yellow oil by a previously reported diazo transfer reaction (387 mg, 79% yield).[63] ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (m, 3H), 6.97 (m, 1H), 3.83 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ165.8, 138.8, 129.0, 126.9, 125.4, 124.7, 121.3, 52.1, 21.7; IR (neat): 2952, 2077, 1698, 1582, 1435, 1342, 1247, 1145, 1054, 775, 738,689, 666 cm^{-1}; HRMS (APCI) calcd for [$C_{10}H_{10}N_2O_2$ + H^+] 191.0821, Found [M + H^+] 191.0832.

Methyl 2-diazo-2-(3-fluorophenyl)acetate, 4-29e



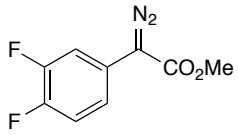
The titled compound was obtained as yellow oil by a previously reported diazo transfer reaction (237 mg, 67% yield).[63] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 2H), 7.14 (m, 1H), 6.85 (m, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ165.3, 164.6 (d, J = 242 Hz), 130.6 (d, J = 8.9 Hz), 128.3 (d, J = 9.7 Hz), 119.05 (d, J = 2.2 Hz), 112.8(d, J = 21.6 Hz), 111.3 (d, J = 25.3 Hz), 52.4; IR (neat): 2955, 2084, 1698, 1611, 1582, 1492, 1435, 1356, 1246, 1216, 1136, 1050, 853, 774, 740, 680 cm^{-1}; HRMS (APCI) calcd for [$C_9H_7FN_2O_2$ + H^+] 195.0570, Found [M + H^+] 195.0625.

Methyl 2-diazo-2-(4-fluorophenyl)acetate, 4-29f



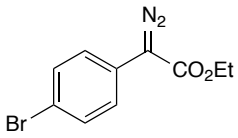
The titled compound was obtained as yellow solid by a previously reported diazo transfer reaction (729.6 mg, 91% yield).[63] ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40 (m, 2H), 7.07 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 162.5, 160.0, 126.1, 121.4, 116.4, 116.2, 52.3; IR (neat): 2082, 1694, 1508, 1436, 1347,1287, 1246, 1191, 1156, 1043, 830, 740 cm^{-1}; HRMS (APCI) calcd for [$C_9H_7FN_2O_2$ + 1 + Na^+] 218.0462, Found [M+ 1 + Na^+] 218.1093.

Methyl 2-diazo-2-(3,4-difluorophenyl)acetate, 4-29j



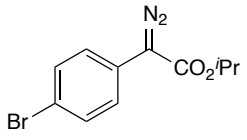
The titled compound was obtained as orange solid by a previously reported diazo transfer reaction The title (937 mg, 88% yield).[63] ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.43 (m, 1H), 7.06 (m, 1H), 7.03 (m, 1H), 3.84 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.3, 152.1, 152.0, 149.6, 149.5, 147.2, 147.1, 122.9, 122.8 119.5, 118.0, 117.8, 113.6, 113.4, 62.9, 52.3; IR (neat): 2082, 1694, 1508, 1436, 1347,1287, 1246, 1191, 1156, 1043, 830, 740 cm^{-1}; HRMS (APCI) calcd for [$C_9H_6F_2N_2O_2$ - N_2] 195.0397, Found [M - N_2] 195.0359.

Ethyl 2-(4-bromophenyl)-2-diazoacetate, 4-29j



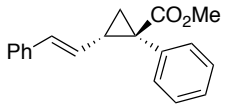
The titled compound was obtained as orange solid by a previously reported procedure (1.2 g, 90% yield).[63] ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.47 (m, 2H), 7.33 (m, 2H), 4.31(q, J = 6.8 Hz, 2H), 1.32 (t, J = 7.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.0, 132.2, 125.5, 125.1, 119.4, 61.4, 14.7; IR (neat): 2981, 2083, 1701, 1489, 1369, 1338, 1276, 1242, 1170, 1078, 1042, 1006, 824, 739 cm^{-1}; HRMS (APCI) calcd for [$C_{10}H_9BrN_2O_2$ - N_2] 241.9942, Found [M - N_2] 242.2589.

Isopropyl 2-(4-bromophenyl)-2-diazoacetate, 4-29k



The titled compound was obtained as orange solid by a previously reported procedure (877 mg, 87% yield).[63] ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40 (m, 2H), 7.07 (m, 2H), 3.84 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.9, 162.5, 160.0, 126.1, 121.4, 116.4, 116.2, 52.3; IR (neat): 2082, 1694, 1508, 1436, 1347,1287, 1246, 1191, 1156, 1043, 830, 740 cm^{-1}; HRMS (APCI) calcd for [$C_9H_7FN_2O_2$ + H^+] 283.0082, Found [M+ H^+] 283.--77.

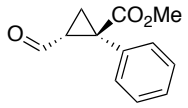
(1*R*, 2*S*)-Methyl 1-phenyl-2-((*E*)-styryl)cyclopropanecarboxylate, 4-31a



The titled compound was obtained by general procedure D as colorless oil in 93% yield (269 mg, >94% de). HPLC: 96% ee: OD-H column, 0.7 % 2-PrOH in hexanes, 1 mL/min, 1mg/mL, t_R = 6.4 min (major) and 7.6 min (minor), UV 254 nm; [α]$^{D}_{20}$: -181° (c = 1 w/v, MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (m, 5H), 7.12 (m, 2H), 7.05 (m, 3H), 6.52 (d, *J* = 15.5 Hz, 1H), 5.18 (dd, *J* = 15.5, 10.0 Hz, 1H), 3.52 (s, 3H), 2.66 (m, 1H), 2.02 (m, 1H), 1.42 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.7, 136.8, 135.6, 131.4, 131.0, 128.5, 128.1, 127.8, 127.0, 126.8, 125.6, 52.12, 35.47, 31.65, 22.26; IR

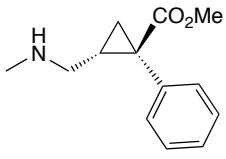
(neat): 1717, 1271, 1244, 1193, 1159, 960, 752, 694 cm^{-1}; HRMS (APCI) calcd for [$C_{19}H_{18}O_2 + Na^+$] 301.1199, Found [$M + Na^+$] 301.1194.

(1*R*, 2*R*)-Methyl 2-formyl-1-phenylcyclopropanecarboxylate, 4-32a



The titled compound was obtained by general procedure E as a colorless oil in 69% yield (136 mg). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 6.41 Hz, 1H), 7.34-7.25 (m, 5H), 3.62 (s, 3H), 2.71 (dd, *J* = 8.54, 6.41 Hz, 1H), 2.10 (dd, *J* = 8.54, 4.88 Hz, 1H), 2.08-2.03 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.1, 171.8, 133.5, 130.8, 128.4, 128.0, 52.8, 37.2, 36.1, 19.1; IR (neat): 1706, 1249, 1155, 699 cm^{-1}; HRMS (APCI) calcd for [$C_{12}H_{12}O_3 + H^+$] 205.0865, Found [$M + H^+$] 205.0860.

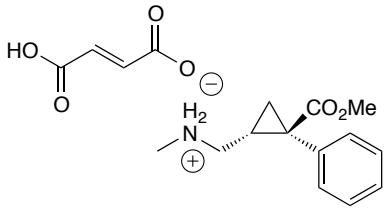
(1*R*,2*R*)-methyl 2-((methylamino)methyl)-1-phenylcyclopropanecarboxylate, 4-33a



The titled compound was obtained by general procedure F as colorless oil in 43% yield (63 mg). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49-7.15 (m, 5H), 3.62 (s, 3H), 2.45 (dd, *J* = 12.3, 5.9 Hz, 1H), 2.32 (s, 3H), 2.14-2.02 (m, 1H), 2.00-1.90 (m, 1H), 1.74 (dd, *J* = 9.1, 4.2 Hz, 1H), 1.24 (dd, *J* = 6.4, 4.5 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.3, 135.6,

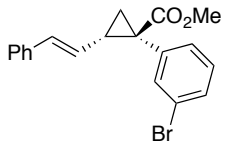
130.8, 127.8, 127.0, 52.1, 36.1, 33.0, 27.7, 20.0; IR (neat): 2949, 2843, 1715, 1434, 1251, 700 cm^{-1}; HRMS (APCI) calcd for [$C_{13}H_{17}O_2N$ + H^+] 220.1338, Found [M + H^+] 220.1331.

(1*R*,2*R*)-methyl 2-((methylamino)methyl)-1-phenylcyclopropanecarboxylate, fumaric acid, 4-34a



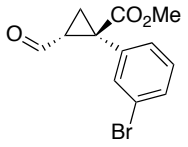
The titled compound was obtained by general procedure H as off-white solid in 51% yield (49 mg). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.38-7.26 (m, 5H), 6.67 (s, 2H), 3.23 (dd, *J* = 12.8, 3.9 Hz, 1H), 2.59 (s, 3H), 2.24-2.12 (m, 1H), 1.95 (dd, *J* = 12.8, 11.2 Hz, 1H), 1.66 (dd, *J* = 5.2, 8.8 Hz, 1H), 1.37 (dd, *J* = 5.2, 6.4 Hz, 1H); ^{13}C-NMR (100 MHz, CD_3OD) δ 175.1, 171.5, 136.3, 135.8, 132.3, 129.7, 129.1, 53.3, 51.1, 34.8, 33.4, 23.5, 21.0; IR (neat): 3000, 1713, 1560, 1261, 1171, 702 cm^{-1}; HRMS (APCI) calcd for [$C_{17}H_{21}NO_6$ + H^+] 336.1477, Found [M + H^+] 336.1482.

(1*R*,2*S*)-methyl 1-(3-bromophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate, 4-31b



The titled compound was obtained by general procedure D as colorless oil in 82% yield (354 mg). HPLC analysis: 91% ee, OD-H column, 1 % 2-PrOH in hexanes, 1mL/min, 1mg/mL, t_R = 6.01 (major) and 7.73 (minor); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.43 (m, 2H), 7.27 (m, 7H), 6.61 (d, *J* = 15.6 Hz, 1H), 5.21 (dd, *J* = 15.6, 10.0 Hz, 1H), 3.67 (s, 3H), 2.72 (m, 1H), 2.08 (dd, *J* = 4.8, 8.8 Hz, 1H), 1.48 (dd, *J* = 4.8, 6.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ173.8, 138.4, 137.2, 134.6, 132.1, 130.8, 130.7, 129.8, 128.7, 128.3, 127.5, 126.1, 122.2, 52.9, 35.5, 32.2, 22.7; IR (neat): 3025, 2949, 1716, 1595, 1433, 1272, 1242, 1159, 955, 752, 702, 691 cm^{-1}; HRMS (APCI) calcd for [$C_{19}H_{17}BrO_2$ + H^+] 357.0490, Found [M + H^+] 357.0491.

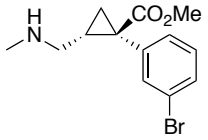
(1*R*,2*R*)-methyl 1-(3-bromophenyl)-2-formylcyclopropanecarboxylate, 4-32b



The titled compound was obtained by general procedure E as colorless oil in 68% yield (190.7 mg). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.63 (d, *J* = 6.4 Hz, 1H), 7.44 (m, 2H), 7.20 (m, 2H), 3.65 (s, 3H), 2.75 (m, 1H), 2.11 (dd, *J* = 9.2, 8.8 Hz, 1H), 2.04 (dd, *J* = 4.8, 6.4 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ197.8, 171.7, 136.1, 134.1, 131.7, 130.3, 130.0,

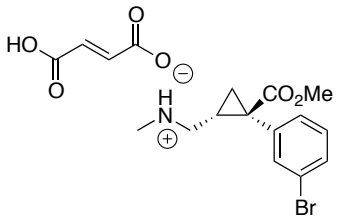
122.8, 53.4, 37.3, 36.5, 19.6; IR (neat): 1724, 1435, 1327, 1253, 1194, 1161, 699 cm^{-1}; HRMS (APCI) calcd for [$C_{12}H_{11}BrO_3 + H^+$] 282.9998, Found [$M + H^+$] 283.0013.

(1*R*,2*R*)-methyl 1-(3-bromophenyl)-2-((methylamino)methyl)cyclopropane-carboxylate, 4-33b



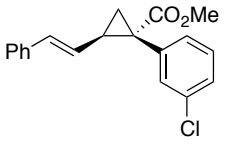
The titled compound was obtained by general procedure F as pale yellow oil in 60% yield (120.4 mg). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.24 (m, 2H), 6.99 (m, 2H), 3.51 (s, 3H), 2.75 (m, 1H), 2.44 (dd, *J* = 5.6, 6 Hz, 1H), 2.31 (s, 3H), 2.03 (m, 1H), 1.93 (m, 1H), 1.73 (dd, *J* = 2.4, 4.0 Hz, 1H), 1.8-1.6 (broad, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ174.7, 163.4, 160.9, 132.8, 132.7, 131.7, 115.4, 115.2, 52.7, 52.4, 36.5, 32.8, 28.0, 20.1; IR (neat): 1719, 1513, 1333, 1259, 1222, 1196, 1162, 838, 816 cm^{-1}; HRMS (APCI) calcd for [$C_{13}H_{16}BrNO_2 + H^+$] 298.0443, Found [$M + H^+$] 298.0442.

(1*R*,2*R*)-methyl 1-(3-bromophenyl)-2-((methylamino)methyl)cyclopropanecarboxylate Fumaric Salt, 4-34b fumaric salt, 4-34b



The titled compound was obtained by general procedure H as a white solid in 51% yield (84.9 mg). $[\alpha]^{D}_{20}$: -27.38° (c = 0.50 w/v, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.21 (m, 2H), 6.98 (m, 2H), 6.56 (s, 2H), 3.50 (s, 3H), 3.16 (dd, *J* = 4.0, 8.8 Hz, 1H), 2.51 (s, 3H), 2.05 (m, 1H), 1.86 (dd, *J* = 12.8, 11.8 Hz, 1H), 1.69 (dd, *J* = 8.8, 7.6 Hz, 1H), 1.37 (t, *J* = 5.6 Hz, 1H); ^{13}C-NMR (100 MHz, CD_3OD) δ174.5, 171.5, 138.5, 136.4, 135.4, 132.4, 131.5, 132.4, 131.5,123.5, 53.5, 51.0, 34.5, 30.8, 23.7, 21.2; IR (neat): 3016, 2818, 2766, 1720, 1605, 1561, 1514, 1437, 1377, 1265, 1233, 1174, 1083, 979, 839, 815 cm^{-1}; HRMS (APCI) calc for $[C_{17}H_{20}BrNO_6 + H^+]$ 413.0474, Found $[M + H^+]$ 413.0548.

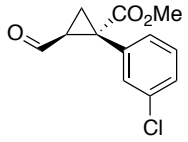
(1*S*,2*R*)-methyl 1-(3-chlorophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate, *ent*-4-31c



(1*S*, 2R)-methyl 1-(3-chlorophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate was obtained by general procedure D as colorless oil in 92% yield (302 mg). HPLC analysis: 92% ee, OD-H column, 1 % 2-PrOH in hexanes, 1mL/min, 1mg/mL, t_R = 5.85 (minor) and 7.58 (major); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.29 (m, 9H), 6.58 (d, *J* = 15.6Hz, 1H), 5.17 (dd,

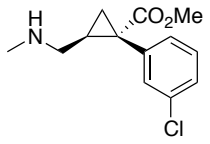
J = 15.6, 10.0 Hz, 1H), 3.63 (s, 3H), 2.67 (m, 1H), 2.04 (dd, *J* = 4.8, 8.8 Hz, 1H), 1.45 (dd, *J* = 4.8, 6.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ173.8, 138.1, 137.2, 134.0, 132.1, 131.8, 130.3, 129.5, 128.7, 128.3, 127.9, 127.5, 126.2, 52.9, 35.6, 32.2, 22.7; IR (neat): 2952, 2924, 2868, 1719, 1596, 1449, 1434, 1273, 1242, 1193, 1160, 1107, 956, 753, 713, 691 cm^{-1}; HRMS (APCI) calcd for [$C_{19}H_{17}ClO_2$ + H^+] 313.0995, Found [M + H^+] 313.0990.

(1*S*,2*S*)-methyl 1-(3-chlorophenyl)-2-formylcyclopropanecarboxylate, *ent*-4-32c



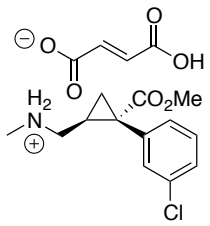
(1*S*, 2*S*)-methyl 1-(3-chlorophenyl)-2-formylcyclopropanecarboxylate was obtained by general procedure E as colorless oil in 72% yield (165.8 mg). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 6.4 Hz, 1H), 7.25 (m, 3H), 7.15 (m, 1H), 3.63 (s, 3H), 2.73 (m, 1H), 2.10 (dd, *J* = 5.2, 8.8 Hz, 1H), 2.03 (t, *J* = 5.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ197.8, 171.6, 135.8, 134.7, 131.2, 130.1, 129.5, 128.8, 53.4, 37.3, 36.5, 19.5; IR (neat): 2953, 2842, 1706, 1597, 1571, 1417, 1327, 1247, 1156, 1000, 937, 892, 798, 778, 754, 709, 692 cm^{-1}; HRMS (APCI) calcd for [$C_{12}H_{11}ClO_3$ + H^+] 239.0475, Found [M + H^+] 239.0477.

(1*S*,2*S*)-methyl 1-(3-chlorophenyl)-2-((methylamino)methyl)cyclopropane carboxylate, *ent*-4-33c



The titled compound was obtained by general procedure F as pale yellow oil in 54% yield (95 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ7.15 (m, 4H), 3.59 (s, 3H), 2.73 (m, 1H), 2.44 (dd, J = 5.2, 12.0 Hz, 1H), 2.31 (s, 3H), 2.03 (m, 1H), 1.91 (dd, J = 8.0, 12.4 Hz, 1H), 1.72 (dd, J =4.8, 8.8 Hz, 1H), 1.87 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ174.2, 138.0, 134.1, 131.3, 129.5, 127.8, 52.7, 52.7, 52.4, 36.5, 33.1, 28.1, 20.6; IR (neat): 2950, 1716, 1597, 1568, 1477, 1434, 1330, 1270, 1250, 1195, 1170, 1077, 894, 865, 797, 780, 759, 711, 694 cm^{-1}; HRMS (APCI) calcd for [$C_{13}H_{16}ClO_2N$ + H^+] 254.0948, Found [M + H^+] 254.0942.

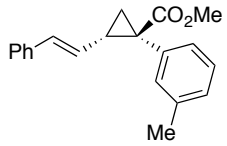
(1*S*,2*S*)-methyl 1-(3-chlorophenyl)-2-((methylamino)methyl)cyclopropane carboxylate Fumaric Salt, *ent*-4-34c



The titled compound was obtained by general procedure H as white solid in 62% yield (85 mg). [α]$^{D}_{20}$: 30.59° (c = 0.13 w/v, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.24

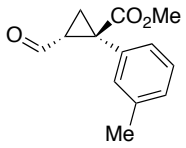
(m, 3H), 7.12 (m, 1H), 6.54 (s, 2H), 3.49 (s, 3H), 3.14 (m, 1H), 2.49 (s, 3H), 2.00 (s, 1H), 1.84 (dd, J = 10.8, 12.8 Hz, 1H), 1.68 (m, 1H), 1.38 (dd, J = 5.2, 6.8 Hz, 1H); ^{13}C-NMR (100 MHz, CD_3OD) δ174.5, 171.6, 138.2, 136.4, 135.5, 132.4, 131.3, 130.9, 129.4, 53.4, 51.1, 34.6, 33.5, 23.7, 21.2; IR (neat): 3020, 2959, 2766, 2360, 1722, 1596, 1567, 1380, 1273, 1259, 1203, 1175, 1078, 979, 921, 713, 696 cm^{-1}; HRMS (APCI) calcd for [$C_{17}H_{20}ClNO_6$ + H^+] 370.1057, Found [M + H^+] 370.1050.

(1*R*,2*S*)-methyl 2-((*E*)-styryl)-1-(*m*-tolyl)cyclopropanecarboxylate, 4-31d



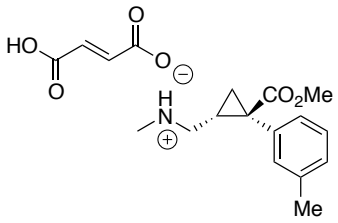
The titled compound was obtained by general procedure D as colorless oil in 80% yield (239 mg). HPLC analysis: 92% ee, OD-H column, 1 % 2-PrOH in hexanes, 1mL/min, 1mg/mL, t_R = 5.44 (major) and 6.15 (minor); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.22 (m, 9H), 6.62 (d, J = 16.0 Hz, 1H), 5.24 (dd, J = 16.0, 10.0 Hz, 1H), 3.61 (s, 3H), 2.70 (m, 1H), 2.36 (s, 3H), 2.06 (dd, J = 4.4, 12 Hz, 1H), 1.49 (dd, J = 4.4, 6.4 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ174.6, 137.8, 137.5, 135.9, 132.5, 131.3, 129.3, 129.1, 128.7, 128.4, 128.1, 127.3, 126.1, 52.8, 35.9, 32.2, 22.9, 21.7; IR (neat): 3025, 2949, 1716, 1605, 1491, 1434, 1271, 1243, 1152, 1102, 1051, 958, 755, 739, 703 cm^{-1}; HRMS (APCI) calcd for [$C_{20}H_{20}O_2$ + H^+] 293.1582, Found [M + H^+] 293.1585.

(1*R*,2*R*)-methyl 2-formyl-1-(*m*-tolyl)cyclopropanecarboxylate, 4-32d



The titled compound was obtained by general procedure E as a colorless oil in 57% yield (92.0 mg). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.53 (d, *J* = 6.8 Hz, 1J), 7.22 (m, 3H), 7.10 (m, 1H), 3.64 (s, 3H), 2.70 (m, 1H), 2.32 (s, 3H), 2.11 (dd, *J* = 4.8, 8.8 Hz, 1H), 2.04 (dd, *J* = 4.4, 6.4 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ198.7, 172.3, 138.6, 133.7, 131.8, 129.3, 128.7, 128.2, 53.3, 37.6, 36.5, 21.6, 19.6; IR (neat): 2953, 1711, 1607, 1490, 1435, 1329, 1254, 1192, 1155, 1104, 983, 902, 788, 739, 703 cm^{-1}; HRMS (APCI) calcd for [$C_{13}H_{14}O_3$ + H^+] 219.1021, Found [M + H^+] 219.1023.

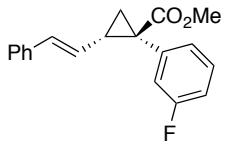
(1*R*,2*R*)-methyl 2-((methylamino)methyl)-1-(*m*-tolyl)cyclopropanecarboxylate Fumaric Salt, 4-34d fumaric salt



The titled compound was obtained by general procedure H as a white solid in 26% yield (38.1 mg). [α]$^{D}_{20}$: -38.21° (c = 0.11 w/v, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.11 (m, 1H), 7.00 (m, 3H), 6.56 (s, 2H), 3.43 (s, 3H), 3.14 (dd, *J* = 4.0, 12.0 Hz, 1H), 2.50 (s, 3H), 2.21 (s, 3H), 2.03 (m, 1H), 1.84 (dd, *J* = 12.8, 11.8 Hz, 1H), 1.65 (dd, *J* = 8.8, 5.2 Hz, 1H), 1.36 (t, *J* = 6.0 Hz, 1H); ^{13}C-NMR (100 MHz, CD_3OD) δ175.2, 171.2, 138.5,

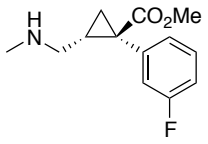
137.7, 136.3, 135.7, 132.9, 129.9, 129.7, 129.4, 53.3, 51.4, 34.8, 33.5, 23.4, 21.5, 21.0; IR (neat): 2921,2852, 1671, 1425, 1275, 1232, 1212, 917 cm^{-1}; HRMS (APCI) calcd for [$C_{18}H_{22}NO_6 + H^+$] 349.1525, Found [M + H^+] 349.1517.

(1*R*,2*S*)-methyl 1-(3-fluorophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate, 4-31e



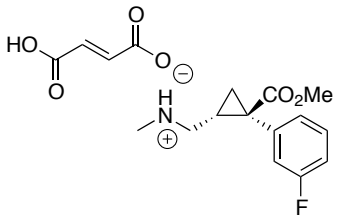
The titled compound was synthesized by general procedure D as colorless oil in 82% yield (439 mg). [α]$^{20}_D$: -29.7° (c = 0.49 w/v, $CHCl_3$); HPLC analysis: 92% ee, OD-H column, 1 % 2-PrOH in hexanes, 1mL/min, 1mg/mL, t_R = 4.95 (minor) and 6.00 (major); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.22 (m, 9H), 6.56 (d, *J* = 16Hz, 1H), 5.18 (dd, *J* = 16, 9.6 Hz, 1H), 3.64 (s, 3H), 2.72 (m, 1H), 2.04 (dd, *J* = 4.4, 8.8 Hz, 1H), 1.46 (dd, *J* = 4.4, 6.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ173.8, 163.8, 161.4, 138.5, 38.4, 137.2, 131.9, 129.7, 129.6, 128.7, 128.3, 127.6, 127.5, 127.4, 126.1, 118.8, 118.6, 114.8, 114.6, 52.8, 35.61, 35.62, 22.8; IR (neat): 3025, 2949, 1716, 1595, 1433, 1272, 1242, 1159, 955, 752, 702, 691 cm^{-1}; HRMS (APCI) calcd for [$C_{19}H_{17}FO_2$ - H^+] 295.1135, Found [M - H^+] 295.1153.

(1*R*,2*R*)-methyl 1-(3-fluorophenyl)-2-((methylamino)methyl)cyclopropane carboxylate, 4-33e



The titled compound was obtained by general procedure D~F as pale yellow oil in 59% yield (209.1 mg). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27 (m, 1H), 7.06 (m, 1H), 7.00 (m, 2H), 2.44 (dd, *J* = 5.6, 6.0 Hz, 1H), 3.31 (s, 3H), 2.05 (m, 1H), 1.93 (dd, *J* = 12.4, 7.6 Hz, 1H), 1.73 (dd, *J* = 4.4, 9.2 Hz, 1H), 1.19 (dd, *J* = 4.4, 6.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ174.3, 163.8, 161.4, 138.5, 138.4, 129.7, 129.6, 127.0, 126.9, 118.4, 118.1, 114.7, 114.5, 52.7, 52.5, 36.6, 33.2, 30.5, 28.3, 20.6; IR (neat): 3025, 2949, 1716, 1595, 1433, 1272, 1242, 1159, 955, 752, 702, 691 cm^{-1}; HRMS (APCI) calcd for [$C_{13}H_{16}FNO_2$ + H^+] 238.1243, Found [M + H^+] 238.1236.

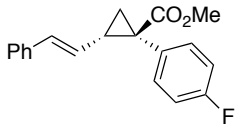
(1*R*,2*R*)-methyl 1-(3-fluorophenyl)-2-((methylamino)methyl)cyclopropane carboxylate Fumaric Salt, 4-34e



The titled compound was obtained by general procedure H as off-white solid in 46% yield (142.1 mg). [α]$^{D}_{20}$: -38.26° (c = 0.31 w/v, MeOH). ^{1}H-NMR (400 MHz, CD_3OD)

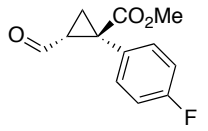
δ 7.20 (m, 1H), 6.91 (m, 3H), 6.50 (s, 2H), 3.45 (s, 3H), 3.10 (dd, *J* = 4.4, 13.2 Hz, 1H), 2.46 (s, 3H), 2.01 (m, 1H), 1.82 (dd, *J* = 12.4, 10.8 Hz, 1H), 1.64 (dd, *J* = 4.8, 8.4 Hz, 1H), 1.36 (dd, *J* = 5.2, 6.4 Hz, 1H); ^{13}C-NMR (100 MHz, CD_3OD) δ174.5, 171.6, 165.4, 163.0, 138.6, 138.5, 136.4, 131.6, 131.4, 128.3, 119.4, 119.2, 116.2, 116.0, 53.4, 51.1, 34.6, 33.5, 23.7, 21.2; IR (neat): 3028, 2804, 2358, 2333, 1716, 1640, 1641, 1587, 1492, 1436, 1384, 1263, 1214, 1169, 979, 925 cm^{-1}; HRMS (APCI) calcd for [$C_{13}H_{16}FNO_2$ + H^+ - fumaric acid] 238.1243, Found [M + H^+ - fumaric acid] 238.1236.

(1*R*,2*S*)-methyl 1-(4-fluorophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate, 4-31f



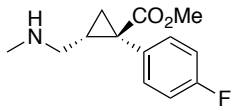
The titled compound was obtained by general procedure D as colorless oil in 89% yield (658 mg, > 94% de). HPLC analysis: 93% ee, OD-H column, 1 % 2-PrOH in hexanes, 1mL/min, 1mg/mL, t_R = 5.91 (major) and 8.00 (minor); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (m, 7H), 7.00 (m, 2H), 6.55 (d, *J* = 16.0 Hz, 1H), 5.16 (dd, *J* = 10.0, 16.0 Hz, 1H), 3.63 (s, 3H), 2.65 (m, 1H), 2.04 (dd, *J* = 4.4, 8.8 Hz, 1H), 1.42 (dd, *J* = 4.4, 6.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.2, 163.4 (d, *J* = 244.0 Hz) 142.5, 137.2, 133.5(d, *J* = 7.4 Hz), 131.9 (d, *J* = 11.2 Hz), 128.7 (d, *J* = 8.2 Hz), 127.5, 126.1, 115.4 (d, *J* = 21.6 Hz), 52.9, 35.2, 32.2, 23.0; IR (neat): 3024, 2948,1720, 1518, 1426,1287, 1159, 1043, 943, 750, 694 cm^{-1}; HRMS (APCI) calcd for [$C_{19}H_{17}FO_2$ - H^+] 295.1135, Found [M - H^+] 295.1153.

(1*R*,2*R*)-methyl 1-(4-fluorophenyl)-2-formylcyclopropanecarboxylate, 4-32f



The title compound was obtained by general procedure E as colorless oil in 70% yield (356.7 mg). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 6.4 Hz, 1H) 7.25 (m, 2H) 7.02 (m, 2H) 3.64 (s, 3H) 2.73 (m, 1H) 2.12 (dd, *J* = 8.4, 9.2 Hz, 1H) 2.03 (t, *J* = 5.2 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.3, 172.1, 168.1 (d, *J* = 247.1 Hz) 132.9 (d, *J* = 9 Hz), 129.6 (d, *J* = 3.7 Hz), 116.0 (d, *J* = 21.6 Hz), 53.4, 37.0, 36.5, 19.7; IR (neat): 1726, 1711, 1605, 1514, 1437, 1329, 1255, 1224, 1195, 1160, 1089,838, 814 cm^{-1}; HRMS (APCI) calcd for [$C_{12}H_{11}FO_3 + H^+$] 223.0770, Found [$M + H^+$] 223.0772.

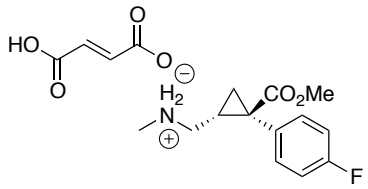
(1*R*,2*R*)-methyl 1-(4-fluorophenyl)-2-((methylamino)methyl)cyclopropane carboxylate, 4-33f



The titled compound was obtained by general procedure F as colorless oil in 64% yield (244.3 mg). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 2H), 7.20 (m, 2H), 3.60 (s, 3H), 2.45 (dd, *J* = 5.6, 6.0 Hz, 1H), 2.33 (s, 3H), 2.05 (m, 1H), 1.93 (dd, *J* = 12.0, 8.0 Hz, 1H), 1.73 (dd, *J* = 4.4, 8.4 Hz, 1H), 1.59 (broad, 1H), 1.19 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ172.1, 138.3, 134.2, 130.7, 130.0, 129.8, 122.3, 52.8, 52.4, 36.5, 33.2, 28.1, 20.6; IR (neat): 2949, 1719, 1595, 1564, 1478, 1434, 1271, 1252, 1196, 1170, 1068, 997, 896,

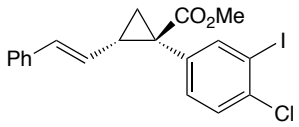
793, 702 cm^{-1}; HRMS (APCI) calcd for [$C_{13}H_{16}FNO_2$ + H^+] 238.1243, Found [M + H^+] 238.1242.

(1*R*, 2*R*)-methyl 1-(4-fluorophenyl)-2-((methylamino)methyl)cyclopropane carboxylate Fumaric Salt, 4-34f



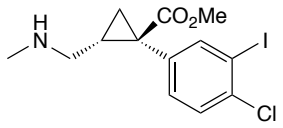
The titled compound was obtained by general procedure H as off-white solid in 48% yield (174.3 mg). [α]$^{D}_{20}$: -54.4° (c = 0.32 w/v, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.37 (m, 1H), 7.34 (m, 1H), 7.14 (m, 2H), 6.53 (s, 2H), 3.48 (s, 3H), 3.12 (m, 1H), 2.48 (s, 3H), 2.03 (m, 1H), 1.84 (dd, *J* = 13.2, 12.4 Hz, 1H), 1.65(dd, *J* = 5.2, 8.8 Hz, 1H), 1.37 (dd, *J* = 5.2, 6.4 Hz, 1H); ^{13}C-NMR (100 MHz, CD_3OD) δ177.5, 174.2, 167.8, 165.4, 138.9, 136.9, 136.8, 134.5, 134.4, 119.2, 118.9, 56.0, 53.8, 36.7, 36.1, 26.2, 23.9; IR (neat): 2794, 1720, 1636, 1565, 1478, 1379, 1272, 1204, 1174, 1068, 979, 794, 703 cm^{-1}; HRMS (APCI) calcd for [$C_{17}H_{20}FNO_6$ + H^+] 354.1353, Found [M + H^+] 354.1348.

(1*R*,2*S*)-methyl 1-(4-chloro-3-iodophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate, 4-31g



The titled compound was obtained by Procedure D as colorless oil (161 mg, 92% yield, 90% ee, >94% de). $[\alpha]^{D}_{20}$: -49.85° (c = 1.03 w/v, MeOH). HPLC analysis: OD-H, 1% i-PrOH, 1 mL/min. 90% ee. t_R = 6.32 min (major), t_R = 8.35 min (minor), UV 254 nm; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 2.0 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.27 – 7.06 (m, 7H), 6.58 (d, *J* = 15.8 Hz, 1H), 5.16 (dd, *J* = 15.7, 9.7 Hz, 1H), 3.63 (s, 3H), 2.65 (d, *J* = 6.7 Hz, 1H), 2.04 (dd, *J* = 9.0, 4.7 Hz, 1H), 1.40 (dd, *J* = 6.7, 4.7 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.4, 171.3, 138.14, 137.32, 136.73, 133.63, 132.82, 129.34, 129.08, 128.26, 127.95, 126.51, 53.30, 35.00, 32.60, 23.19; IR (neat) 2363, 1719, 1462, 1449, 1433, 1273, 1243, 1160, 1018, 958, 753, 692 cm^{-1}; HRMS (ESI) calcd for $[C_{19}H_{16}IClO_2 + H^+]$ 438.9962, Found $[M + H^+]$ 438.9961.

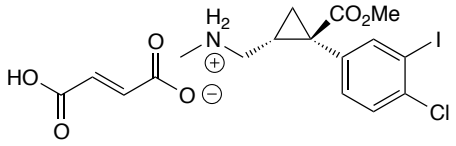
(1*R*,2*R*)-methyl 1-(4-chloro-3-iodophenyl)-2-((methylamino)methyl)cyclopropane carboxylate, 4-33g



The titled compound was obtained by general procedure F as pale yellow oil (71 mg, 53% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.36 (m, 1H), 7.21 (m, 1H), 3.60 (s, 3H), 2.43 (m, 1H), 2.33 (s, 3H), 1.97 (m, 2H), 1.73 (dd, *J* = 4.4, 8.8 Hz, 1H), 1.43 (m,

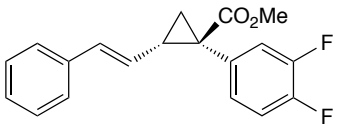
1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.8, 142.7, 137.7, 136.3, 132.5, 129.0, 97.9, 77.5, 77.4, 77.2, 76.9, 52.8, 52.3, 36.5, 32.4, 28.1, 20.7; IR (neat) 2941, 1718, 1577, 1560, 1434, 1271,1068, 997, 896, 793, 692 cm^{-1}; HRMS (ESI) calcd for [$C_{13}H_{15}ICINO_2$ + H^+] 379.9914, Found [M + H^+] 379.9908.

1-((1*R*,2*R*)-2-(4-chloro-3-iodophenyl)-2-(methoxycarbonyl)cyclopropyl)-*N*-methylmethanaminium (*E*)-3-carboxyacrylate, 4-34g



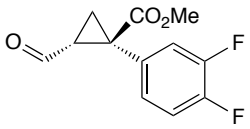
The titled compound was obtained by general procedure H as off-white solid (30 mg, 33% yield). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.80 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.18 (dd, *J* = 2, 8 Hz, 1H), 6.54 (s, 2H), 3.43 (s, 3H), 3.14 (m, 1H), 2.50 (s, 3H), 2.04 - 2.00 (m, 1H), 1.86 (dd, *J* = 11.2, 11.6 Hz, 1H), 1.67 (dd, *J* = 5.2, 4.8 Hz, 1H), 1.34 (t, *J* = 6.4 Hz, 1H); ^{13}C-NMR (100 MHz, CD_3OD) δ 174.2, 171.5, 144.1, 139.5, 135.5, 136.3, 133.8, 130.9, 98.8, 53.6, 50.9, 33.7, 33.5, 31.0, 23.8, 21.2; IR (neat) 2981, 2759, 2451, 1715, 1564, 1489, 1373, 1262, 1107, 982, 821, 719, 669 cm^{-1}; HRMS (ESI) calcd for [$C_{17}H_{19}ICINO_6$ - fumaric acid + H^+] 379.9914, Found [M-fumaric acid - H^+] 379.9911.

(1*R*,2*S*)-methyl 1-(3,4-difluorophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate, 4-31i



The titled compound was obtained by general procedure D as colorless oil (511 mg, 89% yield, 92% ee, >94% de). $[\alpha]^{D}_{20}$: -24.32° (c = 0.43 w/v, MeOH). HPLC analysis: OD-H, 1% i-PrOH, 1mL/min. t_R = 6.79 min (major), t_R = 9.96 min (minor); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.21 (m, 3H), 6.59 (d, *J* = 16.0 Hz, 1H), 5.21 (dd, *J* = 9.6, 16.0 Hz, 1H), 3.61 (s, 3H), 2.71 (m, 1H), 2.09 (dd, *J* = 4.4, 9.2 Hz, 1H), 1.46 (dd, *J* = 4.8, 6.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.6, 151.1, 148.7, 136.9, 133.1, 132.2, 128.7, 127.9, 127.5, 126.0, 120.7, 120.6, 117.1, 116.9, 52.8, 35.0, 32.3, 22.8; IR (neat) 3027, 2952, 1719, 1607, 1518, 1426, 1271, 1247, 1150, 960, 773, 693 cm^{-1}; HRMS (ESI) calcd for $[C_{19}H_{16}F_2O_2 + H^+]$ 315.1197, Found $[M + H^+]$ 315.1191.

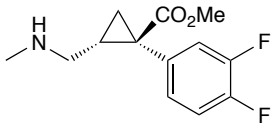
(1*R*,2*R*)-methyl 1-(3,4-difluorophenyl)-2-formylcyclopropanecarboxylate, 4-32i



The titled compound was obtained by general procedure E as colorless oil (261 mg, 67% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 6.0 Hz, 1H), 7.11 (m, 2H), 7.02 (m, 2H), 3.65 (s, 3H), 2.76 (m, 1H), 2.10 (dd, *J* = 5.2, 8.8 Hz, 1H), 2.02 (dd, *J* = 5.2, 6.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 197.6, 171.5, 151.6, 151.5, 151.4, 149.1, 149.0, 148.9, 130.8, 130.7, 127.4, 127.3, 127.2, 120.4, 120.3, 117.7, 117.6, 53.4, 36.9, 36.5,

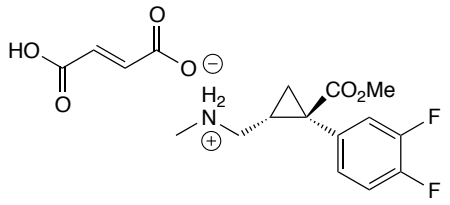
19.8; IR (neat) 2957, 2846, 1708, 1608, 1519, 1427, 1339, 1201, 1152, 1084, 1008, 927, 864, 774, 707 cm^{-1}; HRMS (ESI) calcd for [$C_{12}H_{10}F_2O_3$ - H^+] 239.0520, Found [M - H^+] 239.0526.

(1*R*,2*R*)-methyl 1-(3,4-difluorophenyl)-2-((methylamino)methyl)cyclopropane carboxylate, 4-33i



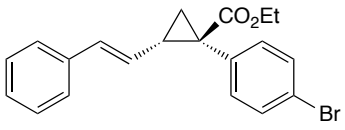
The titled compound was obtained by general procedure F as pale yellow oil (122 mg, 44% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.13 (m, 2H), 7.00 (m, 1H), 3.59 (s, 3H), 2.41 (dd, *J* = 5.2, 11.2 Hz, 1H), 2.31 (s, 3H), 2.01 (m, 1H), 1.94 (dd, *J* = 7.2, 11.6 Hz, 1H), 1.72 (dd, *J* = 4.8, 8.8 Hz, 1H), 1.34 (broad, 1H), 1.14 (dd, *J* = 4.4, 6.4 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.1, 151.1, 148.4, 133.0, 127.4, 127.3, 127.2, 127.1, 120.3, 120.2, 117.1, 116.9, 52.7, 52.4, 36.6, 32.7, 28.3, 20.8; IR (neat) 2801, 1736, 1607, 1519, 1436, 1398, 1273, 1189, 1152, 1117, 1079, 976, 901, 822, 706 cm^{-1}; HRMS (ESI) calcd for [$C_{13}H_{15}F_2NO_2$ + H^+] 256.1149, Found [M + H^+] 256.1143.

1-((1*R*,2*R*)-2-(3,4-difluorophenyl)-2-(methoxycarbonyl)cyclopropyl)-*N*-methylmethanaminium (*E*)-3-carboxyacrylate, 4-34i



The titled compound was obtained by general procedure H as white solid (89 mg, 48% yield). $[\alpha]^{D}_{20}$: -27.59° (c = 0.38 w/v, MeOH); ^{1}H-NMR (400 MHz, CD_3OD) δ 7.06-6.98 (m, 2H), 6.88 (m, 1H), 6.41 (s, 2H), 3.34 (s, 3H), 3.01 (dd, *J* = 3.6, 10.4 Hz, 1H), 2.37 (s, 3H), 1.92 (m, 1H), 1.75 (dd, *J* = 10.8, 12.4 Hz, 1H), 1.55 (dd, *J* = 5.2, 8.4 Hz, 1H), 1.27 (dd, *J* = 4.8, 6.0 Hz, 1H); ^{13}C-NMR (100 MHz, CD_3OD) δ 174.4, 171.6, 150.2, 136.4, 133.4, 129.0, 121.6, 121.5, 118.5, 118.4, 53.5, 50.9, 34.1, 33.5, 23.9, 21.4; IR (neat) 3508, 3023, 2802, 1737, 1608, 1520, 1436, 1350, 1273, 1117, 1079, 976, 901, 862, 741 cm^{-1}; HRMS (ESI) calc for [$C_{17}H_{19}F_2NO_6$ - fumaric acid + H^+] 256.1149, Found [M - fumaric acid + H^+] 256.1143.

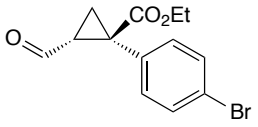
(1*R*,2*S*)-ethyl 1-(4-bromophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate, 4-31j



The titled compound was obtained by general procedure D as colorless oil (108 mg, 91% yield). HPLC analysis: ee = 88%, Chiralcel-OD-H, 1% *i*-PrOH in hexane, 1mL/min, t_R =

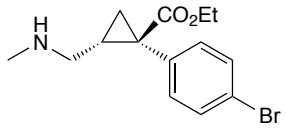
7.15 min (major), 8.78 min (minor), UV 254 nm. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.45 (m, 2H), 7.24 (m, 2H), 7.18 (m, 5H), 6.59 (d, *J* = 15.6 Hz, 1H), 5.21 (dd, *J* = 9.6, 15.6 Hz, 1H), 4.12 (m, 2H), 2.70 (m, 1H), 2.07 (dd, *J* = 4.8, 8.8 Hz, 1H), 1.44 (dd, *J* = 4.8, 4.4 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.2, 137.1, 135.2, 133.5, 131.1, 131.3, 128.7, 128.5, 127.4, 126.1, 121.5, 61.5, 35.4, 31.9, 22.5, 14.3; IR (neat): 3112, 2989, 1713, 1488, 1240, 1178, 1157, 1088, 1069, 1011, 959, 854, 750, 693 cm^{-1}; HRMS (APCI) calcd for [$C_{20}H_{19}BrO_2$ + H^+] 371.0647, Found [M + H^+] 371.0643.

(1*R*,2*R*)-ethyl 1-(4-bromophenyl)-2-formylcyclopropanecarboxylate, 4-32j



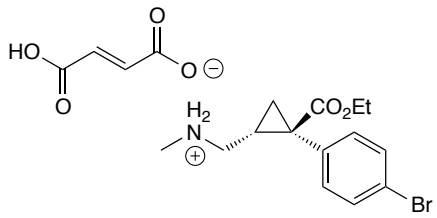
The titled compound was obtained by general procedure E as colorless oil (68 mg, 81% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.59 (d, *J* = 6 Hz, 1H), 7.44 (m, 2H), 7.15 (m, 2H), 4.09 (m, 2H), 2.72 (m, 1H), 2.10 (dd, *J* = 8.8, 4.8 Hz, 1H), 2.01 (dd, *J* = 6.4, 5.2Hz, 1H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 198.1,171.1, 133.0, 132.8, 131.9, 122.4, 62.3, 37.3, 36.4, 19.3, 14.2; IR (neat): 1706, 1489, 1244, 1154, 1088, 1069, 1010, 853, 826, 715 cm^{-1}; HRMS (APCI) calcd for [$C_{13}H_{13}BrO_3$ + H^+] 297.0126, Found [M + H^+] 297.0127.

(1*R*,2*R*)-ethyl 1-(4-bromophenyl)-2-((methylamino)methyl)cyclopropane carboxylate, 4-33j



The titled compound was obtained by Procedure F as colorless oil in 54% yield (39 mg). $[\alpha]^{D}_{20}$: -16.3° (0.53 w/v, MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.02 (m, 2H), 2.37 (dd, *J* = 6.0, 12.4 Hz, 1H), 2.27 (s, 3H), 1.99 (m, 1H), 1.89 (dd, *J* = 12.4, 8.0 Hz, 1H), 1.68 (dd, *J* = 4.4, 9.2 Hz, 1H), 1.20 (broad, 2H), 1.36 (m, 1H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ173.6, 135.2, 132.9, 131.3, 121.4, 61.3, 52.5, 36.6, 32.9, 27.9, 20.1, 14.2; IR (neat): 2949, 1718, 1590, 1567, 1448, 1434, 1271,1068, 997, 896, 793, 699 cm^{-1}; HRMS (APCI) calcd for $[C_{14}H_{18}BrNO_2 + H^+]$ 312.0599, Found $[M + H^+]$ 312.0596.

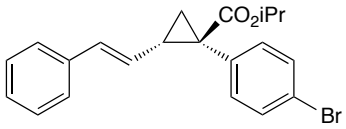
1-((1*R*,2*R*)-2-(4-bromophenyl)-2-(ethoxycarbonyl)cyclopropyl)-*N*-methylmethanaminium (*E*)-3-carboxyacrylate, 4-34j



The titled compound was obtained by procedure H as white solid in 57% yield (31 mg). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.40 – 7.21 (m, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.46 (s, 2H), 3.87 (dd, *J* = 7.2, 6.2 Hz, 2H), 3.09 (q, *J* = 1.6 Hz, 1H), 3.04 (dd, *J* = 12.6, 3.8 Hz, 1H), 2.41 (s, 3H), 2.03 – 1.91 (m, 1H), 1.76 (dd, *J* = 12.7, 10.8 Hz, 1H), 1.62 – 1.52 (m,

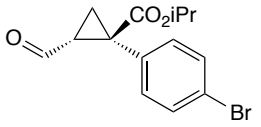
1H), 1.30 (dd, *J* = 6.5, 5.0 Hz, 1H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, CD_3OD) δ 174.1, 171.6, 136.4, 135.3, 134.3, 132.9, 123.1, 63.0, 51.1, 34.5, 33.5, 23.6, 21.0, 14.6; IR (neat) 1716, 1488, 1367, 1273, 1261, 1182, 1010, 974, 826, 789, 755, 718 cm^{-1}; HRMS(ESI) calcd for [$C_{18}H_{22}BrNO_6$ - fumaric acid +H^+] 312.0599, Found [M - fumaric acid +H^+] 312.0596.

(1*R*,2*S*)-isopropyl 1-(4-bromophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate, 4-31k



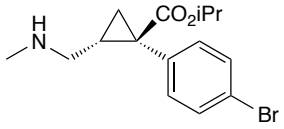
The titled compound was obtained by general procedure D as colorless oil (98 mg, 89% yield, 70% ee, >94% de). [α]$^{D}_{20}$: -28.73° (c = 0.83 w/v, MeOH). HPLC analysis: OD-H, 1% i-PrOH, 1mL/min. t_R=5.97 min (major); t_R=7.45 min (minor), UV 254 nm. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44 (m, 2H), 7.22 (m, 2H), 7.15 (m, 5H), 6.58 (d, *J* = 16.0 Hz, 1H), 5.19 (dd, *J* = 10.0, 15.6 Hz, 1H), 4.98 (m, 1H), 2.66 (m, 1H), 2.04 (dd, *J* = 4.4, 9.2 Hz, 1H), 1.42 (dd, *J*=4.4, 6.4Hz, 1H), 1.16 (t, *J* = 6.4 Hz, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.6, 137.1, 135.4, 133.4, 131.7, 131.3, 128.7, 128.6, 127.4, 126.0, 121.5, 68.9, 35.6, 31.7, 22.2, 21.8; IR (neat) 3112, 2989, 1713, 1488, 1240, 1178, 1157, 1088, 1069, 1011, 959, 854, 750, 693 cm^{-1}; HRMS(ESI) calcd for [$C_{21}H_{21}BrO_2$ + H^+] 385.0803, Found [M + H^+] 385.0801.

(1*R*,2*R*)-isopropyl 1-(4-bromophenyl)-2-formylcyclopropanecarboxylate, 4-32k



The titled compound was obtained by general procedure E as colorless oil (63 mg, 80% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 6.6 Hz, 1H), 7.53 – 7.33 (m, 2H), 7.17 – 7.11 (m, 2H), 5.01 – 4.84 (m, 1H), 2.69 (d, *J* = 8.7 Hz, 1H), 2.07 (dd, *J* = 8.6, 4.9 Hz, 1H), 2.00 (dd, *J* = 6.2, 4.9 Hz, 1H), 1.12 (t, *J* = 4 Hz, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.2, 170.4, 133.1, 132.7, 131.8, 122.3, 69.9, 37.4, 36.2, 21.7, 19.1; IR (neat) 2981, 1708, 1489, 1395, 1249, 1170, 1105, 1087, 1011, 922, 819, 765, 752, 715 cm^{-1}; HRMS (ESI) calcd for [$C_{14}H_{15}BrO_3$ + H^+] 311.0283, Found [M + H^+] 311.0278.

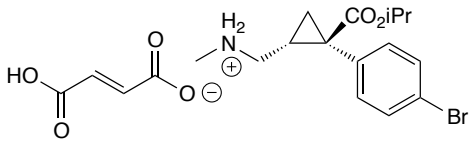
(1*R*,2*R*)-isopropyl 1-(4-bromophenyl)-2-((methylamino)methyl)cyclopropane carboxylate, 4-34k



The titled compound was obtained by general procedure F as colorless oil (51 mg, 77% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 2H), 7.15 – 7.05 (m, 2H), 4.86 (m, 1H), 2.45 (t, *J* = 7.2 Hz, 1H), 2.35 (dd, *J* = 12.2, 5.7 Hz, 1H), 2.25 (s, 3H), 1.96 (dd, *J* = 8.7, 6.3 Hz, 1H), 1.85 (dd, *J* = 12.1, 7.8 Hz, 1H), 1.65 (dd, *J* = 8.8, 4.4 Hz, 1H), 1.13 – 1.09 (m, 1H), 1.06 (d, *J* = 8.6 Hz, 6H), 0.95 (t, *J* = 7.2 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.1, 135.3, 132.8, 131.3, 121.3, 77.5, 77.2, 76.9, 68.7, 52.6, 36.6, 33.1, 27.7, 21.8, 19.8; IR (neat) 2977, 2934, 2785, 1709, 1487, 1386, 1373, 1249, 1179, 1082, 1046,

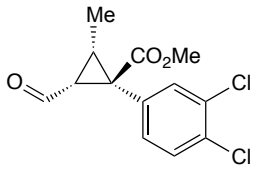
1009, 934, 889, 819, 764, 716 cm-1; HRMS (ESI) calcd for [$C_{15}H_{20}BrNO_2$ + H^+] 326.0756, Found [M + H^+] 326.0750.

1-((1*R*,2*R*)-2-(4-bromophenyl)-2-(isopropoxycarbonyl)cyclopropyl)-*N*-methyl methanaminium (*E*)-3-carboxyacrylate, 4-34k



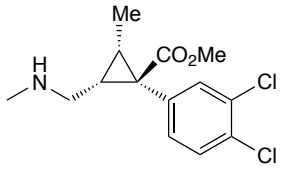
The titled compound was obtained by general procedure H as white solid (36 mg, 53% yield). [α]$^{D}_{20}$: -28.27° (c = 0.75 w/v, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.36 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.49 (s, 2H), 4.78 (m, 1H), 3.08 (dd, *J* = 4.0, 12.8 Hz, 1H), 2.46 (s, 3H), 2.01 (m, 1H), 1.79 (dd, *J* = 10.8, 12.8 Hz, 1H), 1.62 (dd, *J* = 5.2, 8.8 Hz, 1H) 1.33 (dd, *J* = 5.2, 6.4 Hz, 1H) 0.98 (dd, *J* = 6.4, 10.0 Hz, 6H); ^{13}C-NMR (100 MHz, CD_3OD) δ 173.5, 173.2, 136.8, 135.4, 134.3, 132.8, 123.0, 70.8, 51.1, 34.6, 33.5, 23.5, 21.9, 20.8; IR (neat) 2981, 2759, 2451, 1715, 1564, 1489, 1373, 1262, 1107, 982, 821, 719, 669 cm^{-1}; HRMS (ESI) calcd for [$C_{19}H_{24}BrO_6$ - fumaric acid + H^+] 326.0756, Found [M - fumaric acid + H^+] 326.0750.

(1*R*, 2*R*, 3*S*)-methyl 1-(3,4-dichlorophenyl)-2-formyl-3-methylcyclopropane carboxylate, 4-37



The titled compound was obtained by general procedure E as colorless oil (83 mg, 78% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.10 (d, *J* = 6.8 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.02 (m, 1H), 3.61 (s, 3H), 2.68 (dd, *J* = 6.8, 9.6 Hz, 1H), 2.41 (m, 1H), 1.35 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.5, 171.9, 134.1, 132.9, 132.8, 131.7, 130.8, 53.5, 41.1, 38.9, 28.6, 11.1; IR (neat) 2953, 2934, 1725, 1704, 1473, 1435, 1381, 1246, 1198, 1136, 1093, 1031, 936, 745, 705 cm-1; HRMS (ESI) calcd for [$C_{13}H_{12}Cl_2O_3$ + H^+] 287.0242, Found [M + H^+] 287.0237.

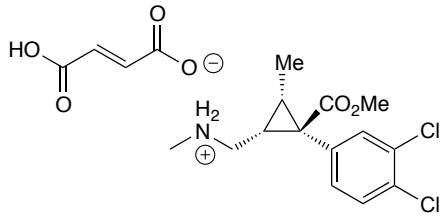
(1*R*,2*S*,3*R*)-methyl 1-(3,4-dichlorophenyl)-2-methyl-3-((methylamino)methyl) cyclopropanecarboxylate, 4-38



The titled compound was obtained by general procedure F as colorless oil (27 mg, 31% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 2H), 7.09 (d, *J* = 2.4 Hz, 1H), 3.54 (s, 3H), 2.48 (dd, *J* = 6.4, 12.4 Hz, 1H), 2.40 (s, 3H), 2.34 (dd, *J* = 6.0, 12.0 Hz, 1H), 1.96 (m, 2H), 1.15 (broad, 1H), 0.95 (d, *J* = 6.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.6, 134.3, 134.2, 132.3, 131.9, 131.6, 130.3, 52.7, 48.2, 36.9, 34.9, 31.2, 25.2, 10.5;

IR (neat) 2950, 2845, 2789, 1715, 1472, 1434, 1380, 1333, 1242, 1208, 1136, 1045, 1030, 830, 743, 706, 675 cm-1; HRMS (ESI) calcd for [$C_{14}H_{17}Cl_2NO_2$ + H^+] 302.0785, Found [M + H^+] 302.0789.

1-((1*R*,2*R*,3*S*)-2-(3,4-dichlorophenyl)-2-(methoxycarbonyl)-3-methylcyclopropyl)-*N*-methylmethanaminium (*E*)-3-carboxyacrylate, 4-39



The titled compound was obtained by general procedure H as white solid (17 mg, 48% yield). [α]$^{D}_{20}$: -25.92° (c = 0.71 w/v, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.38 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.03 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.53 (s, 2H), 3.44 (s, 3H), 3.31 (dd, *J* = 1.6, 5.6 Hz, 1H), 2.56 (s, 3H), 2.43 (dd, *J* = 2.8, 13.2 Hz, 1H), 2.03 (m, 1H), 1.93 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (100MHz, CD_3OD) δ 174.7, 171.4, 136.3, 135.3, 134.6, 133.6, 133.3, 133.2, 131.9, 53.3, 46.6, 36.0, 33.9, 27.1, 26.5, 10.6; IR (neat) 2954, 2763, 1718, 1636, 1556, 1473, 1380, 1257, 981, 829 cm^{-1}; HRMS (ESI) calcd for [$C_{18}H_{21}Cl_2NO_6$ - fumaric acid + H^+] 302.0785, Found [M - fumaric acid + H^+] 302.0789.

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